Lee A. Fleisher, MD

Evidence-Based PRACTICE OF ANESTHESIOLOGY

THIRD EDITION

ELSEVIER SAUNDERS

EVIDENCE-BASED PRACTICE OF ANESTHESIOLOGY

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To my children, Jessica and Matthew, who continue to inspire me by asking important questions as they progress on their own journey of discovery.

And to the numerous faculty, residents, and medical students of the Perelman School of Medicine at the University of Pennsylvania, who strive to improve patient care through both the application and investigation of best practice.

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Foreword

Dr. Lee Fleisher is the individual in the discipline anesthesiology singularly identified with the promulgation of evidence-based medicine (EBM). Through his research, reviews, lectures, and contributions to numerous guideline committees, he is an innovator in promoting the use of EBM to support clinical decision-making. Before I continue, it is appropriate to briefly define EBM for the reader.

In clinical practice, EBM emphasizes the integration of the individual clinician's experience with the best available scientific research to deliver superlative medical care to a patient.[1] Detractors of this concept will state that (1) EBM discounts clinical intuition and experience, (2) pathophysiology has no role in EBM, and (3) EBM subjugates the process of history-taking and physical examination to randomized controlled investigations.[1] Proponents will counter that (1) EBM integrates clinical judgment with the *best available* scientific data, (2) understanding pathophysiology is essential not only to interpret the clinician's findings, but also to systematically evaluate scientific research, and (3) EBM relies on various research pathways (e.g., prospective randomized controlled trials, high-quality observational trials, and review articles) to develop a foundation for exemplary clinical care.

A major concern of physicians is the inclusion of EBM studies in the development of guidelines that have limited clinical relevance. Their unease is based on the perceived inability to deliver the level of care suggested in a guideline coupled with exposure to a malpractice suit. Dr. Fleisher addresses this issue in the first chapter. In an eloquent explanation, Drs. Nickinovich, Connis, Caplan, Arens, and Apfelbaum describe the process of developing a guideline or any of the parallel practice statements that the American Society of Anesthesiologists publishes. It should be reassuring to anesthesiologists that such care is taken to ensure a balance between development of an anesthetic management plan and the appropriate use of the best available scientific data.

It would be easy to create a book that uses EBM as the clinical paradigm and is totally irrelevant to the caregiver. Perhaps it would have rare syndromes that may be seen once in a career. Or the book would emphasize a very expensive, resource-intensive solution to a relatively simple clinical question. However, from the outset Dr. Fleisher astutely looks at "simple" yet common questions that anesthesiologists face every day. The very title of the book alerts the reader to this emphasis *(Evidence-Based **Practice** of Anesthesiology)*. It is relatively easy to develop a book that addresses the clinical concerns of the practitioner. However, Dr. Fleisher takes this book to the next level by creating a chapter template that starts where other editors have left off. After a neutral discussion of the best available scientific research, the contributors add two critical sections: Areas of Uncertainty and, importantly, Author Recommendations. These two portions serve as the bridge from research to clinical practice. It's as if practitioners have one of the world's experts at their side as they develop and implement a plan of care.

This book will serve clinicians at varying points in their career. For residents, educated with EBM as a foundation of teaching in medical school, this becomes a natural extension of their cognitive development. In preparation for the oral board examinations, the chapters in this book serve as a powerful summary in case management on which to base responses. Finally, for experienced clinicians, the observations contained in this book will not only assist in delivery of exemplary case, but also assist in reviewing subject matter for the recertification process.

Perhaps Albert Einstein's succinct observation can be applied to EBM:

> *"Not everything that can be counted counts, and not everything that counts can be counted."*

Paul Barash, MD

REFERENCE

1. Evidence-Based Medicine Working Group. Evidence-based medicine: a new approach to teaching the practice of medicine. JAMA 1992;268:2420–5.

Preface

It has been 4 years since the publication of the second edition and 9 years since the publication of the first edition of *Evidence-Based Practice of Anesthesiology*. I was extremely pleased that many practitioners, especially residents, found useful the approach taken to critical questions in the first two editions. I am indebted to the many individuals who have written for this edition and approached the evidence in a standardized way. In editing the third edition, I maintained the approach and format of the earlier editions, updated important topics with ongoing controversy, and added many new topics for which there is increasing evidence on how best to practice. In many cases, there is new evidence to support and refute practices originally advocated in previous editions that in some cases necessitated changes in recommendations. It is my hope that the field of anesthesiology and perioperative medicine will continue to grow with increasing high-quality investigations to expand our evidence base and help practitioners provide the highest quality of care to the individual patient.

I am indebted to several people who were critical in the publication of the third edition of *Evidence-Based Practice of Anesthesiology*. I would like to particularly acknowledge my executive assistant, Eileen O'Shaughnessy, who kept the authors and myself on track. In addition to my publisher, I would like to thank Heather Krehling, who as my developmental editor ensured the quality of the final product. I hope that the third edition of this book will continue to provide the answers to many of your daily anesthesia questions.

Lee A. Fleisher

CHAPTER 1

Evidence-Based Practice Parameters: The Approach of the American Society of Anesthesiologists

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Practice parameters developed by the American Society of Anesthesiologists (ASA) have been an important resource for physicians and other health-care workers for more than 20 years. The intention of the ASA evidence-based practice parameter is to enhance and promote safe medical practice as well as offer guidance for diagnosing, managing, or treating a variety of clinical conditions. ASA evidence-based practice parameters consist of a "broad body of documents developed on the basis of a systematic and standardized approach to the collection, assessment, analysis and reporting of: scientific literature, expert opinion, ASA member opinion, feasibility data and open forum commentary."[1] Evidence-based practice parameters may take the form of guidelines or advisories.

Before the development of a policy for evidence-based practice parameters in 1991, ASA practice parameters were primarily consensus-based documents, and the majority of these documents were practice standards. Practice standards were typically declarative statements focusing on simple aspects of patient care applicable to virtually all relevant anesthetic situations.[2] The standards were well received within both the anesthesia community and allied medical professions and positioned the ASA and the Anesthesia Patient Safety Foundation of the ASA at the forefront of medical practice by demonstrating the benefits of a proactive approach to patient safety.

Many aspects of practice, however, could not be adequately covered by the relatively limited and prescriptive recommendations of practice standards. When broader and more flexible recommendations for practice were needed, the ASA broadened its scope to encompass practice guidelines. The practice guidelines were initially formulated on the basis of evidence generated by the same consensus-based methodology used in the development of standards. To effectively evaluate the increasing breadth and complexity of issues considered by practice guidelines, the ASA Committee on Standards and Practice Parameters (Committee) determined that a systematic evaluation of scientific evidence was necessary to fully support recommendations driven by expert opinion. Using a method that systematically combined a synthesis of the literature with opinions from experts and other sources, the ASA produced the first two evidence-based practice guidelines in 1993.[3,4] In developing these guidelines, the Committee recognized the unique properties of both the anesthesia literature and the practice of anesthesiology and realized that further methodologic changes were needed. Over the next few years, a more elaborate multidimensional method to guideline development evolved. It contained four critical components: (1) a rigorous review and evaluation of all available published scientific evidence, (2) meta-analytic assessments of controlled clinical studies when appropriate, (3) a statistical assessment of expert and practitioner opinions obtained by formally developed surveys, and (4) the informal evaluation of opinions obtained from invited and public commentary.

PROCESS OF PARAMETER DEVELOPMENT

The process used by the ASA to develop evidence-based practice parameters normally begins when the Committee identifies an issue or clinical problem. The Committee then appoints a task force of 8 to 12 anesthesiologists who are recognized experts on the issue or clinical problem to advise the Committee on the need for a practice parameter. Task force members are carefully chosen to not only provide representation from both private practice and academia but also ensure representation across major geographic areas of the United States. Occasionally, nonanesthesiologists may also be appointed to a task force if the Committee determines that their appointment would add specific subspecialty expertise (e.g., the appointment of a radiologist to the magnetic resonance imaging task force). Conflict of interest issues are fully evaluated before individuals are selected to serve on a task force, and such information is fully transparent to the reader.

If the task force determines that sufficient evidence is available, the process of defining goals and objectives within the mandate established by the Committee begins.

During this conceptualization phase, approximately 75 to 150 peer-review consultants are identified as secondary external sources of opinion, practical knowledge, and expertise. Consultants typically are recognized experts in the subject matter and, like the task force members, represent a balance of practice settings and geographic locations. Depending on the clinical topic, individuals from nonanesthesia medical specialties or organizations may be selected as consultants.

An initial step in the development of an evidence-based practice parameter is to survey the task force members to identify target conditions, patient or clinical presentations, providers, interventions, practice settings, and other characteristics that help define or clarify the parameter. On the basis of the survey responses, members of the task force collectively develop a list of clinical interventions and expected outcomes. The list, typically referred to as "evidence linkages" between interventions and outcomes, forms the foundation on which evidence is collected and organized and provides structure for formulation of recommendations. When possible and appropriate, evidence linkages are designed to describe comparative relationships between interventions and outcomes. For example, the linkage statement "spinal opioids versus parenteral opioids improve maternal analgesia for labor" identifies a specific intervention (spinal opioids), a comparison intervention (parenteral opioids), and a specific clinical outcome (maternal analgesia) thought to be affected by the intervention. Once all evidence linkages for the parameter are specified, the task force then begins the process of collecting evidence.

SOURCES OF EVIDENCE

The multiple sources of information used by a task force in developing an evidence-based practice parameter are displayed in Table 1-1. During the search for evidence, the task force considers two major sources: literature-based evidence and opinion-based evidence. Within the domain of literature-based evidence, meta-analytic findings are reported when sufficient numbers of randomized controlled trials (RCTs) are available, and descriptive outcome data summaries (e.g., means, ranges, and sensitivity/specificity values) are reported for interventions not subject to evaluation by RCTs. For opinion-based evidence, consensus-based information obtained from formal surveys as well as informal sources (e.g., open forum commentary and Internet comments) is considered. The final determination of whether the document is a guideline or an advisory is based on the totality of evidence accumulated.

TABLE 1-1 **Sources of Evidence for Practice Parameters**

Source of Evidence	Type of Evidence
Literature-Based Evidence	
Randomized controlled trials	Comparative statistics
Nonrandomized prospective studies	Comparative statistics
Controlled observational studies	Correlation/regression
Retrospective comparative studies	Comparative statistics
Uncontrolled observational studies	Correlation/regression/ descriptive statistics
Case reports	No statistical data
Opinion-Based Evidence	
Consultants	Survey findings/expert opinion
ASA members	Survey findings/opinion
Invited sources	Expert opinion
Open forum commentary	Public opinion
Internet commentary	Public opinion

The Literature Search

The initial literature search includes a computerized search of PubMed and other large reference sources/databases and usually yields 2000 to 5000 citations for each practice parameter. Manual searches are also conducted when supplemental references are supplied by the consultants and members of the task force.

In the selection of published studies, three conditions must be met. First, the study must assess one or more of the interventions being considered. Second, the study must report an anesthetic or clinical outcome or set of findings that can be tallied or quantified, thereby eliminating reports that contain only opinion (e.g., editorials and news reports). Third, the study must be an original investigation or report. Review articles, books or book chapters, and manuscripts that report findings from previous publications are not used as sources of evidence. After the initial electronic review, letters, editorials, commentaries, and other literature with no original data are removed from consideration. Typically, only 1000 to 2500 articles prove suitable for retrieval and further review.

Evaluating and Summarizing the Literature

The literature review process focuses on studies that report outcomes relevant to an identified intervention. A standard classification system separates findings by strength and quality of research design, statistical findings, and type of data. RCTs offer the strongest evidence; findings from studies using other research designs are separately categorized as observational. Observational studies contain critical information not necessarily found in RCTs. For example, a nonrandomized comparative study may provide evidence for the differential benefits or risks of select interventions. Observational studies may report frequency or incidence data revealing the scope of a problem, event, or condition or may report correlations that associate clinical interventions and outcomes. In addition, when case reports describe adverse events that are not normally reported in controlled studies, they can be a source of important cautionary notations within a recommendation or advisory. Case reports also may be the first indication that a new drug or new technique is associated with a previously unrecognized benefit or unwanted side effect.

One of the strengths of the ASA protocol for developing evidence-based practice parameters is that the primary search and evaluation of the literature are jointly conducted by the clinicians and methodologists of the task force. Consequently, the clinical and practical significance of a study, as well as its research design and statistical aspects, are appropriately and thoroughly evaluated. The protocol is evaluated with the use of formal reliability testing by task force members and methodologists. Interobserver agreement values for research design, type of analysis, linkage assignment, and study inclusion are calculated with both two-rater agreement pairs (kappa) and multirater chance-corrected agreement (Sav) calculations.[5,6] These values are reported in the final published document.

Evaluating and Summarizing Consensus Opinion

Although literature-based scientific evidence is a critical part of the process of developing an evidence-based practice parameter, the literature is *never* used as the sole source of evidence. Scientific findings are always supplemented by the practical knowledge and opinions of expert consultants. The consultants participate in formal surveys regarding conceptualization, application, and feasibility, and they review and comment on the initial draft by the task force. Opinion surveys of the ASA membership also are conducted to obtain additional consensus-based information used in the final development of an evidence-based practice parameter. The evidence obtained from surveys of consultants and ASA members represents a valuable and quantifiable source, critical to the formulation of effective and useful practice parameters.

In addition to survey information and commentary obtained from consultants and practitioners, the task force continually attempts to maximize the amount of consensus-based information by obtaining opinions from a broader range of sources. These sources include comments made by readers of a draft of the practice parameter posted on the ASA website (www.asahq.org) and comments from attendees of public forum presentations of the practice parameters scheduled during major national meetings. After collection and analysis of all scientific and consensus-based information, the draft document is further revised, and additional commentary or opinion is solicited from invited sources, such as the ASA Board of Directors and presidents of ASA component societies.

Meta-Analytic Evidence

When sufficient numbers of controlled studies are found addressing a particular evidence linkage, a formal meta-analysis for each specific outcome is conducted. For studies containing continuous data, either general variance-based methods or combined probability tests are used. When studies report dichotomous outcomes, an odds-ratio procedure is applied. In summarizing findings, an acceptable significance level typically is set at $p < 0.01$ (one-tailed) and effect size estimates are determined.

Reported findings in the anesthesia literature often use common outcome measures, thereby enhancing the likelihood that aggregated (i.e., pooled) studies will be homogeneous. Because homogeneity is generally expected, a fixed-effects meta-analytic model is used for the initial analysis. If the pooled studies for an evidence linkage are subsequently found to be heterogeneous, a random-effects analysis is performed, and possible reasons for the heterogeneous findings are explored. The heterogeneous findings are reported and discussed as part of the literature summary for an evidence linkage.

Whenever possible, more than one test is used so that a better statistical profile of the evidence linkage can be evaluated. For example, when a set of studies allows for more than one meta-analysis (e.g., using both continuous and dichotomous findings), separate meta-analyses are conducted. To be conclusive, the separate findings for the results of the analysis must agree. Additionally, the results should be in agreement with the directional evaluation of the literature and with consensus opinion before an unequivocal supportive recommendation is offered. If the results do not agree, the disparity is fully reported in the summary of evidence and acknowledged in caveats or notations to the recommendation.

DISTINCTION BETWEEN A GUIDELINE AND AN ADVISORY

For an evidence-based practice parameter to become a guideline, all sources of evidence (meta-analytic findings, non–meta-analytic literature, responses from consultants, and responses from ASA members) must agree. If, given the nature of the topic, sufficient numbers of controlled studies are not available, a practice advisory is formulated to assist practitioners in clinical decision making and matters of patient safety.

Use of the evidence-based practice advisory was instituted by the Committee and authorized by the ASA in 1998 in response to the need for expansion of the process to areas for which RCTs were sparse or nonexistent. This innovation gave the ASA tremendous flexibility in applying the evidence-based process to a broader scope of topics.

The evidence-based protocol for a practice advisory is identical to that used in the creation of evidence-based practice guidelines. A systematic literature search and formal evaluation of the literature is conducted. Survey information is obtained from consultants and a sample of the ASA membership, and informal input is accepted from public postings regarding draft copies on the ASA website, open forum presentations, and other invited and public sources.

The available evidence is then synthesized, and a practice advisory document is prepared. The resultant document summarizes the current state of the literature, characterizes the current spectrum of clinical opinion, and provides interpretive commentary from the task force.

GUIDELINE/ADVISORY DISSEMINATION

A typical practice guideline or advisory requires approximately 2 years for completion at a cost of $200,000 to

$300,000. Periodic updates occur 5 to 7 years after publication, unless circumstances require an earlier update. These documents are published in *Anesthesiology* and are available on the journal's website (http://journals.lww.com/anesthesiology) and are free of charge on the ASA website (www.asahq.org). Supporting material also is available on the journal's website or can be obtained, on request, from the ASA.

Since adopting the evidence-based model in 1991, the ASA has developed and approved 14 evidence-based practice guidelines, 10 guideline updates, 8 evidence-based practice advisories, and 5 advisory updates. Currently, no evidence-based practice standards are planned.

Anesthesiologists and other anesthesia care providers are generally interested in easily accessible, specific recommendations/advice about how to provide optimal care to their patients; therefore ASA evidence-based practice guidelines and advisories are presented in a format that emphasizes the clinical utility of the recommendations/advisory statements. Detailed rationales or descriptions of techniques, exhaustive critiques of the literature, or elaborate cost–benefit analyses are usually of secondary concern and are made available in an appendix or from a separate source. Documents are brief and succinct. Supportive information is summarized within the guideline or advisory and can be studied in greater detail in an appendix, at the ASA website, or by request.

The general structure of an ASA practice guideline or advisory consists of an introductory section, a guidelines/advisory section, and supporting information (e.g., tables, figures, or appendices). The introductory section contains the ASA definition of practice guidelines or advisories and is followed by a discussion of the focus, application, and methodology used in the guideline/advisory development process. The guideline recommendations or advisory statements are serially divided into subsections, each based on a separate evidence linkage. Each evidence linkage subsection is, in turn, divided into two parts: (1) a summary of the evidence and (2) an articulation of the recommendations or advice.

The *evidence summary* subsection describes and classifies the literature, generally including statements concerning its availability, the strength of evidence obtained from the literature, and details about particular aspects of the literature necessary for a clear interpretation of the evidence linkage. Consultant and membership survey findings are also summarized, and other opinion-based information is discussed when warranted.

Because it is assumed that the intended readers of the document are knowledgeable regarding the topic, the *recommendations or advisories* subsections are concise, with explanations added only if required for clarification. Cautionary notations may accompany a recommendation or advisory when deemed necessary by the task force.

SUMMARY

Evidence-based practice parameters are important decision-making tools for practitioners, and they are particularly helpful in providing guidance in areas of difficult or complex practice. These documents can be instrumental in identifying areas of practice that have not yet been clearly defined and can improve research in anesthesiology by (1) identifying areas in need of additional study, (2) suggesting direction for the development of more efficacious interventions, and (3) emphasizing the importance of robust outcome-based research methods. By recognizing the value of merging empirical evidence with the practical nature of opinion and consensus, the ASA has taken a leadership role in improving specific areas of clinical practice, patient care, and safety.

The ASA is committed to the development of practice guidelines and practice advisories by using an evidence-based process that examines testable relationships between specific clinical interventions and desired outcomes (Box 1-1). The process recognizes that the quality of evidence is highly variable and that it comes from many sources, including scientific studies, case reports, expert opinion, and practitioner opinion. By providing a

BOX 1-1 Strengths of the ASA Evidence-Based Process

- Specific outcome data related to a specific intervention are collected and evaluated
- A broad-based literature search from a wide variety of published articles
- Systematic evaluation of evidence from qualitatively different sources
  - Randomized controlled studies used in meta-analyses to evaluate causal relationships
  - Nonrandomized observational comparison studies to provide supplemental information
  - Other observational literature (e.g., correlational, descriptive/incidence literature) to provide an indication of the scope of a problem
  - Case reports to describe adverse events not normally found in controlled studies
  - Opinion-based evidence to evaluate clinical and practical benefits
- Evidence from the literature is directionally summarized to clarify and formalize evidence linkages and to reduce bias inherent in selective reviews
- Reliance on randomized clinical trials to demonstrate causal relationships and reduce bias inherent in nonrandomized studies or case reports
- General use of identical outcome measures, instead of pooling different measures
- Consensus information obtained from both formal (e.g., surveys) and informal (e.g., open forums, Internet commentary) sources
- One-to-one correspondence between evidence linkages and recommendations
- Brevity in reporting evidence
  - Simple summary statements of literature findings for each evidence linkage, thereby avoiding exhaustive literature reviews or critiques
  - Specific clinical recommendations without lengthy discussion or detailed rationale
  - Scientific documentation is provided in appendices or is available separately
  - Bibliographic information is available separately
- Periodic updating to reflect new medications, technologies, or techniques

consistent and transparent framework for collecting evidence and for considering its strengths and weaknesses, the ASA evidence-based process results in practice parameters that clinicians regard as scientifically valid and clinically applicable.

Some physicians have voiced concern that guidelines and advisories will be treated as de facto standards, thereby increasing liability and creating unnecessary restraints on clinical practice. The ASA emphasizes the nonbinding nature of practice guidelines. It defines them as "recommendations that may be adopted, modified, or rejected according to clinical needs and constraints." Because the process of evidence-based guideline and advisory development emphasizes consensus formation and communication throughout the practicing community, guidelines and advisories will continue to be relied on by anesthesiologists and other practitioners in their ongoing efforts to maintain a high quality of patient care and safety.

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CHAPTER 2

Update on Preprocedure Testing

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INTRODUCTION

High-quality preprocedure assessment requires evidence-based risk assessment and management in a setting of efficiency and cost containment. Preprocedure testing should be targeted such that the results will enable the clinician to evaluate the status of existing medical conditions and establish diagnoses in patients who have significant risk factors for specific clinical conditions. Therefore testing should be ordered in an evidence-based framework and targeted toward the particular patient and procedure. There is little to suggest that routine screening with batteries of tests improves preoperative management or surgical outcomes. Statistically, the more tests ordered, the more the chance of a false-positive result. Significant resources can be wasted. Because the evidence is not definitive in many cases, testing protocols may vary significantly from institution to institution. Knowledge of the current evidence will inform clinicians so that the testing ordered is appropriate and cost-effective.

OPTIONS/THERAPIES

Historically, patients received batteries of screening tests before surgical procedures. This was routinely done with little thought to the sensitivity and specificity of this testing in identifying abnormalities that might impact perioperative management. Over the past several decades, an increasing number of publications have emphasized that routine preoperative testing has not been a cost-effective way to identify significant abnormalities. In addition, the economic impact of this testing in the setting of the high volumes of procedures performed is enormous. For example, in the year 1996 the direct cost to Medicare of routine testing before cataract surgery alone was estimated as $150 million annually.[1] Institutions whose providers continue to order routine screening tests will be negatively affected financially, because Medicare and many other payers will no longer reimburse additionally for these investigations.

Clinicians should base test ordering patterns on consideration of the specific procedure being performed and the details of the patient's history and physical examination. Test ordering should be done within the context of known evidence-based indications for specific preprocedure investigations. The options can include testing based on the surgical procedure, patient disease, age, or any combination of these factors. There are certainly some instances in which the evidence may not be as clear. Institutions have developed protocols and algorithms to incorporate what is evidence-based as well as to generate a reasonable overall framework that will eliminate test ordering based purely on clinician "style." The anesthesiologist has the proper skill set to play a key role in the development of these institutional protocols.

An understanding of predictive value is essential for informing rational preprocedure test ordering. Most test results will plot in a normal distribution, where normal results are defined as within two standard deviations of the mean. Therefore healthy individuals with the lowest 2.5% and the highest 2.5% of values will be arbitrarily defined as having abnormal (false-positive) results. The more tests ordered, the more likely that a false-positive result will occur.

The evidence demonstrating the utility of ordering some of the most frequently used preprocedure tests will now be discussed.

EVIDENCE

Preoperative Radiologic Studies

The preoperative clinician should target ordering of preoperative radiology studies to specific issues raised by the patient's history and physical examination. For example, concern over the status of current heart failure or active pulmonary infection may prompt the preoperative clinician to order chest radiographs. In addition, radiologic studies may be indicated to define cervical spine or tracheal anatomy of concern so that safe airway management can be provided. In these instances the ordering preoperative clinician needs to ensure that accountability for review of the results of these studies exists in the perioperative workflow.

There needs to be clear definition between radiologic studies ordered by the surgeon to define indications for the operation and studies ordered by the preoperative clinician for the purpose of preoperative assessment and management. For example, surgeons may order chest radiographs as part of a general screening in patients undergoing procedures for cancer diagnosis. The ordering physician is responsible for reading and acting on the results of the test. If systems to ensure accountability are not adequate, patients may have abnormal chest radiograph results present in the system that have not been reviewed and acted on by the ordering clinician. Special attention needs to be paid when there are short intervals between surgical evaluation and procedure date, in which all test results may not have been adequately reviewed. It is prudent for institutions to develop standards to clearly

delineate accountability for preoperative test review; for example, at our institution it is reinforced with a documented policy that the clinician who orders the study is responsible for any result. These measures should be taken to avoid the unfortunate circumstance in which, for example, a nodule is present on a preoperative chest radiograph that was ordered but not reviewed, and the patient returns later with a cancer diagnosis.

The lack of value of screening radiographs has been documented in a number of studies. In existing pulmonary conditions such as chronic obstructive pulmonary disease (COPD), it is unlikely the expected abnormalities revealed on a preoperative chest radiograph will affect perioperative management. In a literature review of articles published between 1966 and 2004, an association between preoperative screening with chest radiographs and a decrease in perioperative morbidity and mortality could not be established.[2] Up to 65% of the changes seen were associated with chronic disorders and had little impact on management. Postoperative pulmonary complications did not differ between patients who had preoperative screening chest radiographs and those who did not. These authors concluded that, although the prevalence of chest radiograph abnormalities increases with age and risk factors, most abnormalities found were chronic and were not shown to affect anesthetic management or perioperative outcome. Chest films ordered because of concern about the possibility of acute heart failure or acute pneumonia were the only possible exceptions, which led to the authors' recommendation that asymptomatic patients do not warrant screening chest radiographs, regardless of age.

In contrast, the American College of Physicians considers that chest radiographs may be helpful in patients older than 50 years who are undergoing abdominal aortic aneurysm (AAA), upper abdominal, or thoracic surgery.[3] The American Heart Association suggests that patients with severe obesity (body mass index > 40 kg/m^2) also have chest radiographs performed preoperatively.[4] The thought in these cases is that screening radiographs may reveal undiagnosed heart failure or abnormalities suggestive of significant pulmonary hypertension. However, there are no studies supporting the fact that these recommendations have been correlated with a change in perioperative outcomes. It is our recommendation based on this review that the preoperative anesthesiologist only order chest radiographs when suspicion of an acute process exists. The surgeon may decide to order a preoperative chest radiograph for other reasons, including as part of an overall screening for metastatic disease, but should be responsible for reviewing and acting on the results.

The Canadian Anesthesiologist Society guidelines recommending that preoperative chest radiographs not be done in asymptomatic patients is supported by a systematic review noting that most abnormalities found are chronic and the majority are cardiomegaly and COPD.[2] Abnormalities, with the possible exception of acute heart failure, were not found to affect anesthetic or surgical management or perioperative outcome.[5] The Task Force of the American Society of Anesthesiology has reviewed the evidence on preoperative chest radiographs.[6] This group states that although chest radiograph abnormalities may be more frequent in patients who are older, have stable COPD, have stable cardiac disease, smoke, or have resolved recent upper respiratory infections, there is no evidence that chest radiograph results in these patients will affect outcome or management.

Preoperative Pulmonary Function Testing

In specific cases, the anesthesiologist might find the results of spirometry helpful for discussing the complete risk–benefit of surgery with the patient, planning perioperative management, and anticipating potential pulmonary complications. For example, in severe scoliosis, studies have shown that poor preoperative pulmonary function test (PFT) results were correlated with a high incidence of postoperative pulmonary complications.[7]

Similarly, patients with degenerative neurologic diseases with a restrictive pulmonary component may also benefit from preoperative PFTs. For example, in patients with multiple sclerosis severe enough to result in an inability to ambulate, PFT results may help to assess the ability of the patient to wean successfully from the ventilator postoperatively. In patients with myasthenia gravis, PFTs are part of the algorithm used to predict the probability of extended postoperative ventilation.[8] In one study, the results of preoperative values for forced vital capacity (FVC), forced expiratory flow $(FEF)_{25\text{-}75\%}$, and midexpiratory flow $(MEF)_{50\%}$, along with patient gender, successfully predicted the actual ventilatory outcomes in 88.2% of patients.[8]

For some specific surgeries, preoperative spirometry can help predict long-term mortality. For example, patients with AAAs frequently are smokers with COPD. Lower FEV_1 and lower FVC values preoperatively were independently associated with an increased risk of long-term mortality after endovascular AAA repair. This suggests that evaluation of lung function should be considered in patients scheduled for AAA repair suspected of having significant COPD.[9]

Preoperative Urine Analyses and Culture

Routine urinalysis is not generally recommended for most surgical procedures and is not necessary for preanesthesia assessments in asymptomatic patients. The concern is that in cases with urinary tract infections there is a risk of bacteremia. Therefore a relationship may exist between undiagnosed and untreated urinary tract infection and postsurgical infections, particularly in surgery in which a prosthesis is placed. However, the literature on this point is controversial. In addition, although this is a relatively inexpensive test, it is done in such high volumes that the aggregate costs may outweigh the clinical benefits.[10] For example, in a study published in 1989, given the best estimate of increase in risk of wound infection related to the presence of urinary tract infection, the cost was $1.5 million per wound infection prevented.[9] The ASA Task Force concluded that preanesthesia urinalysis is not recommended, except for specific procedures such

as prosthesis implantation and urologic procedures or when urinary tract symptoms exist.[10]

Preoperative Coagulation Studies

Review of the current literature suggests that preoperative routine screening coagulation studies should not be performed because of the lack of significant impact on preoperative management and outcome. If a good preoperative history is taken, unexpected coagulation defects are extremely infrequent. If the patient has a low risk of bleeding by history and physical examination, it is very unlikely that excessive surgical bleeding will result from an inherent abnormality.[11] A systematic review of the literature from 1966 to 2005 was done in an attempt to provide a rational approach to the use of bleeding history and coagulation tests before procedures and summarized some key recommendations.[12] Firstly, indiscriminate coagulation screening before procedures to predict the risk of bleeding in unselected patients is not recommended. Secondly, a bleeding history that includes family history of coagulation issues, history of excessive bleeding with previous procedures, and current use of prescription antithrombotic or antiplatelet agents should be taken in all patients before invasive procedures. In addition, clinical conditions that predispose patients to bleeding (e.g., significant liver disease) should be noted. If the patient's history is negative for these factors, no further coagulation testing is needed. If this history is positive, coagulation testing should be targeted for the type of clinical features present. A recent study focused on a comparison of an assessment of patient history versus preoperative hemostasis screening in adult neurosurgical patients supports these recommendations. The study found that patient history was as predictive as laboratory testing for all outcomes and had higher sensitivity.[13] In addition, these authors estimate that hemostatic screening limited to neurosurgical patients with a positive history would save an estimated $81 million annually in the United States, on the basis of approximately 2.1 million neurosurgical procedures performed.

Of note, the anesthesiologist needs to be aware that the anticoagulant effect of some agents, such as enoxaparin, is not adequately assessed by routine coagulation studies. In addition, patients may be taking nonprescription substances not regulated by the Food and Drug Administration (FDA) that could potentially have an impact on coagulation, although no definitive data exist on the effects of these nonprescription agents.

It must be recognized that unnecessary ordering of coagulation studies will also result in wasting resources dealing with insignificant abnormal results. For example, one of the most commonly seen abnormalities after routine screening is an elevated prothrombin time (PT) or partial thromboplastin time (PTT). Appropriate interpretation of this test requires knowledge that the in vitro result may not reflect the in vivo response, as outlined in a systematic review.[12] For example, normal biologic variation, with definition of the normal range as above two standard deviations from the mean, means that 2.5% of healthy patients will have an abnormal result. Unnecessary further investigation may result in excess cost and potential delay of the procedure. In addition, some clinically important bleeding disorders, such as von Willebrand's disease, will be missed if the presence of normal routine coagulation studies is assumed to ensure appropriate hemostasis.

The volume and age of the blood sample tested has a major impact on the reliability of results. An inadequate sample size, prolonged storage, or excessively traumatic venipuncture will result in an inaccurate result. Finally, the presence of certain conditions, such as the presence of a lupus anticoagulant, will falsely prolong the results and is not indicative of excessive bleeding.

In view of the aforementioned issues, when an abnormal coagulation result is obtained, the study should be repeated and the sample analyzed before any additional workup is undertaken. In many cases no abnormality is identified on repeated testing. A study of 1603 prospective routine screening tests in preoperative tonsillectomy patients demonstrated 35 abnormal test results; of these, only 15 remained abnormal on retesting.[14] A total of 11 patients in this study were shown to have inhibitors, one had mild hemophilia A, and several had no determined etiology. No relationship with the predictability of postoperative bleeding was demonstrated. These authors note that the large number of false-positive results and the absence of an impact on surgical bleeding raise doubts about the value of routine preprocedure coagulation testing.

There are no studies supporting the use of preoperative coagulation testing before the use of regional anesthesia, and the Preanesthesia Task Force did not have a recommendation on this issue.[10]

Preoperative Hematocrit and Complete Blood Count

The evidence would suggest that a targeted history and physical examination should determine whether a preprocedure hematocrit level and/or complete blood count should be done. (See Chapter 23 for a complete discussion on preoperative hemoglobin.) Laboratory tests not targeted by a history and physical examination rarely affect care or outcome and can unnecessarily increase costs. For example, a study of 142 general surgery patients showed that if laboratory tests, including hematocrit, had been ordered only as dictated by patient history and physical examination, patient charges could have been reduced by more than $400,000 in one year.[15] Anemia has been shown to be present in about 1% of asymptomatic patients, but surgically significant anemia in unselected patients is rare.[16] However, there are data in male veterans correlating 30-day postoperative mortality rates after major noncardiac surgery with abnormal preoperative hematocrit levels. Nonetheless, it is unclear whether it actually is the comorbidity or the low hematocrit level that contributes to the increase in mortality.[17] The Anesthesia Task Force concluded that routine hematocrit testing is not warranted and that characteristics such as type and invasiveness of procedure, extremes of age, and history of liver disease, anemia, bleeding, and other hematologic disorders be considered in determining the need for this testing.[10]

In view of the evidence just mentioned, individual institutions have generally established protocols regarding indications for preoperative hematocrit testing. These may be based on age, as well as on the invasiveness of surgery and potential for blood loss. In considering the very low possibility of revealing significant white blood cell and platelet abnormalities on routine screening with complete blood counts, these are generally not included as part of these protocols.[15]

Preoperative Serum Chemistry and Glucose

Preoperative blood testing for serum chemistry values should be specifically targeted to clinical characteristics. Significant electrolyte abnormalities noted on routine screening are extremely rare.[15] The Anesthesia Task Force notes that the presence of endocrine abnormalities, extremes of age, renal dysfunction, liver dysfunction, and the use of certain medications or therapies should be considered when making the decision to order analysis of serum chemistry.[10]

It is important to note, however, that renal insufficiency (creatinine > 2.0 mg/dL) is one of the independent risk factors that was correlated with an increased risk of postoperative cardiac complications.[18] The current American College of Cardiology/American Heart Association (ACC/AHA) algorithm defines this as one of the clinical risk factors that should be used in determining the need for further cardiac evaluation in patients with low functional status undergoing moderate- to high-risk procedures.[19] Because the incidence of renal dysfunction increases with age, some institutional protocols may include age requirements for renal function testing in patients having more invasive procedures, particularly if additional cardiac risk factors are present.[20]

Similarly, the literature indicates that insulin-dependent diabetes is an independent risk factor for postoperative cardiac complications in patients with low functional status undergoing moderate- to high-risk surgery.[18] Non–insulin-dependent diabetes has not been correlated with increases in postoperative cardiac complications. Previous work has suggested that there is no correlation between routine screening blood glucose levels and significant changes in perioperative management or outcome.[19] The degree of long-term glucose control in known diabetic patients is likely better determined by obtaining results of hemoglobin A_{1c} testing rather than random glucose testing. Better control of perioperative glucose management in known diabetic patients has been correlated with fewer wound infections and less mortality after cardiac bypass surgery.[21] Therefore preoperative testing using hemoglobin A_{1c} and fasting glucose measurements may be of help in planning appropriate insulin management in these patients.

More recent work indicates that increased preoperative prediabetes glucose levels in patients having noncardiac, nonvascular surgery were associated with a 1.7-fold increased cardiovascular mortality risk compared with normoglycemic preoperative glucose levels.[22] These authors noted that prediabetes glucose levels in patients without a history of diabetes were associated with increased risk of cardiovascular complications even after adjustment for a broad range of comorbidities. They suggest that screening for glucose abnormalities in surgical patients should be considered to identify patients at risk for postoperative cardiovascular events. However, no data exist on whether appropriate treatment of these patients when identified preoperatively would have prevented these complications or whether there is benefit to delaying elective surgery to achieve better preoperative glucose control. A medical record study of about 3000 patients undergoing noncardiac surgery showed that patients without a known history of diabetes who had perioperative hyperglycemia experienced worse outcomes and higher mortality at a glucose level similar to that of those with known diabetes.[23] These authors suggest that perhaps there is a lack of adaptation to hyperglycemia, and they recommend presurgical screening and the need to address glycemic control in these patients.

Urine Toxicology Screen

The significant prevalence of substance abuse in the general population and the potential dangerous interactions with perioperative medications prompt consideration of screening for at-risk patients. Cocaine use, which has particularly concerning implications for anesthesia, can be found in all sociodemographic groups. A careful history, paying special attention to habits regarding illicit substance use, should be taken by the clinician to guide the need for preoperative screening.

Screening tests for illicit drug use generally involve urine testing. Urine testing for toxic substances is simple to perform, can yield rapid results, and provides information about many of the drugs of concern during the perioperative period.[24] Of note, depending on the amount and type of drug taken, a preoperative urine test may be positive for several days after use of a substance. Anesthesiologists should be familiar with the particular type of urine drug testing done at their institutions and which drugs are screened for with a routine test. Those most commonly screened for include opioids, alcohol, cocaine, phencyclidine, and amphetamines. If suspicion of illicit drug use exists, the clinician should consider the timing of the preoperative assessment relative to the surgery to decide whether testing is warranted during the preoperative visit or on the day of the procedure. A positive urine toxicology screen is an indication of drug use within the past few days but will not indicate if drug use is short- or long-term. These patients may be unreliable historians.[25] Therefore preoperative urine screening may be required immediately before the procedure so that the absence of an interaction of these agents with perioperative medications is ensured.

CONTROVERSIES/AREAS OF UNCERTAINTY

Preoperative management must be performed within a context of both clinical and financial accountability. As increasing scrutiny is brought to bear on health care

costs, clinicians are increasingly challenged to provide high quality in a setting of cost containment. Resources for preoperative assessment, both labor and testing, are increasingly difficult to negotiate. Clinicians must demonstrate the impact of high-quality preoperative evaluation on optimization of surgical outcomes and the facilitation of efficient operating room workflow. It is certain that strategies for optimizing operating room throughput and ensuring quality and safety rely on effective preoperative evaluation processes.

The evolving and ongoing recommendations to decrease routine preoperative screening tests appear warranted by continuing evidence. Recent data have demonstrated that a history and physical examination is the best determinant of appropriate laboratory testing for an individual patient and that routine screening tests are unlikely to affect management.[26] In addition, routine screening is likely to result in significant numbers of false-positive results, which must be evaluated. Unfortunately, because of difficulties in coordinating the various elements of the preoperative assessment, laboratory orders may often be based on templates without in-depth knowledge of individual patient conditions. In addition, the value of having baseline reports for electrocardiograms, chest radiographs, or blood tests has not been demonstrated, although these are frequently requested. Finally, there are no clear guidelines as to how long a preoperative test is valid. Although many institutions set timeframes for this, there is no good evidence supporting such protocols. Clinical judgment is the best guide for any individual patient. For example, a preoperative electrocardiogram from a week ago may not be valid clinically if symptomatology has changed since it was performed.

These practices attempting to substitute protocol for clinical judgment may streamline processes in which resources do not allow adequate clinician oversight of preoperative test ordering. However, they may add unnecessarily to the overall procedure costs. Many preoperative processes rely on these protocols because of an inability to develop successful workflows to target testing. Appropriate process improvement will allow institutions to develop systems that are acceptable to anesthesiologists and surgeons and that will result in focused preoperative test ordering. This will reduce unnecessary resource use and overall procedure costs and allow targeted testing, which may impact management.

GUIDELINES

The most recent Practice Advisory from the American Society of Anesthesiology Task Force (2012) contains a review and synthesis of current evidence and consensus on preoperative testing.[10] The task force concludes that routine preoperative screening does not make a significant difference in preoperative assessment and management. Selective testing should be done after considering specific information regarding the individual patient.

The task force was unable to define parameters for specific tests or for the timing of preoperative tests on the basis of the available literature. It suggests individualization based on history, medical record review, physical examination, and type of procedure.

AUTHORS' RECOMMENDATIONS

- Preoperative testing in general should be targeted to the individual patient's history, review of medical records, physical examination, and type of procedure.
- There is no demonstrated value to routine preoperative screening chest radiographs. Radiographs may be of help in defining the status of current heart failure or active pulmonary infection. Chest radiographs may be helpful in patients older than 50 years who are undergoing abdominal aortic aneurysm or thoracic surgery.
- Preoperative pulmonary testing should be considered in patients with severe limitations from degenerative diseases resulting in restrictive pathology.
- In institutions that do not mandate preprocedure pregnancy testing, obtaining an accurate menstrual history is critical, and testing should be ordered when appropriate.
- Routine urinalysis is not indicated for most surgical procedures; exceptions are prosthesis implantation, urologic procedures, and the presence of urinary symptoms.
- Routine coagulation studies and measurement of hematocrit and serum chemistry values are not recommended.

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CHAPTER 3

Is a Preoperative Screening Clinic Cost-Effective?

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INTRODUCTION

Each year, between $11 and $30 million are spent on preoperative testing; this includes the cost of laboratory tests and related consultations.[1,2] For an anesthesiologist, the preoperative evaluation is an important feature of a patient's overall anesthetic experience. The preoperative evaluation may be performed in many settings; however, regardless of the type of evaluation performed, two central features of the evaluation are risk stratification and optimization of medical conditions. Ideally, the evaluation will improve both the presurgical process and the outcome after anesthesia and surgery. Rarely, the assessment may alert the anesthesiologist, surgeon, or patient of potential issues that may lead to postponement or reconsideration of the benefits of surgery versus the risks identified. Currently, 80% of all surgeries are outpatient or same-day admissions, and it is not surprising that this has led to an increase in the development of preoperative assessment pathways that can accommodate the outpatient surgical setting. Although the American Society of Anesthesiologists (ASA) Guidelines for preoperative assessment recommend that patients with complex medical conditions or those undergoing complex surgery be seen by an anesthesiologist before the day of surgery, they do not recommend a particular venue.[3] Outpatient evaluation clinics have become more relevant as ambulatory surgery has expanded and same-day admissions have become more prevalent.[4]

When evaluating the need for or value of a preoperative testing clinic, it is important to understand the wide range of factors involved in the preoperative process, many of which are beyond the anesthesiologist's usual realm of practice. Once a patient is scheduled for surgery there are several steps that occur. Although the particular sequence of steps for an individual patient will depend on the health care institution, many requirements are common to all systems. For instance, all patients will need a hospital identification number to be booked in the operating room (OR) scheduling system and insurance and demographic information verified. The patient's prior medical record will need to be accessed if electronic or obtained for the holding area or preoperative assessment clinic. If testing has been done, the results will potentially need to be reviewed as well as collated in the chart for the day of surgery. In addition, the surgical history and physical examination, consent forms, anesthesiology paperwork, and nursing assessment forms will need to be in the patient-verified chart before entering the OR. Ideally, the finished chart will contain all the paperwork needed for the perioperative period, including order sheets, requisition forms, and prescriptions.

Optimally, a cost-effective preoperative screening clinic would fulfill these duties efficiently, reducing duplication of work in other areas of the hospital and contributing positively to OR efficiency. With the increasing use of electronic health record and anesthesia information systems, it is hoped that a more efficient and reliable system will emerge, seamlessly collating a patient's relevant medical data into a single source.

OPTIONS

The preoperative screening clinic is one example of a preoperative assessment alternative; others include the telephonic interview, Internet health screen, primary care physician evaluation, and mail-in health quiz. Frequently, a visit to a preoperative clinic is combined with another tool such as the health survey, and these results are used to identify patients requiring laboratory testing or a consultation with the anesthesiologist. Since the mid-1990s, preoperative testing clinics have gained in popularity. A survey of anesthesiology programs found the presence of a preoperative testing clinic in 88% of university and 70% of community hospitals in 1998.[5] Similar results were obtained after a survey in Ontario, Canada: 63% of 260 hospitals had preoperative clinics.[6]

EVIDENCE

The Preoperative Process

The evidence supporting the implementation of preoperative testing clinics is largely derived from retrospective studies.[7,8] Historical data suggest that the introduction of a system for preoperative testing is associated with increased patient satisfaction,[9] as well as reductions in unnecessary laboratory testing and outside consultations.[10-12] Previous data also support a reduction in day-of-surgery cancellations and OR delays and reaffirm the cost savings gained through reductions in unnecessary laboratory testing.[13-15] From these studies, it is apparent that local factors such as OR volume and type, patient mix, and even geographic considerations[16]

TABLE 3-1 **Cost Savings**

Author, Year	Study Type	Reduction in Laboratory Testing	Reduction in Consultations	Reduction in Same-Day Cancellations	$ Saved per Patient
Fischer, 1996[10]	Retrospective	55.1%	Yes	116 (87.9%)	112.09
Pollard, 1996[31]	Retrospective			5 (19.4%)	
Starsnic, 1997[22]	Retrospective	28.63%			20.89
Vogt, 1997[2]	Retrospective	72.5%			15.75
Finegan, 2005[23]	Prospective double cohort	Yes			29.00
Tsen, 2002[12]	Retrospective		Yes		
Ferschl, 2005[15]	Retrospective			Yes: 50%	
Cantlay, 2006[28]	Retrospective			Yes	
Hariharan, 2006[13]	Prospective			Yes: 52%	
Correll, 2006[14]	Retrospective			Improved recognition of medical problems	

will strongly influence the decision to have or use a preoperative clinic. Evidence in areas of benefit that have been attributed to preoperative clinics will be considered individually (Table 3-1).

Very few randomized controlled trials (RCTs) have addressed the cost of having versus not having a clinic. Schiff and colleagues[17] randomly assigned 207 patients to be seen either in an anesthesia preoperative evaluation clinic (APEC) or in the inpatient ward setting. After exclusions and patient refusal, data were available for analysis on 94 patients seen in the APEC and on 78 patients interviewed in the ward. The total time for the consultation was shorter for the APEC 18.3 ± 5.6 versus 26.7 ± 8.4 minutes for the ward visits ($p < 0.001$). The type of anesthesia, complexity of the surgery, and preanesthetic visit location significantly influenced the length of the preoperative visit. They calculated that, on the basis of the cost of the anesthetist, the APEC could result in a calculated savings of 6.4 Euro per patient. All patients answered a questionnaire addressing how much they understood after the preanesthetic interview. The authors found that more information was passed on to the patients seen in the APEC compared with those seen in the ward visits ($p < 0.01$). On analysis they found that younger, more educated patients seen in the APEC had the highest information gain scores. They did not study day-of-surgery admissions or outpatient surgery patients, and all patients were scheduled for surgery requiring a general endotracheal anesthesia, thus limiting the broad applicability of their findings.

The most recent American College of Cardiology/American Heart Association (ACC/AHA) perioperative guidelines[16] provide recommendations for the preoperative workup in patients with significant cardiac risk factors undergoing noncardiac surgery. The European Society of Anesthesiology recently published similar guidelines.[18] These guidelines help identify and design perioperative strategies that aim to reduce perioperative risk of morbidity and mortality. In general, patients with known coronary disease should receive a careful cardiac baseline assessment; this includes a review of current testing results and new tests as warranted by the history and physical examination. When older than 50 years, even asymptomatic patients may require careful cardiac evaluation if there are associated cardiac risk factors. The advantage of the preoperative testing clinic is the ability of the anesthesiologist to oversee the appropriate testing and consultations. When used appropriately, these types of guidelines can lead to a standardized preoperative approach that can be undertaken in several different settings, including inpatient and outpatient settings. It remains to be shown whether this can lead to perioperative cost savings.

Laboratory Testing

Inappropriate laboratory testing is costly. Large-scale preoperative laboratory testing in healthy individuals leads to an increase in false-positive results and inappropriate workups[7,11,19,20] (see Chapter 2). Several studies in healthy patients have demonstrated that screening laboratory testing rarely provides new information that would not otherwise have been obtained from a thorough history and physical examination.[2,11,20] When compared with outside referral physicians, anesthesiologists order fewer preoperative laboratory tests,[21-23] and this may be associated with financial benefit. Starsnic and colleagues[22] examined testing patterns in two groups of patients. Each group had approximately 1500 patients; laboratory tests were ordered by either their surgeon (group S) or by an anesthesiologist seeing them in the preoperative clinic (group A), although in group A surgeons were still allowed to order additional tests if required. Except for concurrence on the complete blood count, anesthesiologists consistently ordered fewer tests compared with surgeons, which resulted in a 28.6% reduction in testing and an estimated cost savings of $20.89 per patient. In a similar study, Vogt and Henson[2] found that 72% of tests ordered by surgeons were "not indicated" according to anesthesiologists, and the net cost of unindicated preoperative tests was $15.75 per patient. Fischer[10] compared a 6-month period before and after the introduction of a clinic directed by anesthesiologists and observed a 59.3% reduction in laboratory testing, or $112.09 per patient. Power and Thackray[21] reported a 38% reduction in preoperative laboratory testing, leading to an estimated

saving of $25.44 per patient in 201 elective ear, nose, and throat (ENT) patients after the introduction of testing guidelines that included a review by an anesthesiologist. More recently, Finegan and colleagues[23] performed a prospective double-cohort study. In group 1, testing followed usual practice according to pre-established surgery-specific clinical pathway guidelines. In contrast, testing for group 2 was instituted only through the anesthesiologist attending or resident's recommendation. Group 1 included 507 patients with a mean preoperative laboratory cost of $124 compared with only $95 for the 431 patients in group 2 ($p < 0.05$). When a subgroup analysis was performed, the average cost of residents' ordering was $110, similar to group 1, whereas attending physicians' cost averaged $74, approximately $36 less than residents ($p < 0.05$). Although group 2 had slightly more complications, these were not related to the preoperative tests. This study supports a reduction in unnecessary laboratory testing when directed by anesthesiologists and demonstrates that education and experience may also contribute to laboratory savings.

Despite these positive results, reductions in laboratory testing cannot all be attributed to preoperative clinics because laboratory testing can be reduced even without a preoperative clinic visit. In one of the few RCTs available on preoperative testing, Schein and colleagues[1] looked at preoperative testing patterns in cataract surgery patients. They randomly assigned 18,189 patients scheduled for cataract surgery into two groups; all patients had a history and physical examination by a health care provider. The "testing" group received additional routine laboratory tests and an electrocardiogram (ECG). In comparison, the "no-testing" group only had tests ordered if indicated by the history and physical examination. They found no difference in outcome of patients with or without testing, and both groups had a similar rate of 31 adverse events per 1000 surgeries.

Thus, despite the dearth of RCTs, the current evidence supports anesthesiology-directed preoperative laboratory testing. This practice can result in substantial cost saving and benefit to the patient.[24,25] The positive evidence does not mean that a preoperative testing clinic is always cost-effective because it may be possible to influence testing patterns in the absence of a clinic visit. Savings in preoperative laboratory screening may be achieved by improved education of other physicians and the development of clinical pathways by anesthesiologists for surgical patients.[26]

Consultations

Cardiology consultations are a frequent source of frustration in preoperative testing and often do not result in significant alterations in management; instead, they may lead to delays, additional cost, and inconvenience to the patient and hospital. Fischer[10] found that the introduction of the preoperative clinic led to a significant reduction in the number of cardiology, pulmonary, and medical consultations. After the introduction of stringent guidelines for consultation, Tsen and colleagues[12] reduced the rate of cardiology consultations in patients undergoing noncardiac surgery from 1.46% (914 patients) to only 0.49% (279 patients) ($p < 0.0001$), despite an increase in patient acuity over the 6-year study period. They also found that after the introduction of an ECG educational program, they were able to reduce consultations for ECG abnormalities from 43.6% to 28.5% ($p < 0.0001$).

These groups were able to demonstrate that consultations, cancellations, and delays in surgical bookings could be reduced through the use of preoperative testing clinics.[10,12] In addition, their data support the development of guidelines for preoperative assessment and education for those involved in preoperative assessment.[27,28]

Defining the "role of the consultant" is important in the preoperative setting. Unfortunately, many consultations are vague and do not lead to substantial requirements for additional testing or provide new recommendations for perioperative care. All consultations should provide a careful assessment of risk, and the success of a consultation is improved when the question is specific. An additional role of the consultant should be to advise on future health and additional postoperative strategies to reduce the patient's future risk, if possible.[16]

Same-Day Cancellations

OR cancellations are associated with high cost, and every effort is made to decrease these. One major purported benefit of the preoperative screening clinic is a reduction in day-of-surgery delays because the clinic can ensure that patients are medically ready for surgery. Preliminary research suggests that evaluation of ASA physical status III and IV patients in a preoperative evaluation clinic (PEC) is associated with the largest net benefit in terms of reductions in day-of-surgery delays and cancellations.[29,30]

There are several reports from individual institutions describing reduction of OR cancellations after the introduction of a preoperative testing clinic, although no randomized trials on preadmission screening clinics have been conducted. Correll and colleagues[14] collected data on more than 5000 patients seen in their preoperative clinic over a 14-month period. In that time, 680 medical issues were identified that required further investigation before surgery; 115 of these issues were new medical problems. New problems had a greater possibility of delay (10.7%) or cancellation (6.8%) compared with existing problems: 0.76% and 1.8%, respectively. In a similar study, Ferschl and colleagues[15] compared preoperative testing status between patients assigned to same-day surgery and general ORs. Over a 6-month period, 6524 patient charts were reviewed. They found that 8.4% (98 of 1164) of same-day surgery patients' appointments were cancelled if seen in the clinic versus 16.5% (366 of 2252) of those of patients not seen in the clinic ($p < 0.001$). This was even more dramatic for the general OR patients; they found a cancellation rate of 5.3% for those using the clinic (87 of 1631) compared with 13.0% (192 of 1477) in those not using the preoperative clinic ($p < 0.001$). In addition, the preoperative clinic patients were more likely to go to the OR earlier or on time compared with those in the non–preoperative clinic group. These data support the findings reported by Fischer,[10] who was

able to demonstrate an 87.9% reduction in OR cancellations from 1.96% (132 of 6722) to 0.21% (16 of 7485) after the formation of the preoperative clinic. Earlier studies have also supported reductions in both cancellations and length of stay after the introduction of a preoperative testing clinic. However, these data were collected at the same time that institutions were changing from an inpatient to an ambulatory surgery model, so the impact of the clinic per se is questionable.[31-33]

More recently, a survey addressing the impact of PECs on perceived prevalence of day-of-surgery delays was distributed to attendees at the 2005 ASA annual meeting.[34] Twenty-three percent (1857) of attendees completed the survey; of these, 69% worked at institutions using a PEC. For patients evaluated in a PEC, respondents reported that the incidence of "perceived delays over 10%" was 23% of patients compared with 57% of patients not using a PEC, who were instead first evaluated by an anesthesiologist on the day of surgery ($p < 0.001$). Sixteen percent of respondents reported that they had a system to evaluate patients before surgery, but not through a PEC; in this group of patients the incidence of perceived delays over 10% was 22%, which was similar to the PEC group. In institutions where PEC was available, the perceived prevalence of day-of-surgery delays due to missing information was higher at 63% versus 42% of respondents at institutions without a PEC ($p < 0.001$). Overall, these data suggest that assessment before the day of surgery reduces, but does not eliminate, delays on the day of surgery. There are several reasons why a PEC might not eliminate delays totally. These include different criteria by anesthesiologists in the PEC versus on the day of surgery, incomplete recommended workups or pending results, and the patients in institutions with PECs may have more complex conditions compared with those in facilities without any PEC mechanism. It is important to note that in this study an anesthesiology evaluation, not the PEC per se, led to similar delay rates. Similar results were described by Ferschl et al,[15] who found that an anesthesiologist-directed preoperative interview reduced day-of-surgery cancellations and delays for outpatients. In this study, however, among same-day surgical admissions, preoperative evaluation only reduced cancellations, not delays on the day of surgery.

The studies by Holt et al[34] and Ferschl et al[15] suggest that the preoperative evaluation can account for some of the cancellations or delays encountered in the OR; however, there are other factors to be considered. Fischer[10] found that 90% of cancellations occurred just before the patient entered the OR. Fischer evaluated the impact of cancellations over a 2-year period and found that, on average, a cancellation resulted in 97 minutes of OR downtime; this was in addition to the usual 30 minutes of turnover time between cases. Frequent causes of cancellations identified were alterations in the surgeon's schedule, patient's preference, and OR scheduling limitations (i.e., cases running overtime and emergency add-ons). These issues will not be influenced by the presence of a preoperative screening clinic.[25] It is conceivable that the preoperative screening clinic could provide a "bank" of available patients for call-up at short notice in the event of a gap in the OR schedule, but there are no data documenting the success of this approach.

Preoperative Clinic Structure

The implementation of educational programs and the development of clear guidelines and protocols can result in improved efficiency in the clinic, as well as improved communication and patient satisfaction. Recent studies have shown that development of proactive, cooperative comanagement models for perioperative management of high-risk patients undergoing complex surgery improves both quality and efficiency.[35,36] The staffing models of preoperative clinics may be diverse, and clinics staffed by anesthesiology attendings, residents, dedicated nurse practitioners, and nurses have been described.[9,12,37,38] The structure of a preoperative clinic may present significant opportunities for cost savings. Cantlay and colleagues[28] described improved outcomes after introducing a clinic with consultant anesthesiologists to evaluate complex vascular patients. Varughese and colleagues[37] reported significant financial benefit with the creation of a nurse practitioner–assisted PEC. At this hospital, they substituted nurse practitioners for two anesthesiology attending staff in the preoperative clinic; one attending remained assigned to the clinic for consultations. The nurse practitioners received training in preoperative assessment. After the introduction of the nurse practitioners into the clinic, the incidence of complications, preoperative patient time, and patient satisfaction were monitored at three intervals during a 1-year period. There was no change in patient satisfaction, complication rates, or time spent in the preoperative clinic. After the substitution of the nurse practitioners in the clinic, the group was able to provide two more anesthesiologists to the OR. The increase in anesthesiologist availability resulted in a significant increases in margin for the hospital and the group by increasing billable hours for the physicians, and the addition of two new ORs led to increased case numbers. Clearly, the opportunity at this institution was unique; however, it provides an example of redistribution of resources resulting in a more effective preoperative clinic.

Very few studies have evaluated the consequences of the organization of patient flow of a preoperative assessment clinic on its performance. One such study by Edward et al[39] evaluated the performance of clinics at two Dutch university hospitals that were designed differently. This was done by measuring patient flow time, various procedure times, and total waiting time. They found a significant difference in patient flow time between the two clinics. The patient flow time was longer when ECGs and venipuncture were performed at the general outpatient laboratory than when they were done at the preoperative assessment clinics because of longer waiting times. Also, more tests were requested when they were performed at the preoperative assessment clinic. Based on analysis of patient flow and clinic operations, alterations were made in clinic processes at a tertiary hospital preoperative clinic. These led to increased patient satisfaction and a reduction in waiting time with minimal economic impact.

The Patient

On one hand, anesthetic assessment in an outpatient clinic reduces preoperative patient anxiety[40] and improves costs.[29] On the other hand, it is possible that the savings of the outpatient preoperative clinic may, in fact, represent cost shifted to the patient. For instance, a visit to the preoperative screening clinic may require additional time off work for the patient or the caregiver. Similarly, geographic constraints in rural areas of the country can make the preoperative clinic visit a scheduling challenge.[25-27] Seidel and colleagues[19] examined geographic barriers to visiting the preoperative clinic and found that, for patients having surgery at an urban tertiary care center, the likelihood of attending preoperative clinic visits was diminished if the patient lived farther away from the hospital.

Unexpected Area of Benefit

One value of the preoperative clinic that is underappreciated is the opportunity for compliance with various regulations. Since the institution of the Patient Self-Determination Act in 1991, all health care facilities receiving Medicare and Medicaid funding need to recognize advance directives such as a living will and durable power of attorney. Most often, this involves providing patients with a written information sheet and inquiring if they have completed the forms. The preoperative clinic visit provides an unusual opportunity for discussion, at a time when families are frequently already involved and the patient is not yet hospitalized. Grimaldo and colleagues[41] randomly assigned elderly patients attending a PEC into "standard" and "intervention" groups. The intervention group attended a session addressing the importance of discussing end-of-life issues and preferences with their families. They found that 87% of patients in the intervention group had discussions with proxies versus 66% in the control group ($p = 0.001$). This is an unexpected benefit of the preoperative clinic. For assessment of the impact on cost, it would be useful to compare the preoperative screening clinic cost with the cost of compliance in a nonclinic setting in terms of hospital personnel, time, and space. Additionally, in any instance in which the preoperative screening clinic may improve compliance with hospital or government regulations, the cost of the clinic may be considered a wise investment if the risk of noncompliance is substantial and carries significant consequences.

AREAS OF UNCERTAINTY

Preoperative assessment should not be viewed as synonymous with a preoperative screening clinic, and although there appear to be demonstrable benefits of a preoperative screening clinic, there are few data directly comparing the clinic model with other approaches to preoperative assessment. Shearer and colleagues[26] describe a model of preadmission testing using general practitioners in Canada. In this model, the anesthesiology department provides a workshop to "accredit" general practitioners in preoperative assessment. Patients requiring a preoperative assessment are triaged to be seen in a preoperative screening clinic by anesthesiology, to go directly to surgery, or to be seen by an accredited general practitioner for preoperative assessment. They found a low rate of cancellations (less than 1% of elective surgery), which was not different between the groups using this system. This type of model for preoperative assessment provides an alternative to the preoperative screening clinic but re-emphasizes the need for patients to undergo a preoperative evaluation of some type.

AUTHORS' RECOMMENDATIONS

An organized approach to the preoperative assessment is clearly beneficial to patients, physicians, and institutions, and the preoperative screening clinic is a key component. There is good evidence that anesthesiology-directed laboratory testing results in a reduction in tests and costs, and a preoperative screening clinic can result in a reduction in OR cancellations. The ultimate organization of the preoperative assessment at a given institution will depend heavily on factors such as the hospital size, patient mix and volume, types of surgery performed, referral bases, and geographic challenges of the area. Key points include the following:

- At a minimum, preoperative laboratory testing guidelines should be directed by anesthesiologists.
- When possible, standards and guidelines for preoperative testing and consultation should be produced by anesthesiologists.
- A preoperative screening clinic should be established for patients undergoing invasive surgery and for patients with complex conditions who may require further evaluation or interventions before surgery.
- An anesthesiologist should be available for consultation during the preoperative visit.
- If the establishment of a preoperative screening clinic is not feasible, anesthesiologists should be involved in creating alternative preoperative pathways or protocols (e.g., telephone screenings and medical chart reviews).
- Alternative preoperative pathways, for example, primary care visits or telephone interviews, should be established for patients who cannot visit the clinic and should be coordinated by the clinic.
- A system should be in place to monitor cancellations and delays attributed to the preoperative assessment.

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CHAPTER 4

Who Should Have a Preoperative 12-Lead Electrocardiogram?

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INTRODUCTION

The resting 12-lead electrocardiogram (ECG) is the one of the most widely used diagnostic tests in medicine, and preoperative ECG is the most commonly obtained cardiovascular diagnostic test before surgery.[1-2] Many epidemiologic studies have demonstrated an association between abnormal ECG findings and an increased risk of death from cardiovascular causes in the general population.[3-8] Evidence to support the value of routine preoperative ECG to predict adverse perioperative cardiovascular events is conflicting, however, in part because of the wide variability in study design, population, and clinical endpoints.

The routine use of many screening tests has been called into question. An ideal preoperative screening test should be inexpensive, have high positive and negative predictive values, add to information obtained from the clinical history and physical examination, and change or modify perioperative decision making to prevent perioperative complications.[9-10] Extensive preoperative testing can lead to false-positive results, additional expensive and invasive workups, and unnecessary delay or cancellation of necessary procedures.[11-12] Sandler demonstrated, in a prospective study of medical patients, that more than 50% of clinical diagnoses and nearly 50% of management decisions were based on history alone, and routine studies contributed to less than 1% of all diagnoses.[13] Several studies in the surgical population have found that routine preoperative screening evaluations rarely found abnormal test results not predicted by history alone, and when abnormalities were detected, management was not significantly altered.[14-16] Wilson et al[16] and Narr et al[17] demonstrated that fitness for elective surgery can safely be predicted by a history and physical examination, and tests can be obtained intraoperatively or postoperatively, as indicated.

More than 100 million ECGs are obtained annually, at a cost of approximately $5 billion.[18] With more than 45 million inpatient and 53.3 million ambulatory procedures performed annually in the United States,[19] preoperative screening undoubtedly accounts for many of the ECGs obtained. The prevalence of abnormal preoperative screening ECG results has been estimated to be anywhere between 25% and 50%; the clinical implication of abnormal ECG findings is less clear, however, in that a change in management was observed in 0% to 2.2% of patients.[9,20-22] Callaghan et al[23] found that 18% of all preoperative ECGs are ordered without a clear indication, whereas Nash et al[24] found that 30% of preoperative ECGs are never interpreted by an anesthesiologist.

Thus it is important from the standpoints of both patient risk stratification and public health to evaluate which patients will benefit from preoperative ECG screening. Evidence to support or refute the use of preoperative ECG screening is conflicting in the literature. As such, although guidelines exist from several medical societies, there is no consensus as to who may benefit from preoperative ECG. The purpose of this chapter is to summarize the available data in different populations as well as to review the current recommendations from different medical societies.

OPTIONS

An ECG could be obtained on all adult patients or could be required only in patients with specific risk factors. Patient factors that may merit further evaluation include a known history of or risk factors for cardiovascular disease, poor functional status, or new physical examination findings suggestive of cardiovascular disease. The type and invasiveness of surgical procedure may also be considered. Historically, age has been used as a criterion for preoperative cardiac evaluation, although more recently this practice has been called into question. Current approaches to obtain a preoperative ECG should consider three key questions: (1) What is the likelihood of cardiovascular disease in this patient, (2) What is the risk of this surgical procedure, and (3) Will the results of this test change perioperative management?

EVIDENCE

It is difficult to compare the current literature because of the wide variability in patient populations, outcomes measured, and overall study design. Despite these limitations, several general patient populations tend to emerge in the literature. We will discuss the current literature in the following groups: asymptomatic patients, patients with known risk factors for cardiac disease, the elderly population, and patients undergoing "high" versus "low" risk surgery.

Asymptomatic Patients

Evidence to support or refute routine preoperative ECG in asymptomatic patients undergoing nonvascular, noncardiac surgery is perhaps the most widely variable, in large part because of the differences in patient groups and outcomes measured. Carliner and colleagues[25] prospectively evaluated 200 patients undergoing elective major noncardiac surgery under general anesthesia. Using a multivariable model, they found that ST-T wave abnormalities, abnormal Q waves, and left ventricular hypertrophy (LVH) on preoperative ECG were the only statistically significant independent predictors of perioperative cardiac events. A smaller series by Younis et al[26] examined 100 patients undergoing major noncardiovascular surgery. Although Q waves on resting ECG were predictive of adverse perioperative cardiac events on univariate analysis, they were not significant on multivariate analysis.

A prospective evaluation of 660 patients undergoing noncardiac, nonvascular surgery by Biteker et al[27] found that 394 (59.7%) of patients had at least one abnormality on preoperative ECG, and 127 (19.2%) had a change in preoperative management. Thirty patients (4.5%) underwent additional preoperative testing, and a diagnosis of new or unstable cardiac disease was made in 21 cases (3.1%). Twelve of the 30 went on to surgery without delay. Patients with an abnormal preoperative ECG had a higher incidence of perioperative cardiovascular events. On multivariate analysis, only QTc prolongation was an independent predictor of perioperative cardiovascular events.

Several studies refute the claim that preoperative ECG results change perioperative management in a healthy population. A systematic review by Munro et al[22] found that preoperative ECG results were abnormal in up to 32% of cases and led to a change in management in less than 2% of cases, and the effect on patient outcome was unknown. Rabkin and Horne[28] corroborate this claim with their finding of new ECG abnormalities in 165 of 812 patients in a retrospective analysis but a delay or cancellation in only 13 cases. None of the documented reasons for delay or cancellation was related to the preoperative ECG abnormality. The choice of anesthesia was influenced in only two cases. Patient outcomes were not evaluated. Perez et al[29] retrospectively evaluated 3131 patients of whom 2406 had a preoperative ECG. Only 5.6% had an unexpectedly abnormal ECG result, and a change in management occurred in only 0.5% of cases.

In a retrospective review, Turnbull and Buck[9] found that of 101 abnormal preoperative ECG results, only four were significant by the criteria of Goldman et al,[30] and no preoperative change in management occurred in any case. Four patients had a cardiac complication, and in two of these cases, the cardiac risk was apparent from the history and physical examination alone. Gold et al[20] found similar results, in that less than 2% of patients with abnormal ECG results experienced an adverse perioperative cardiovascular event and preoperative ECG was useful in only half of the cases. On a review of the literature, Goldberger and O'Konski[31] did not support routine preoperative ECG for all-comers but rather the selective use of screening for subsets of patients, including those with signs or symptoms of cardiac disease or those with risk for occult heart disease. Similarly, Barnard et al[32] found preoperative screening ECG to be of limited value for relatively healthy patients.

Risk Factors

Over the last several decades, many studies have validated certain disease processes that are associated with adverse perioperative cardiovascular outcomes.[30,33-35] Although they may be clinically asymptomatic, patients with ischemic heart disease (IHD), congestive heart failure, cerebrovascular disease, diabetes mellitus, and chronic renal insufficiency are at increased risk of cardiovascular morbidity and mortality. Hollenberg et al[36] used continuous perioperative ECG monitoring to identify predictors of postoperative cardiac ischemia in patients at high risk of or with known coronary artery disease. They identified five major predictors for perioperative ischemia, including four factors ascertainable by clinical history (definitive history of coronary artery disease, hypertension, diabetes mellitus, or use of digoxin) and LVH by ECG. The clinical risk increased with the number of risk factors present.

Landesberg and colleagues[37] investigated the association between preoperative ECG abnormalities and perioperative myocardial ischemia, infarction, and cardiac death in 405 patients undergoing major vascular surgery. They found that LVH by voltage criteria, ST segment depression, or both better predicted postoperative cardiac morbidity and mortality than clinical risk factors, including history of myocardial ischemia or infarction, angina pectoris, or diabetes mellitus.

Payne and colleagues[38] performed a prospective observational cohort study of 345 patients undergoing major vascular surgery or laparotomy to evaluate the correlation between abnormal preoperative ECG and postoperative adverse cardiac events. They found that patients with an abnormal preoperative ECG had a significantly higher incidence of major adverse cardiac events. Multivariable analysis demonstrated that a clinical history of hypertension or prolongation of QTc or left ventricular strain by ECG were predictive of postoperative adverse cardiac events. More importantly, however, they examined the relationship between a history of known IHD and an abnormal result on preoperative ECG. They found that patients with a history of IHD and a normal result on preoperative ECG had the lowest rate of adverse postoperative cardiac events (2.4%) compared with no IHD and a normal result on ECG (8.6%), IHD and an abnormal result on ECG (24.2%), and no IHD and an abnormal result on ECG (20.3%) ($p = 0.001$).

Jerger et al[39] prospectively examined 172 patients with known coronary artery disease undergoing major noncardiac surgery to determine the association between preoperative ECG and long-term outcomes of all-cause mortality and major adverse cardiac events at 2 years. The overall prevalence of preoperative ECG abnormalities was between 38% and 53%, depending on the criteria used. After controlling for baseline clinical findings, the authors found ST depression and faster

heart rate to be independent risk factors for all-cause mortality, as were renal failure and prior revascularization. Faster heart rate, advanced age, hypertension, peripheral arterial disease, and congestive heart failure were independent predictors of major adverse cardiac event.

Other studies, however, failed to find significant utility of routine preoperative ECG in this patient population. Tait and colleagues[40] performed a retrospective chart review of 1000 American Society of Anesthesiologists (ASA) 1-2 patients undergoing low- to intermediate-risk surgery. Patients were allocated to cardiovascular risk or no risk as defined by a history of hypertension, hyperlipidemia, arrhythmia, diabetes mellitus, peripheral vascular disease, angina, or coronary artery disease. They found that patients with cardiovascular risk factors were more likely to have abnormal ECG results; however, there was no difference in the occurrence of adverse perioperative cardiac events.

In another study, Noordzij et al[41] retrospectively studied 23,036 patients undergoing noncardiac surgeries with a primary endpoint of 30-day cardiovascular death. Cardiovascular death was observed in 199 patients (0.7%), and the incidence was higher in those with abnormal preoperative ECG results; however, the absolute difference in the incidence of cardiovascular death in patients undergoing low- or intermediate-risk surgery was only 0.5%, which casts doubt on its clinical usefulness in this population.

van Klei and colleagues[42] evaluated 2967 patients undergoing noncardiac surgery and found that both left and right bundle branch blocks identified on the preoperative ECG were associated with an increase in postoperative myocardial infarction and death but failed to predict adverse perioperative cardiac events beyond clinical risk factors identified by history alone.

Preoperative Electrocardiogram and the Elderly

A wealth of epidemiologic data supports an increased prevalence of coronary artery disease with increasing age. The probability that a previously asymptomatic man at average risk will have myocardial ischemia, myocardial infarction, or cardiac death is less than 4 per 1000 at 40 years of age; this number increases to 18 per 1000 at 60 years of age.[43] The prevalence of cardiovascular disease in patients 80 years and older is estimated to be greater than 30% in patients seen for noncardiac surgery.[44] Furthermore, at least 25% of myocardial infarctions in the aging population are believed to be clinically silent, and the risk for recurrent cardiac ischemia is similar to those with recognized cardiac events.[45] It is for this reason that some advocate routine preoperative ECG screening for the elderly. Nevertheless, data to support age alone as a valid reason for routine ECG screening are variable.

Several studies have demonstrated an increased incidence of abnormal ECG results in patients with advanced age.[19,46] Seymour and colleauges[46] suggest that, given the high prevalence of abnormal preoperative ECG results in the elderly population, preoperative screening should be performed routinely to ascertain "new" from "old" abnormalities, despite its poor ability to predict postoperative cardiovascular complications. Roizen[47] suggests, on the basis of pooled data from multiple studies, routine preoperative ECG screening for men older than 40 years and women older than 50 years for all moderate- to high-risk procedures. Correll and colleagues[48] found several risk factors, including history of heart failure, hyperlipidemia, angina, myocardial infarction, valvular heart disease, and age older than 65 years, to be predictive of a preoperative ECG result that would potentially affect perioperative management. In fact, in this study, age older than 65 was the most predictive risk factor of abnormal preoperative ECG results. Of note, there were no statistical differences in major postoperative cardiac complications between the two groups; this study was not powered, however, to detect differences in this endpoint.

Other studies refute the usefulness of preoperative ECG in the elderly population. Liu and colleagues[49] prospectively observed 513 patients aged 70 years or older undergoing noncardiac surgery. Abnormal preoperative ECG results were found in 386 (75.2%) of patients, but the presence of abnormalities on preoperative ECG was not associated with an increased risk of postoperative cardiac complications. They also examined the possibility that patients with abnormal preoperative ECG results had changes in the preoperative or intraoperative period that might affect outcomes. None of the cases cancelled or postponed by the anesthesiologist was due to ECG abnormalities. Intraoperative care was the same in terms of use of beta- or calcium channel blockade, nitroglycerin, and invasive hemodynamic monitoring.

Schein and colleagues[50] prospectively assigned 19,189 elderly patients scheduled to undergo cataract surgery to either routine preoperative testing or no preoperative testing. They found neither a difference in the overall rate of intraoperative or postoperative complications nor a difference in intraoperative or postoperative events.

Surgical Procedure

It has been widely demonstrated in the literature that the risk of cardiovascular morbidity and mortality is correlated with the type of surgery[19,33,50-52]; that is, "high-risk" procedures such as emergency or vascular surgery are associated with a higher rate of adverse perioperative events than "low-risk" procedures such as ambulatory or endoscopic procedures. Perhaps the mostly extensively studied group is patients undergoing major vascular surgery, who, by virtue of both high-risk surgery and underlying disease processes, are at increased risk of perioperative cardiac events.[32,34-37,41-42,53] Patients undergoing lower risk procedures are at significantly lower cardiac risk. In the ambulatory surgery population, for example, preoperative ECG has not been shown to be predictive of adverse perioperative events, presumably because of the relatively low risk of the procedures performed as well as the relatively healthy patient population.[19,20,44] As such, the decision to obtain a preoperative ECG should take into account the relative risk of the surgery itself in addition to the individual patient's clinical risk factors and history.

CONTROVERSIES

The question, then, is, when faced with an abnormal preoperative ECG result, will it affect perioperative management? One of the more compelling arguments for obtaining a preoperative ECG is to potentially identify patients with asymptomatic coronary artery disease who may benefit from preoperative medical management. However, even in patients with significant risk of cardiac events, preoperative coronary revascularization is not routinely recommended if appropriate medical therapy is employed.[54-55] Payne and colleagues[38] found that patients with abnormal preoperative ECG results were a previously unrecognized high-risk group for perioperative cardiac events; indeed, the incidence of perioperative cardiac events was higher in this group than in patients with known cardiac disease and a normal ECG result. It is speculated that the higher number of adverse events was due to a lower rate of usage of beta blockade, antiplatelet agents, and statins in this group. These drugs are known to decrease morbidity and mortality after major surgery,[56] although immediate initiation of beta blockade may cause harm.[57] Thus identifying patients at risk and instituting or maximizing medical therapy preoperatively may reduce the incidence of perioperative cardiac complications.

AREAS OF UNCERTAINTY

It is important to recognize that the ability to make direct comparisons between studies in the current literature is greatly limited due to variability in study design, populations, and measured outcomes. Most importantly, the retrospective design of most studies limits the ability to draw conclusions regarding the effect of testing on medical decision making, which is the key question. For example, the utility of an abnormal ECG result may be underestimated in the face of an abnormal history or physical examination, whereas in reality the significance of the history and physical examination findings may have been underestimated until the ECG was evaluated.[58] Even with more rigorous study design, the ability to draw conclusions regarding the impact of ECG interpretation on clinical decision making and management would be challenging.

GUIDELINES

Several medical societies have issued recommendations regarding preoperative ECG screening. A summary of the recommendations made by two leading groups follows.

ASA Task Force on Preanesthesia Evaluation

The ASA released a practice advisory regarding preanesthesia evaluation in 2002 and updated this report in 2012.[59] This task force recommended against routine preoperative testing but endorsed the use of selective preoperative testing based on information obtained from the history, physical examination, and the invasiveness of the planned procedure. Specifically, the task force found that important clinical characteristics to consider in regard to the utility of preoperative ECG include significant cardiovascular disease, respiratory disease, and type or invasiveness of surgery. The task force was unable to come to a consensus regarding a minimum age for obtaining a preoperative ECG, recognizing that age alone may not be an indication for preoperative ECG screening. Rather, ECG may be indicated in patients with known cardiovascular risk factors. The task force found that the current literature did not allow for an unambiguous assessment of the appropriate timing of clinical testing; however, the consensus was that results obtained within 6 months of surgery are acceptable provided no change is seen in the patient's clinical condition.

American College of Cardiology (ACC) / American Heart Association (AHA) Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery

The ACC/AHA released guidelines for perioperative cardiovascular evaluation for noncardiac surgery in 2002, and the most recent update to these recommendations was made in 2007.[60] Recommendations in the 2007 update are placed in classes based on risk–benefit ratios, and for each recommendation in each class, a level of evidence is provided (Level A: highest level of evidence; Level C: lowest level of evidence). With regard to preoperative ECG, the recommendations are as follows:

Class I (Benefit of Preoperative ECG Greatly Outweighs Risk)

- Recommended in patients with at least one clinical risk factor (including history of IHD, history of compensated or prior heart failure, history of cerebrovascular disease, diabetes mellitus, and renal insufficiency) who are undergoing vascular surgical procedures (Level of Evidence: B)
- Recommended in patients with known coronary artery disease, peripheral arterial disease, or cerebrovascular disease who are undergoing intermediate-risk surgical procedures (including intraperitoneal and intrathoracic surgery, carotid endarterectomy, head and neck surgery, orthopedic surgery, or prostate surgery) (Level of Evidence: C)

Class IIa (Benefit of Preoperative ECG Is Greater Than Risk, but Additional Studies Are Needed)

- Reasonable in patients with no clinical risk factors who are undergoing vascular surgical procedures (Level of Evidence: B)

Class IIb (Benefits of Preoperative ECG Equal to or Greater Than Risks)

- May be reasonable in patients with at least one clinical risk factor who are undergoing intermediate-risk operative procedures (Level of Evidence: B)

Class III (Risk Outweighs Benefits and Procedure Is Not Indicated)

- Not indicated in asymptomatic persons undergoing low-risk surgical procedures (Level of Evidence: B)

In contrast to the ASA task force, the ACC/AHA recommendations suggest preoperative ECG should be obtained within 30 days of surgery.

AUTHORS' RECOMMENDATIONS

A preoperative ECG should be considered in patients in whom the test has a high likelihood of affecting perioperative management. The patient's clinical history and cardiovascular symptoms, physical examination, and invasiveness of the surgical procedure should be considered in this assessment. Age alone should not be used as an indication for a preoperative ECG.

A preoperative ECG should be considered in the following groups:

- Patients with at least one cardiovascular risk factor undergoing vascular or high-risk surgery
- Patients with known coronary, peripheral arterial, or cerebrovascular disease undergoing intermediate-risk surgery
- Patients with at least one cardiovascular risk factor undergoing intermediate-risk surgery
- Patients with an unknown or low functional capacity undergoing an intermediate- or high-risk procedure
- Patients currently taking medication that may potentially affect the ECG result (e.g., antiarrhythmics, methadone)
- Any patient in whom a preoperative ECG has the potential to affect clinical management

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CHAPTER 5

Is Routine Preoperative Pregnancy Testing Necessary?

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INTRODUCTION

Surgery on a pregnant woman raises several concerns. These include the effect of surgery and anesthesia on the developing fetus and the potential to trigger preterm labor. The hazards to the fetus could come from teratogenic effects of drugs administered during the perioperative period or, in a more advanced pregnancy, alterations in uteroplacental blood flow, as well as from maternal hypoxia or acidosis.[1] It is reported that up to 15% of known pregnancies miscarry before 20 weeks, and up to 50% of unrecognized pregnancies miscarry during the first trimester.[2] Because the period of organogenesis is during the first trimester, elective surgery is usually postponed to avoid potential teratogenicity and intrauterine fetal death. Although it is unclear which factors account for it, increased risk of spontaneous abortion is observed in women undergoing general anesthesia during the first or second trimester of pregnancy.[1-5] Premature labor is more likely in the third trimester. Some studies have also suggested the presence of a strong association between central nervous system (CNS) defects and first-trimester anesthesia exposure.[6,7]

Consequently, the issue of ruling out pregnancy before surgery is a crucial one. Unfortunately, medical history alone is often unreliable in ruling out pregnancy, especially in the adolescent female population.[8] It is in this very population in which obtaining a routine pregnancy test may present an ethical and a legal problem. The patient may refuse to have the test done and may, in some states, have the legal right to keep that information private from her parents.[9] On the other hand, the adult population of female patients of childbearing age may very well have the same or even a higher risk of unknown pregnancy before a surgical procedure.[10,11] Routinely testing those patients for pregnancy may present a trust issue with women who believe that their history excludes that possibility. Moreover, calculation of the cost incurred if pregnancy screening is done routinely before each surgery adds to the controversy of the issue.[12,13]

OPTIONS

Should preoperative pregnancy testing be performed on all female patients of childbearing age or just in select populations? Whether these select populations should include only those whose history is suggestive of pregnancy or whose history is unclear is still unresolved. The general practice of anesthesiologists differs according to the institutions in which they work, as well as by their personal judgments and convictions. Instituting policies for preoperative pregnancy testing should be based on the patient's best interests in correspondence with state law and ethical responsibility.[11]

The American Society of Anesthesiologists (ASA) Committee on Ethics has stated that patients should be offered but not required to undergo pregnancy testing unless there is a compelling medical reason to know that the patient is pregnant.[14]

The ASA Practice Advisory for Preanesthesia Evaluation was amended by the ASA House of Delegates on October 15, 2003, to reflect this. "The Task Force recognizes that patients may present for anesthesia with an early undetected pregnancy. The Task Force believes that the literature is inadequate to inform patients or physicians on whether anesthesia causes harmful effects on early pregnancy. Pregnancy testing may be offered to female patients of childbearing age and for whom the results would alter the patient's management."[15] The most common policies on preoperative pregnancy testing were outlined in a recent ASA newsletter.[16] One approach is to test every female patient of childbearing potential regardless of whether she consents. The justification for this is that consent to surgery and anesthesia is also consent to a pregnancy test. An alternative policy is one that allows patients to refuse testing after anesthetic and surgical risks to a possible pregnancy have been explained. However, after refusal the patient is asked to waive all legal rights relating to undetected pregnancy. In some anesthesiology departments the patient is informed and consulted but may be tested regardless of whether she consents.[16]

In a survey distributed to members of the Society of Obstetric Anesthesia and Perinatology (SOAP), almost one third of 169 respondents required preoperative pregnancy testing for all childbearing-age female patients through mandatory departmental policy. Of surveyed anesthesiologists, however, 66% required testing only when history indicated possible pregnancy.[17] When surveyed, members of the ASA were asked whether pregnancy testing should be done routinely for all patients versus select populations; 17% believed it was a necessary routine test, whereas 78% chose the latter.[15] The finding of a positive result has a very important impact on clinical management because it will lead to either delays or cancellations of surgery.[8,10,11,18,19]

EVIDENCE

Several studies have been conducted to examine the reliability of a preoperatively obtained medical history to indicate the possibility of pregnancy (Table 5-1). These studies included patients from different age groups. One study by Malviya and colleagues[20] in the adolescent population showed that none of the patients who underwent testing were found to have a positive urine pregnancy test. Data from the study indicated that most of the patients denied the possibility of pregnancy, whereas very few were not sure. The authors concluded that a detailed history should be obtained in all postmenarchal patients, and unless indicated by that history, pregnancy testing would not be required. It is noteworthy that 17 patients in that study refused testing.

Several other studies, on the other hand, demonstrated that the medical history was often inconclusive and occasionally misleading. This was true for both adults and adolescents. Two studies, by Azzam and colleagues[18] and Pierre and colleagues,[8] demonstrated positive pregnancy test results in adolescent patients undergoing surgery. Incidence rates were 1.2% and 0.49%, respectively. The medical history in the Pierre study did not always correlate with test results.

Three additional studies included patients from all age groups.[10,11,19] Manley and colleagues,[19] using either serum or urinary human chorionic gonadotropin (hCG), tested 2056 females undergoing ambulatory surgery. There was an incidence of 0.3% of unrecognized pregnancies. Wheeler and Cote[11] tested 261 patients ages 10 to 34 years, all of whom denied the possibility of pregnancy. Three patients (1.3%) had positive tests. Two of them were adults. Interestingly, the authors in the studies by both Azzam and colleagues[18] and Wheeler and Cote[11] point out that, although positive results were documented in teenagers, no positive result was detected in patients younger than 15 years of age. In a study on adolescents, Hennrikus and colleagues[21] tested 532 females between ages 12 and 19. They found five patients to have positive urine hCG results, and the youngest was 13 years of age.

Evidence was most compelling in the adult population in the study done by Twersky and Singleton,[10] which examined 315 consecutive females of childbearing potential undergoing elective surgery. Seven patients (2.2%) tested positive for serum beta-hCG. None of them were teenagers. The highest percentage of positive pregnancy tests was found among patients undergoing laparoscopic sterilization. A study done in the United Kingdom included 125 patients undergoing laparoscopic sterilization, of whom six had positive pregnancy tests (5%).[22] The authors did not specify if the history of these patients indicated the possibility of being pregnant.[23]

AREAS OF UNCERTAINTY

Cost

When doing a routine test, it is always important to consider whether the findings obtained from that test provide an advantage over those not tested. Would a higher cost be incurred if those results were unknown? In a retrospective study, Kahn and colleagues[13] found the average cost per urine pregnancy test to be $5.03, and the cost per true-positive result to be $3273. After these results, they speculated that the costs of preoperative pregnancy testing were validated by removing the potential risk to the mother and fetus along with a potential decrease in litigation. On the basis of the "numbers needed to treat" approach, Kettler[12] calculated the cost of detecting one pregnancy when using routine preoperative testing. The cost was $1050 in the adolescent population and $7750 in the adult population. Evaluation of cost needs to be weighed against the cost of spontaneous abortion, radiation exposure, or possible congenital abnormalities after an anesthetic and surgical procedure conducted in a patient with an unknown pregnancy.

Which Test to Be Done

Whether to do a urine pregnancy test versus a serum pregnancy test has also been a matter of inconsistency.[24] The studies mentioned earlier used them interchangeably (see Table 5-1). In general, it is believed that a urine pregnancy test, which is quicker and readily available, is a reliable one. It decreases the time required to obtain the result, which, in turn, decreases operating room delays.[25]

How Sensitive

Several urine hCG kits report a sensitivity of 99.4% and a specificity of 99.5%.[21,24] The significance of a positive pregnancy test is evaluated by the positive predictive value of the test processed. On the basis of the data and incidence of pregnancy detected from one preoperative evaluation study,[19] Lewis and Cooper[26] demonstrated that pregnancy testing had a low positive predictive value. This means that there will be patients with positive pregnancy tests who are not actually pregnant and will have their surgery delayed, secondary to the false-positive test result. A false-positive result could be due to production by neoplasms, from trophoblastic disease, or from a so-called biochemical pregnancy in which an early miscarriage occurs and the only evidence for pregnancy was the positive test result.[21,27] A false-negative result could occur if the sample was taken too early after implantation and the level of hCG was below the detection cutoff of 20 IU/L offered by the most sensitive kits or if the urine sample was too dilute (e.g., not a first morning specimen).[28] Cole and Khanlian[29] reported a urine hCG range of 1.2-15.2 IU/L on the day of implantation and that only 63% of pregnancies exceeded the 20 IU/L cutoff on the first day of missed menses. However, given the low prevalence of actual pregnancy in the surgical population, positive predictive values vary and would be higher in other studies that resulted in higher incidence rates. Larger studies with bigger patient samples and unified testing methods are needed to resolve this issue.

TABLE 5-1 **Detecting the Incidence of Pregnancy during Preoperative Evaluation Using History and Laboratory Testing**

Study	Design	Duration	No. of Cases	Patient Population	Age in Years	Type of Test	Time of Test	No. of Positive Results	Correlation with History
Manley et al[19]	Prospective	36 mo	2056	All females of childbearing potential	*	Urine or serum β-hCG	Within 6 days of surgery	Total 7 (0.3%)	No†
Gazvani et al[22]	Prospective	23 mo	125	Females undergoing laparoscopic sterilizations	*	Urine β-hCG	*	Total 6 (5%)	*
Azzam et al[18]	Retrospective	24 mo	412	Adolescents	10.5-20	Urine β-hCG	*	Total 5 (1.2%); <14 old: 0 (0%) ≥15 old: 5 (2.4%)	*
Twersky and Singleton[10]	Prospective	*	315	All females of childbearing age	*	Serum β-hCG	*	Total 7 (2.2%) <23 old: 0	No†
Malviya et al[20]	Prospective	26 mo	525	Adolescents	10-17	Urine β-hCG	Day of surgery	1 (questionable result; deemed negative)	Yes‡
Pierre et al[8]	Prospective	21 mo	801	Adolescents	12-21	Urine β-hCG	*	Total 6 (0.49%)	No†
Wheeler and Cote[11]	Prospective	15 mo	235	Adolescents and adults	10-34	*	*	Total 3 (1.3%); <15 old: 0 (0%) ≥15 old: 3 (2.3%)	No†
Hennrikus et al[21]	Retrospective	36 mo	532	Adolescents	12-19	Urine β-hCG	Day of surgery	Total 5 (0.9%)	*
Kahn et al[13]	Retrospective	12 mo	2588	All females of childbearing potential	*	Urine β-hCG	Day of surgery	Total 8 (0.3%)	No†

β-hCG, beta-human chorionic gonadotropin.
*Was not specified in the study.
†History indicated the possibility of pregnancy in all patients who tested positive.
‡History did not indicate the possibility of pregnancy in all patients who tested positive.

When to Test

Production of hCG begins with implantation, which occurs on day 8, 9, or 10 postconception in 84% of women,[27] and levels remain elevated throughout gestation. In many cases, pregnancy testing takes place within 7 days before surgery. However, the concentration of beta-hCG in early pregnancy doubles every 1.4 to 2 days.[21,26] Therefore there is a concern that an undetectable level at 7 days before surgery may become detectable on the day of surgery.[30,31] Thus it seems that testing on the day of surgery may identify more pregnant patients than testing earlier. It should be noted, however, that testing on the day of surgery allows the potential for cancellation of surgery, hence complicating the surgical schedule, at a cost to the organization of a case that cannot be substituted.

GUIDELINES

The ASA, in its statement on routine preoperative laboratory testing, did not see any one test to be a requirement for all patients. Rather, testing guidelines should be tailored by each individual anesthesia department and according to its influence on select populations.[32] In 2002, a task force was appointed by the ASA to review available literature, obtain expert and public opinion, and create the consensus-based "Practice Advisory for Preanesthesia Evaluation."[15]

The task force agreed that preoperative tests should not be ordered routinely. Rather, preoperative tests should be done or required on a selective basis for purposes of guiding and optimizing perioperative management. The indications for testing should be documented and based on medical and physical examination. The task force, however, recognized that a history and examination might be insufficient for identification of early pregnancy. In its 2003 amendment, in keeping with the ethical guidelines of anesthesia practice, it recommended that all female patients of childbearing potential should be offered pregnancy testing rather than being required to undergo testing, in light of the equivocal evidence-based linkages between pregnancy testing and anesthesia outcome. It gives individual physicians and hospitals the opportunity to set their own policies and practices relating to preoperative pregnancy testing. Although legitimate or illegitimate consequences can ensue (*Ballard v. Anderson*, 4 Cal. 3d 873, 1971; *Truman v. Thomas*, 27 Cal. 3d 285, 1980; *Rechenbach v. Haftkowycz*, 654 Ohio 2d 374, 1995), medicolegal concerns alone should not be the driving force guiding policies. Some hospitals respect the patient's right of refusal after a thorough explanation of anesthetic risks during pregnancy but require the patient to sign a waiver releasing the physicians and hospital from potential litigation over an unknown pregnancy.[16] Additionally, policies should address who shall discuss the results with the patient and who is allowed to be notified of the results (e.g., partner, family, insurance company, and employer).[14] Individual institutions should develop guidelines centered on the content and reliability of the patient's medical history, balanced by the physician's judgment.

AUTHORS' RECOMMENDATIONS

Medical tests are performed based on the contribution they offer to patient care and safety (Table 5-2). In this case we must ask ourselves the following question: How important is it to know whether a patient is pregnant before performing surgery?

Even though the prevalence of pregnancy is expected to be low in patients undergoing surgery, the discovery of the fewest number of cases is extremely significant. As important as this would be to protect the patient and fetus, it is also important to protect the physician from unwarranted litigation. The argument has been, is this cost-effective? If we factor in the costs generated by abortions, miscarriages, and even malpractice lawsuits secondary to a suspected anesthetic teratogenic effect, one may conclude that pregnancy testing is indeed cost-effective. There have been concerns regarding the methods of informing patients before obtaining a pregnancy test. Some studies informed all patients, whereas others did not because the test was mandatory.

- We believe that even if the test is made to be mandatory, this should not preclude obtaining a well-documented informed consent. Patients still have the right to refuse testing, at which point the physician also has the right to refuse to render services after explaining the rationale behind the test and the safety issues involved.
- Mandatory testing offers the advantage of avoiding the conflicts that physicians are presented with when some adolescent patients are asked about the test or their sexual history. The same applies to parents or adult patients, who may be offended by a detailed sexual history. As for young patients who are at the onset of their menses, there is no evidence that testing is helpful. Several studies have shown that patients younger than 13 years have negative test results. However, we prefer to have those patients tested if they consent because there are occasions in which they may not disclose all of their history or that history may be inaccurate.
- A policy must be in place addressing which physicians should be involved in informing the patient of the results and who may be informed of the results. In the case of an unexpected positive result, an obstetric/gynecologic consultation should be arranged.
- In terms of what test to perform, serum testing is very sensitive and may be sufficient when done within a week of the surgical date. However, if a urine pregnancy test is used, it should preferably be done on the day of surgery so that it can identify the greatest number of pregnant patients. However, a negative urine test does not preclude early pregnancy, and this must be discussed with the patient during informed consent.

In conclusion, based on current evidence, pregnancy testing is a cost-effective method and should be offered to all verbally consenting females of childbearing potential. This does not substitute for an appropriate pregnancy history and physical examination.

This will remain a controversial issue, and larger studies are needed. They should include a larger number of patients from all age groups and use a unified method of testing, as well as a well-documented informed consent.

TABLE 5-2 **Recommendations for Preoperative Pregnancy Testing**

Population Type	Recommendations
Menstruating females younger than 13 yr	No pregnancy test unless history is either indicative of sexual activity or inconclusive
Patients of childbearing age (older than 13 yr of age until 1 yr after last reported menses)	Preoperative pregnancy test should be offered to all patients regardless of history, except in patients with a history of hysterectomy or bilateral salpingo-oophorectomy
Testing on the day of surgery	Urine pregnancy test is sufficient
Testing within 1 wk of surgery	Serum pregnancy test is preferable
All patients	Well-documented informed consent must be obtained from patients or their guardians
All patients	There must be an established system involving an obstetric/gynecologic consultation for disclosing an unexpected positive result to the patient
All patients	A thorough and detailed history should be obtained from all patients

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CHAPTER 6

What Are the Risk Factors for Perioperative Stroke?

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INTRODUCTION

Perioperative stroke is a potentially devastating complication of surgery that has an incidence that varies widely with the surgical procedure. A perioperative stroke can occur intraoperatively or in the postoperative period; however, this window of risk is not standardized because studies have used intervals of 3 to 30 days.

A recent review[1] on this topic illustrated the representative incidences based on surgical procedure. These categories included general surgery (0.08% to 0.7%),[2] peripheral vascular surgery (0.8% to 3.0%),[3] resection of head and neck tumors (4.8%),[4] carotid endarterectomy (CEA) in symptomatic patients (3.3% to 6.4%),[5] CEA in asymptomatic patients (1.2% to 3.0%),[5] isolated coronary artery bypass graft (CABG) surgery (1.4% to 3.8%),[6-7] combined CABG with valve surgery (7.4%),[6-7] isolated valve surgery (4.8% to 8.8%),[6] double or triple valve surgery (9.7%),[6] and aortic repair (8.7%).[7] Beating-heart CABG has a lower incidence of stroke than does CABG with bypass (1.9% versus 3.8%, respectively).[6]

This variability in perioperative stroke incidence certainly reflects the underlying surgical anatomy, risk of vascular compromise and injury, and patient's overall preoperative health status. As such, there are likely no simple answers to this complex perioperative complication. The problem has been approached by different specialties with a variety of preventive measures, including intense intraoperative monitoring, novel approaches to the surgical procedure, and development of predictive models. Regardless, the incidence of perioperative stroke has remained a concern.

The implication from the aforementioned reviews is that to achieve an appreciable reduction in the incidence of stroke, it will require universal as well as selective improvements by each surgical subspecialty. A fair appraisal of perioperative stroke thus requires that we present data for general surgery, carotid surgery, and cardiac surgery separately.

PATHOPHYSIOLOGY

Proposed mechanisms of perioperative ischemic strokes include thrombotic, embolic, lacunar, hematologic (hypercoagulable state), and hypoperfusion processes.[8]

EVIDENCE

Evidence from studies of cardiac surgery supports that perioperative hemorrhagic stroke is of the lowest incidence. In cardiac surgery, for example, Likosky and colleagues[9] examined 388 patients who had strokes after isolated CABG surgery. This study used the Northern New England Cardiovascular Disease Study Group classification system, and imaging was performed with computed tomography (CT) or magnetic resonance imaging (MRI). The study revealed that 62.1% of strokes were embolic, 3.1% lacunar, 1.0% thrombotic, 8.8% due to hypoperfusion, 1.0% hemorrhagic, 10.1% multiple causes, and 13.9% unclassified. About 45% of strokes were detected within the first postoperative day, and a slow decrement of detection was seen over time (about 20% more by postoperative day 2, about 12% more by postoperative day 3, and less than 5% beyond postoperative day 10).[9]

The source of emboli (cardiac or artery-to-artery) during any surgery could include arrhythmias such as atrial fibrillation, aortic arch atherosclerosis, perioperative myocardial infarction, and manipulations of the heart and carotid arteries.[10] The release of particulate matter from the cardiopulmonary bypass pump must also not be forgotten. A rare source may also be paradoxical emboli from a patent foramen ovale or fat emboli during orthopedic procedures.[10] In a study of 2630 CABG patients,[11] 2.0% had postoperative strokes. The event occurred after a mean of 3.7 days. In 19 of 52 patients (36.5%), atrial fibrillation preceded the stroke, with a mean of 2.5 episodes of atrial fibrillation before the event.

Tissue injury from surgery results in a prothrombotic state, which lasts up to 14 to 21 days postoperatively. This is supported by decreased levels of tissue plasminogen activator and increased plasminogen activator inhibitor type 1 activity, fibrinogen degradation products, thrombin–antithrombin complex, thrombus precursor protein, and D-dimer.[12-14] Other factors such as the use of general anesthesia, under-resuscitation leading to postoperative dehydration, and bed rest may all aggravate a hypercoagulable state.[8] Often, antiplatelet and anticoagulant agents are also held in the perioperative period. This may certainly exacerbate a hypercoagulable state and further increase the risk of perioperative stroke.[15,16] This practice has slowly changed, and it is being found that these agents are likely safe in a large majority of surgeries.[17]

Gottesman and colleagues[18] presented a different view of stroke in cardiac surgery. They studied 98 patients who had MRI after a clinical stroke. The group identified watershed infarcts in 68% of the diffusion-weighted imaging sequences of MRI versus 37% of brain CTs. In fact, 48% of diffusion-weighted MRI scans demonstrated bilateral watershed infarcts versus 22% of CT scans. Patients with bilateral watershed infarcts were more likely to have undergone an aortic procedure than a simple or second CABG. These patients trended toward longer bypass times (nearly significant; $p = 0.055$). Univariate and multivariate logistic regression revealed that patients with a drop in mean arterial pressure (MAP) of at least 10 mm Hg from their preoperative baselines were greater than four times more likely to develop bilateral watershed infarcts as those with a small or no decrement in blood pressure. Importantly, absolute intraoperative blood pressure was almost identical in the bilateral watershed infarct group versus other infarct patterns. Watershed infarcts may be due to a mechanistic interplay of hypoperfusion and embolization.[19] The theory is that a state of reduced perfusion (due to reduced MAP or due to carotid arterial narrowing) may impede washout of microemboli showered during cardiac surgery; these particulates then have a predilection to settle in watershed areas.

In keeping with this theory, a randomized study by Gold and colleagues[20] of 248 patients undergoing elective CABG revealed that patients maintained at a higher MAP (80 to 100 mm Hg) during bypass had a lower incidence of stroke. This group also conducted a follow-up study in 412 patients undergoing elective CABG comparing a higher MAP (80 mm Hg) with a patient's prebypass baseline MAP but did not detect a difference in the stroke rate.[21] These studies have been criticized for lack of power to draw any widely applicable conclusions. In contrast, van Wermeskerken and colleagues[22] analyzed outcomes from 2862 patients undergoing CABG. After controlling for bypass time and preoperative stroke risk index, the authors found that patients with a lower pressure during bypass (MAP < 50 mm Hg) had a decreased incidence of stroke and coma.

In general, hypoperfusion is believed to be an uncommon cause of perioperative stroke. The term *hypoperfusion* can imply global hypoperfusion (i.e., resulting in bilateral watershed infarctions) or relative hypoperfusion through a pre-existing stenosis (i.e., unilateral watershed infarction due to carotid stenosis). The aforementioned study from van Wermeskerken and colleagues[22] supports a limited role of hypoperfusion. In addition, Whitney and colleagues[23] concluded that hypoperfusion ischemia is rare during CEA, even when the contralateral carotid is occluded. Naylor and colleagues.[24] reviewed the literature to assess the role of carotid stenosis as a perioperative stroke risk factor for CABG. Ninety-one percent of screened CABG patients had insignificant disease and had a less than 2% risk of stroke. The risk increased to 3% for asymptomatic unilateral stenosis of 50% to 99%, 5% in bilateral 50% to 99% stenosis, and 7% to 11% in those with an occluded carotid. As a consequence of such data, the current practice is to perform CEA before CABG or even intraoperatively immediately before CABG. Venkatachalam and colleagues[25] recently reviewed the perioperative stroke risk of patients who underwent staged or combined CEA–CABG and found a 4% risk for combined CEA–CABG, 2% for CEA followed by CABG, 5% for CABG followed by CEA, and 2% for carotid endovascular revascularization followed by CABG.

Studies looking specifically at the mechanisms of stroke in the general surgery patient are rare and, in general, are not contemporary studies. Hart and Hindman[26] performed a retrospective review of 24,500 general surgery patients. Forty-two percent of strokes were believed to be embolic, and atrial fibrillation was present in 33% of patients at the time of the events. Interestingly, most perioperative strokes in the general surgery population occur well into the postoperative period: on average on the seventh day.[2,26-30] A recent case control study[31] reiterated the relative rarity of intraoperative strokes; evidence was found for only 10 of 61 strokes occurring intraoperatively. Of these studies, Parikh and Cohen[27] found the highest incidence (53%) of cerebrovascular accident (CVA) within 24 hours after surgery.

Again, taken as a whole, these observations highlight the fact that the mechanisms of perioperative stroke should be reviewed in each surgical population separately.

SYSTEMATIC REVIEW

No meta-analysis has specifically assessed the risk factors for perioperative stroke in the general surgery population. The best level evidence is in the form of prospective observational studies, but given that an extensive literature search identified only one such study, several retrospective and case control investigations were included for review. A retrospective analysis of patients undergoing noncarotid vascular surgery is also included (Tables 6-1 and 6-2).

The existing meta-analyses in cardiac surgery compared conventional CABG and off-pump CABG in terms of global outcomes. Table 6-2 only addresses stroke. The 2003 and 2011 analyses[38,40] included nonrandomized trials, but it was believed that the inclusion of these data did not bias their results.

The existing data on perioperative stroke in cardiac surgery are limited to multiple prospectively collected, retrospectively analyzed observational studies. One case control design and multiple retrospective studies are found in the literature. The data are summarized in Table 6-3, and a small study by Bucerius and colleagues[6] with similar surgical breakdown has been included for comparison. Also included at the end of the table are two recent larger prospective studies on thoracic aortic surgery because these studies likely best fit in the cardiac surgery category.

There are several meta-analyses exploring different aspects of perioperative stroke in carotid surgery. These are applicable to this chapter only in a broad sense but are nonetheless interesting. Only the most recent meta-analyses on this topic were included (Table 6-4).

TABLE 6-1 **Perioperative Stroke Studies in the General Surgery Population**

Study, Year	Number of Subjects	Study Design	Stroke Incidence	Significant Risk Factors
1982[26]	24,500 (general surgical procedures excluding carotid and cardiac surgery)	R	0.07%	Atrial fibrillation Cardiac disease
1988[28]	2463 (noncardiac, noncarotid artery surgery)	PO	0.2%	Previous cerebrovascular disease Heart disease PVD (eightfold increased risk) Hypertension (threefold-fourfold increased risk)
1990[32]	173 (patients with prior CVA subsequently underwent general surgery)	R	2.9%	Use of preoperative heparin sodium (usually as a substitute for warfarin) General anesthesia (as opposed to regional)[26] Hypotension in recovery room[26]
1993[27]	24,641 (general and vascular general surgery excluding CEA)	R	0.08%	Hypertension Smoking Previous neurologic symptoms Abnormal rhythm on ECG
1998[31]	61 cases (general surgery) 122 randomly assigned control subjects (matched for age, sex, procedure, and year of procedure)	CC	N/A	Previous cerebrovascular disease (AOR_1, 12.57; AOR_2, 14.70)* COPD (AOR_1, 7.51; AOR_2, 10.04) PVD (AOR_1, 5.35) Higher MAP on admission (AOR_2, 1.05) Blood urea at time of stroke (AOR_2, 1.04) Postoperative MI (4 cases versus 0 control) Diffuse intravascular coagulation (4 cases versus 0 control)
2000[33]	1455 cases (surgery) 1455 control subjects (age and sex matched)	CC	N/A	Perioperative period after general anesthesia extending for 30 days postoperatively (OR adjusted for known independent stroke risk factor: 3.9 for all surgeries and 2.9 for general surgery)
2004[34]	2251 (abdominal aortic aneurysmectomy) 2616 (aortobifemoral bypass) 6866 (lower extremity bypass) 7442 (major lower extremity amputation)	R	0.4%-0.6%	Preoperative ventilation (OR, 11) Previous stroke or TIA (OR, 4.2) Postoperative MI (OR, 3.3) Need to return to operating room (OR, 2.2)
2005[35]	172,592	PO	0.03%	Most cases in ASA 3 patients† 26% of stroke cases had prior history of CVA
2009[36]	201,235 (total hip replacement) 131,067 (hemicolectomy) 39,339 (lobectomy) 327,628 control subjects (CABG)	R	0.2% (total hip replacement) 0.7% (hemicolectomy) 0.6% (lobectomy)	Age Female sex Diabetes mellitus Atrial fibrillation Congestive heart failure History of prior stroke Renal disease Cardiac valvular disease
2010[37]	18,745 (total joint arthroplasty)	CC	0.2%	Noncoronary cardiac disease (OR, 4.13) Urgency of surgery (OR, 5.89) General anesthesia (OR, 3.54) Intraoperative arrhythmia (OR, 1.06)

AOR, adjusted odds-ratio; *ASA,* American Society of Anesthesiologists anesthesia preoperative assessment score (1-5); *CABG,* coronary artery bypass grafting; *CC,* case control; *CEA,* carotid endarterectomy; *COPD,* chronic obstructive lung disease; *CVA,* cerebrovascular accident (stroke); *ECG,* electrocardiogram; *MAP,* mean arterial pressure; *MI,* myocardial infarction; *OR,* odds ratio; *PO,* prospective observational; *PVD,* peripheral vascular disease; *R,* retrospective; *TIA,* transient ischemic attack.

*AOR_1 is from the univariate analysis. AOR_2 is from the multivariate analysis. Noted values are those that reached statistical significance.

†Requested copy of study from author. Unable to obtain. Data entered from abstract only.

TABLE 6-2 **Meta-Analyses of Conventional CABG and Off-Pump CABG: Outcome Analysis**

Study, Year	Number of Trials	Number of Subjects (intervention/no intervention)	Intervention (30-day stroke percent)	Control (30-day stroke percent)	Outcomes (OR/RR with confidence interval)
2003[38]	53 (38 trials included data on stroke)	34,126 (not noted/not noted)	Not noted	Not noted	OR, 0.55 (0.43-0.69)
2005[39]	37 (21 trials included data on stroke)	2859 (1425 off-pump CABG versus 1434 conventional CABG)	0.4	1.0	OR, 0.68 (0.33-1.40)
2011[40]	10 (7 trials included data on stroke)	15,034 (2887/12,147)	0.38	1.87	RR, 0.27 (0.14-0.53)
2012[41]	43 (21 trials included data on stroke)	6336 (3196/3140)	Not noted	Not noted	OR, 0.80 (0.52-1.22)

CABG, coronary artery bypass grafting; *OR,* odds ratio; *RR,* relative risk.

TABLE 6-3 **Perioperative Stroke Risk Factor Studies in the Cardiac Surgery Population**

Study, Year	Number of Subjects	Study Design	Stroke Incidence	Significant Risk Factors (Multivariate Analysis Unless Otherwise Noted)
1992[42]	130	?P	3.85%	Protruding aortic arch atheroma (OR, 5.8; CI, 1.2-27.9)
1996[43]	189	P	4.76% by 1 wk postoperatively	Univariate analysis on aortic atheromatous grade by TEE: advancing aortic atheroma grade was a predictor of CVA ($p = 0.00001$)
1999[44]	4518	PO	2.0% CVA; 0.7% TIA	Known cerebral vascular disease (OR, 2.5); renal failure (OR, 1.6); MI (OR, 1.5); DM (OR, 1.5); age > 70 (OR, 1.5); also associated with postoperative low EF and atrial fibrillation
1999[45]	2972	PO	1.6% (0.6% early and 1.0% delayed)	Early stroke (immediately after surgery): history of stroke (OR, 11.6); ascending aortic atherosclerosis (OR, 2.0); duration of cardiopulmonary bypass (OR, 1.1); female sex (OR, 6.9) Delayed stroke: history of stroke (OR, 27.6); DM (OR, 2.8); female sex (OR, 2.4); ascending aortic atherosclerosis (OR, 1.4); combined endpoints of atrial fibrillation and low cardiac output (OR, 1.7)
2000[46]	1987 CABG only 84 CABG and CEA	PO	1.7% CABG; 4.7% combined	Age: 76 versus 71.9 yr (OR, 1.09); hypertension (OR, 2.67); extensively calcified aorta (OR, 2.82); prolonged bypass time (OR, 1.01; CI, 1.00-1.02)
2000[47]	472	P	3.4%	Severity of extracranial carotid artery stenosis (OR, 6.59)
2000[48]	19,224	P	1.4%	Calcified aorta (OR, 3.013); prior stroke (OR, 1.909); increasing age—null of 60 (OR, 1.522 per 10 yr); pre-existing carotid artery disease (OR, 1.590); duration of CPB (OR, 1.27 per 60 min); renal failure (OR, 2.032); PVD (OR, 1.62); cigarette smoking in past year (OR, 1.621); DM (OR, 1.373)
2001[49]	6682	PO	1.5%	Age > 70 (OR, 5.4); LVEF < 40% (OR, 4.1); history of CVA/TIA (OR, 3.0); normothermic CPB (OR, 2.2); DM (OR, 1.9); PVD (OR, 1.9)
2001[50]	16,528	PO	2.0%	CRI (OR, 2.8); recent MI (OR, 2.5); previous stroke (OR, 1.9); carotid artery disease (OR, 1.9) hypertension (OR, 1.6); DM (OR, 1.4); age > 75 yr (OR, 1.4); preoperative moderate/severe LV dysfunction (OR, 1.3); postoperative low cardiac output syndrome (OR, 2.1); postoperative atrial fibrillation (OR, 1.7)
2002[51]	2711	PO	2.7%	Past stroke (OR, 2.11); hypertension (OR, 1.97); age 65-75 (OR, 2.39); age ≥ 75 (OR, 5.02)
2002[52]	4077 (45 stroke cases; 4032 "no stroke" control subjects)	P, CC	1.1%	Increasing age (OR, 1.06 per year); unstable angina (OR, 2.69); preoperative creatinine > 150 mcg/mL (OR, 2.64); previous CVA (OR, 2.26); pre-existing PVD (OR, 2.99); salvage operation (OR, 16.1)
2003[53]	2972 (1900 men; 1072 women)	PO	2.8% women, 0.95% men ($p < 0.001$)	Women: history of stroke (OR, 44.5); ascending aortic atherosclerosis (OR, 2.1); low cardiac output (OR, 6.7); DM (OR, 2.2) Men: history of stroke (OR, 305.8)
2003[54]	4567	PO	2.5%	Cerebrovascular disease (OR, 2.66); PVD (OR, 2.33); number of periods of aortic cross clamping (OR, 1.31 for each period); LV dysfunction (OR, 1.82); increased age (OR, 1.28 for each 10 years); nonelective surgery (OR, 1.83; $p = 0.08$)

TABLE 6-3 **Perioperative Stroke Risk Factor Studies in the Cardiac Surgery Population** (Continued)

Study, Year	Number of Subjects	Study Design	Stroke Incidence	Significant Risk Factors (Multivariate Analysis Unless Otherwise Noted)
2003[55]	11,825	P	1.5%	Prediction model incorporated known preoperative RFs: age, DM, urgent surgery, EF < 40%, creatinine ≥ 2.0; additional intraoperative and postoperative RFs: CPB 90-113 min (OR, 1.59), CPB ≥ 114 min (OR, 2.36), atrial fibrillation (OR, 1.82), prolonged ionotrope use (OR, 2.59)
2003[6]	16,184 total: group 1—8917 CABG only; group 2—1842 beating heart CABG; group 3—1830 aortic valve surgery; group 4—708 mitral valve surgery; group 5—381 multiple valve surgery; group 6—2506 CABG + valve surgery	PO	4.6% overall; 3.8% in 1; 1.9% in 2; 4.8% in 3; 8.8% in 4; 9.7% in 5; 7.4% in 6	History of CVD (OR, 3.55); PVD (OR, 1.39); DM (OR, 1.31); hypertension (OR, 1.27); urgent operation (OR, 1.47); preoperative infection (OR, 2.39); prior cardiac surgery (OR, 1.33); CPB time > 2 h (OR, 1.42); intraoperative hemofiltration (OR, 1.25); high transfusion requirement (OR, 6.04); beating heart CABG (OR, 0.53; CI, 0.37-0.77)
2005[56]	4380	PO	1.2%	History of stroke (OR, 6.3); DM (OR, 3.5); older age (OR, 1.1); temperature of CPB was insignificant
2005[57]	783 total: group 1—582 CABG only; group 2—101 single VR; group 3—70 combined CABG + VR; group 4—30 multiple VR	R	CVA and TIA: 1.7% in 1; 3.6% in 2; 3.3% in 3; 6.7% in 4	Previous neurologic event (OR, 6.8); age > 70 (OR, 4.5); preoperative anemia (OR, 4.2); aortic atheroma (OR, 3.7); duration of myocardial ischemia (OR, 2.8); number of bypasses (OR, 2.3); LVEF < 0.35 (OR, 2.2); insulin-dependent DM (OR, 1.5)
2006[58]	810	PO	CVA and TIA: 1.85%	Redo cardiac surgery (OR, 7.45); unstable cardiac status (OR, 4.74); history of cerebrovascular disease (OR, 4.14); PVD (OR, 3.55); preoperative use of statins (OR, 0.24; CI, 0.07-0.78)
2007[59]	5085	PO	2.6%	Female sex (OR, 1.7); age > 60 (OR, 1.2 per 5-yr interval); aortic surgery (OR, 3.9); previous stroke (OR, 2.1); critical preoperative state (OR, 2.5); poor ventricular function (OR, 2.0); DM (OR, 1.7); PVD (OR, 1.8); unstable angina (OR, 1.7); pulmonary hypertension (OR, 1.8)
2007[60]	720	PO	3.9% in men; 1.3% in women ($p = 0.066$)	Prior cerebral infarction (OR, 1.987 per grade); atherosclerosis of ascending aorta (OR, 1.990 per grade)
2011[61]	9122 (7839 CABG, 297 off-pump CABG, 986 combined CABG and valve procedures)	PO	2.7% (overall); 1.6% (early: on extubation); 1.1% (late: symptom-free period after extubation)	For early strokes: age ≥ 80 (OR, 5.63); creatinine >200 μmol/L (OR, 4.90); severe aortic wall calcification (OR, 5.32); CPB time >150 min (OR, 2.96) For late strokes: female sex (OR, 2.18); unstable angina (OR, 1.86); prior CVA (OR, 2.16); inotropic support (OR, 2.17); postoperative atrial fibrillation (OR, 2.56)
2007[62]	171 serial TEVAR cases	PO	5.8%	Prior stroke (OR, 9.4); involvement of the proximal descending thoracic aorta (OR, 5.5); CT demonstrating severe atheromatous disease of aortic arch (OR, 14.8)
2007[63]	606 stent/graft cases	PO	3.1% stroke; 2.5% paraplegia	Stroke: duration of the intervention (OR, 6.4); female sex (OR, 3.3) Paraplegia: left subclavian artery covering without revascularization (OR, 3.9); renal failure (OR, 3.6); concomitant open abdominal aorta surgery (OR, 5.5); three or more stent grafts used (OR, 3.5)

CABG, coronary artery bypass grafting; *CC,* case control; *CEA,* carotid endarterectomy; *CI,* confidence interval; *CPB,* cardiopulmonary bypass; *CRI,* chronic renal insufficiency; *CT,* computed tomography; *CVA,* cerebrovascular accident (stroke); *DM,* diabetes mellitus; *EF,* ejection fraction; *LV,* left ventricular; *MI,* myocardial infarction; *OR,* odds ratio; *P,* prospective; *PO,* prospective observational; *PVD,* peripheral vascular disease; *R,* retrospective; *RF,* risk factor; *TIA,* transient ischemic attack; *TEE,* transesophageal echocardiography; *TEVAR,* thoracic endovascular aortic repair; *VR,* valve replacement.

TABLE 6-4 **Summary of Meta-Analyses on Carotid Surgery and Stroke**

Study, Year	Number of Trials	Number of Subjects (intervention/no intervention)	Intervention	Control	Outcomes
1999[64]	23 publications from 3 randomized studies (NASCET, ECST, VACSP)	6078 (3777/2301)	Surgery	Medical treatment	Stenosis 70%-99% (absolute RR, 6.7%; NNT, 15 to prevent stroke or death) Stenosis 50%-69% (absolute RR, 4.7%; NNT, 21) Stenosis < 49% (absolute risk increase, 2.2; NNH, 45)
2004[65]	7 randomized; 41 nonrandomized	554 in randomized; 25,622 in nonrandomized	Local anesthesia for CEA	General anesthesia for CEA	Meta-analysis of nonrandomized studies showed significant reduction in risk of stroke (31 studies), but this was not shown in analysis of randomized studies. Conclusion is that there is insufficient evidence.
2005[66]	62 (16 studies evaluated perioperative CVA and gender differences)	9131 female; 17,559 male	Female	Male	Female sex (OR, 1.28; CI, 1.12-1.46) Also evaluated risk of nonfatal perioperative CVA based on age: age ≥ 75 (OR, 1.01; CI, 0.8-1.3); age ≥ 80 (OR, 0.95)
2005[67]	3 randomized studies (asymptomatic carotid stenosis)	5223	CEA	Medical	Perioperative CVA or death rate: 2.9% Perioperative CVA or death or subsequent ipsilateral CVA: benefit for CEA (RR, 0.71; CI, 0.55-0.90)
2009[68]	10 randomized studies	2593 (1304/1289)	CEA	Endovascular treatment	CVA (OR, 1.37; CI, 0.99-1.90) Death (OR, 1.14; CI, 0.54-2.40) MI (OR 0.24; CI, 0.05-1.04)
2011[69]	3 randomized studies (symptomatic carotid stenosis)	6090 (3336/2754)	CEA	Medical	Overall CVA or death rate: 7.1% For near occlusion (risk ratio, 0.95; CI, 0.59-1.53) For 70%-99% occlusion (RR, 0.53; CI, 0.42-0.67) For 50%-69% occlusion (RR, 0.77; CI, 0.63-0.94) For 30%-49% occlusion (RR, 0.97; CI, 0.79-1.19) For <30% occlusion (RR, 1.25, CI; 0.99-1.56)

CEA, carotid endarterectomy; *CI,* confidence interval; *CVA,* cerebrovascular accident (stroke); *ECST,* European Carotid Surgery Trial; *MI,* myocardial infarction; *NASCET,* North American Symptomatic Carotid Endarterectomy Trial; *NNH,* number needed to harm; *NNT,* number needed to treat; *OR,* odds ratio; *PVD,* peripheral vascular disease; *RR,* risk reduction; *TIA,* transient ischemic attack; *VACSP,* Veterans Affairs Cooperative Studies Program.

Because the aforementioned meta-analyses did not address the main theme of this section (risk factors for perioperative stroke), Table 6-5 includes the major multicenter randomized clinical trials for CEA.

INTERPRETATION OF DATA

The data presented are vast, but unfortunately the quality of many studies is suboptimal, especially in the general surgery group. Most studies of perioperative stroke in general surgery are older and often without rigorous statistical analysis. Several risk factors are commonly seen in this subset: prior history of CVA, heart disease, hypertension, diabetes, peripheral vascular disease, and atrial fibrillation. The most powerful predictor is probably prior history of CVA.[31]

In the cardiac literature, the concept of increased surgical risk in women is prevalent and unique. In addition, older age, a diseased proximal aorta, peripheral vascular disease, history of stroke, poor cardiac function, chronic renal insufficiency, hypertension, diabetes, atrial fibrillation, urgent surgery, and prolonged bypass time are prevalent risk factors in multivariate analyses. The most powerful predictors are likely prior CVA, surgery on the aorta, aortic disease burden, and perhaps female sex.[45,53] The two studies on aortic surgery again reveal female sex and surgery on the proximal aorta as substantial risk factors.[62,63]

TABLE 6-5 **Summary of Randomized Controlled Trials of Carotid Endarterectomy**

Study, Year	Number of Subjects (intervention/no intervention)	Study Design	Intervention	Control (no intervention)	Outcomes
1991[70]	Mild stenosis (0%-29%): 219 intervention/155 no intervention; Severe stenosis (70%-99%): 455 intervention/323 no intervention	RCT of symptomatic carotid stenosis	CEA	No CEA	Perioperative CVA/death (30 days): 3.7% severe stenosis, 2.3% mild stenosis Adverse 30-day outcome predicted by high blood pressure (SBP, >160 mm Hg), rapid surgery (>1 hr)
1991[71]	328 intervention; 331 no intervention	RCT of severe (70%-99%) symptomatic (TIA or nondisabling CVA within past 120 days) carotid stenosis	CEA	Medical management	Perioperative CVA (30 days): 5.5% Absolute risk reduction for intervention group for 2 years: 17% Medical management group*: 0-5 RF: 17% risk CVA in 2 yr 6 RF: 23% risk CVA in 2 yr ≥7 RF: 39% risk CVA in 2 yr
1995[72]	825 intervention; 834 no intervention	RCT of asymptomatic carotid stenosis ≥ 60%	CEA	Medical management	Perioperative CVA/death (30 days after randomization): 2.3% Trend toward better outcome in men but not statistically significant ($p = 0.1$) NNT, 19 (to prevent one stroke in 5 yr)
1998[73]	1108 intervention; 1118 no intervention	RCT of symptomatic carotid stenosis (50%-69%)	CEA	Medical management	Perioperative CVA risk: 6.16% Univariate analysis: contralateral carotid occlusion (RR, 2.3); left-sided carotid disease (RR, 2.3); daily dose of less than 650 mg ASA (RR, 2.3); absence of history of MI or angina (RR, 2.2); lesion on imaging ipsilateral to operative artery (RR, 2.0); DM (RR, 2.0); DBP > 90 mm Hg (RR, 2.0)
1998[74]	1811 intervention; 1213 no intervention	RCT of all symptomatic carotid stenosis	CEA	Medical management (as long as possible)	Perioperative CVA risk: 6.8% Cox proportional hazards model of major stroke or death within 5 days postoperatively: female sex (HR, 2.39); age in years at randomization (HR, 0.959 per year); occluded symptomatic carotid (HR, 12.77)
1999[75]	1395 intervention; 1409 no intervention	DBRCT of all patients scheduled for CEA	Low-dose ASA (81 or 325 mg)	High-dose ASA (650 or 1300 mg)	Perioperative any CVA/death (30 days): 4.7% in low dose and 6.1% in high dose (RR, 1.29; CI, 0.94-1.76). Univariate analysis for perioperative stroke/death: contralateral carotid occlusion (RR, 2.3); history of DM (RR, 1.9); taking 650 mg ASA or more (RR, 1.8); endarterectomy of the left carotid (RR, 1.6); ipsilateral TIA or CVA in prior 6 months (RR, 1.4); history of contralateral CVA (RR, 1.47); insulin therapy (RR, 1.78)
2004[76]	1560 intervention/ 1560 no intervention	RCT of asymptomatic carotid stenosis ≥ 60%	Immediate CEA	Medical management	Perioperative CVA (30 days): 2.79%. Perioperative CVA RF not assessed. Conclusion: in those younger than 75 years of age with asymptomatic stenosis of 70% or more, CEA cut 5-yr stroke risk from 12% to 6%

ASA, aspirin; *CEA,* carotid endarterectomy; *CHF,* congestive heart failure; *CI,* confidence interval; *CVA,* cerebrovascular accident (stroke); *DB,* double-blind; *DBP,* diastolic blood pressure; *DM,* diabetes mellitus; *HR,* hazard ratio; *MI,* myocardial infarction; *NNH,* number needed to harm; *NNT,* number needed to treat; *OR,* odds ratio; *RCT,* randomized controlled trial; *RF,* risk factor; *RR,* risk reduction; *SBP,* systolic blood pressure; *TIA,* transient ischemic attack.

*Selected RFs: age > 70, male sex, SBP > 160, DBP > 90, recency (<31 days), recent event was stroke not TIA, degree of stenosis (>80%), presence of ulceration on angiogram, history of smoking, hypertension, MI, CHF, DM, intermittent claudication, elevated lipid levels.

Review of the carotid literature reveals that increased disease burden on the surgical side as well as contralateral occlusion (which will lessen collateral flow) are substantial factors. Prior stroke or transient ischemic attack (TIA) (on the surgical side), hypertension (especially diastolic blood pressure > 90 mm Hg), diabetes, and left-sided carotid surgery are also significant risk factors. Finally, women do not benefit from carotid surgery as much as men; this has been a constant significant finding or trend across nearly all studies.

AREAS OF UNCERTAINTY

In the cardiac literature, the most common question is whether off-pump CABG reduces perioperative stroke. This was assessed by four meta-analyses. It appears that off-pump CABG has a trend toward preventing perioperative stroke. It is also likely that a "no-touch" technique substantially reduces stroke risk in those with a heavily diseased aorta. In addition to technique, additional controversies revolve around intraoperative technologies to help prevent stroke (i.e., transesophageal echocardiography [TEE], epiaortic ultrasound, and intra-aortic filtration devices), as well as the timing of CEA for patients who have concomitant carotid artery stenosis.

In the carotid literature, many of the controversies are those that are addressed in the meta-analyses. One question is whether the use of local anesthesia instead of general anesthesia will reduce stroke risk. The conclusion is that we need more prospective studies to come to a verdict, although there is a suggestion that local anesthesia may be superior.[65] The ASA and Carotid Endarterectomy (ACE) trial[75] seemed to clear up the controversy as to whether high-dose aspirin was superior to more conventional low-dose treatment. Studies also are attempting to identify which subset of the population will benefit most from CEA. Again, it appears that women benefit less. Finally, as technology improves and our ability to diagnose carotid stenosis evolve, the exact cutoff for surgery and the optimal timing should be clarified.

SUMMARY

Stroke is simply a devastating event, the incidence of which is augmented in the perioperative period. The most obvious consequence of perioperative stroke is worsened outcomes, particularly in terms of hospital mortality. A representative number for hospital mortality after CABG is about 24.8%[48] and about 33% for thoracic endovascular aortic repair (TEVAR).[62] In another large database of 35,733 patients, the 1-year survival rate after stroke in the CABG population was 83%.[77] Additionally, intensive care unit stay and hospital stay were increased, as well as health dollars spent.

One positive view of this phenomenon of perioperative cerebral ischemia is that, as an aggregate, surgery patients have a 0.08% to 0.7% base chance of having a perioperative stroke.[1] The risk of this event is altered by the presence or absence of risk factors (see Table 6-1). This basic risk of stroke likely overlaps into all surgical procedures, including CABG and CEA. The success of the many predictive scales for postoperative stroke relies on accurately incorporating these risk factors. The augmented risk in CABG and CEA is likely from technical aspects of the surgery itself (accounting for postoperative events), as well as the more tumultuous postoperative course (e.g., electrolyte abnormalities, dehydration, arrhythmias, infections, and repeated procedures).

In the cardiac literature, it appears that continued improvement in stroke rates is very feasible based on proper use of alternate techniques and multiple available technologies. As discussed earlier, off-pump CABG likely has a lower stroke risk as compared with conventional CABG.[38,39] One study revealed a promising off-pump CABG perioperative stroke/TIA rate of 0.14%,[78] an exceptionally low risk rate.

Another major issue is how to deal with clot burden in the ascending aorta and arch. A study by Mackensen and colleagues[79] demonstrated that cerebral emboli, as detected by intraoperative transcranial Doppler, were significantly associated with atheroma in the ascending aorta and arch but not in the descending aorta. These emboli may be responsible for intraoperative stroke, as well as other cerebral injuries that may lead to postoperative delirium or long-term cognitive dysfunction. Logically, the use of novel available technologies may reduce these outcomes. In Europe, the use of intra-aortic filtration appeared to improve neurologic outcomes postoperatively.[80,81] In one study,[80] 402 patients were nonvoluntarily assigned to intra-aortic filtration. The predicted number of strokes was estimated with the use of the Stroke Risk Index. Six neurologic events occurred, whereas the Stroke Risk Index predicted 13.7.

Both epiaortic ultrasound and TEE have been used to assess clot burden of the ascending aorta and aortic arch. In cases in which aortic atheroma is severe (>5 mm), altering technique (no-touch, off-pump) may be paramount in importance. In one study, using both TEE and epiaortic ultrasound resulted in no strokes in the high-risk group (22 patients).[82] In cases of moderate disease (3 to 5 mm), careful choice of aortic cannulation site and minimal cross-clamping (single clamp) seemed to have improved outcomes.[82,83] In addition to the studies already discussed, there is evidence that a no-touch technique, in the right setting, may improve overall outcomes, aside from overt stroke. In a review of 640 off-pump CABG cases,[84] 84 patients had their surgeries modified with a no-touch technique. In the no-touch group, the postoperative delirium rate improved (8% versus 15%, $p = 0.12$), and there was a lower incidence of stroke (0% versus 1%), although numbers were too small to reach statistical significance.

The improvements in carotid surgery will likely revolve, in part, around optimal patient selection, timing, and intervention. Current investigations, for example, are considering the optimal use of carotid artery stenting (CAS). Meta-analyses of randomized controlled trials significantly favored CEA over CAS with regard to death or any stroke at 30 days, risk of death, any stroke or myocardial infarction at 30 days, ipsilateral stroke at 30 days, any stroke at 30 days, death or stroke at 6 months, and the risk of procedural failure.[68,85] CAS, however, may be

suitable in patients with difficult anatomy, concomitant coronary disease awaiting revascularization, and in those patients with contralateral carotid occlusion.[86-88]

Finally, one must mention the possibility of identifying, using, and developing novel neuroprotective drugs. There is evidence that preoperative use of statins may be protective for cardiac surgery.[58] In addition, one study showed that perioperative beta-blockade during cardiac surgery may reduce the risk of neurologic injury.[89] Several anesthetic agents such as thiopental and isoflurane may also provide some level of neuroprotection,[90] but this topic is controversial.

GUIDELINES

There are no specific guidelines on the risk factors for perioperative stroke.

AUTHORS' RECOMMENDATIONS

- Precise history, especially with regard to history of stroke or transient ischemic attack
- Optimal medical management for stroke risk factors. Consider initiation of statin therapy before coronary artery bypass grafting (CABG)[58]
- Continuation of antiplatelet therapy and anticoagulation whenever feasible
- Preoperative echocardiogram: to help risk stratify those patients with atrial fibrillation (heart failure and atrial fibrillation in combination increases risk of stroke)
- Consider the use of regional techniques instead of general anesthesia when feasible (i.e., carotid endarterectomy [CEA])
- Intraoperatively: maintain mean arterial pressure as near as possible to preoperative baseline, especially in patients at highest risk of stroke
- Intraoperatively: maintain glycemic control as per American Diabetes Association guidelines (as close as possible to 110 but < 180 mg/dL). Some studies support this goal in cardiac surgery, but evidence remains controversial[91-94]
- CABG patients: screening carotid ultrasound with prior CEA, if necessary
- CABG patients: intraoperative use of transesophageal echocardiography and/or epiaortic ultrasound to optimize aortic cannulation and clamping (versus use of no-touch technique)
- CABG patients: strongly consider use of beta-blockade[89]
- Postoperative CABG: monitor for atrial fibrillation with telemetry for at least 3 days; consider anticoagulation for 30 days after return of sinus rhythm
- Postoperative CABG: maintain electrolytes and intravascular volume
- Postoperative CABG and CEA: initiate antiplatelet therapy, as this can reduce risk of perioperative cerebrovascular accident without increasing bleeding risk[77,78]
- Avoid and promptly treat postoperative (or preoperative) infections
- Prompt neurologic consultation once a potential deficit is identified. Depending on surgical procedure, options such as intravenous tissue plasminogen activator, intra-arterial tissue plasminogen activator, mechanical thrombectomy, and clot retrieval may be considered

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CHAPTER 7

Should We Delay Surgery in the Patient with Recent Cocaine Use?

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INTRODUCTION

Prevalence and Epidemiology

Cocaine abuse and addiction continue to be a problem that plagues the United States and many other countries. Data from the U.S. Drug Abuse Warning Network (DAWN) showed that cocaine accounted for 43% of the 2.1 million drug abuse emergency department visits that occurred during 2009.[1] The National Survey on Drug Use and Health (NSDUH) estimates that 5 million Americans are regular users of cocaine, 6000 use the drug for the first time each day, and more than 30 million have tried cocaine at least once.[2] On the basis of these data, practicing anesthesiologists will likely come across cocaine-abusing patients, regardless of the setting of their practices.

The classic profile of patients reported to experience cocaine-related myocardial ischemia is typically a young, nonwhite, male cigarette smoker with no other significant risk factors for atherosclerosis.[3] However, this profile no longer holds true as the problem becomes more severe and is not confined to a particular race or gender. Cocaine abuse in parturients has been the focus of attention lately, and the reported incidence is between 11.8% and 20%.[4,5]

Pharmacokinetics and Mechanism of Action

Cocaine produces prolonged adrenergic stimulation by blocking the presynaptic uptake of sympathomimetic neurotransmitters, including norepinephrine, serotonin, and dopamine. The euphoric effect of cocaine, the cocaine high, results from prolongation of dopamine activity in the limbic system and the cerebral cortex. Cocaine can be taken orally, intravenously, or intranasally. Smoking the free base (street name for the alkalinized form of cocaine) results in very effective transmucosal absorption and a high plasma concentration of cocaine. It is metabolized by plasma and liver cholinesterase to water-soluble metabolites (primarily benzoylecgonine and ecgonine methyl ester [EME]), which are excreted in urine. The serum half-life of cocaine is 45 to 90 minutes; only 1% of the parent drug can be recovered in the urine after it is ingested.[6] Thus cocaine can be detected in blood or urine only several hours after its use. However, its metabolites can be detected in urine for up to 72 hours after ingestion, which provides a useful indicator for recent use.[7] Hair analysis can detect use of cocaine in the preceding weeks or months.[8] Table 7-1 summarizes the pharmacokinetics of cocaine with different routes of administration.

ANESTHETIC IMPLICATIONS OF COCAINE ABUSE

Acute effects of cocaine toxicity of interest to the anesthesiologist can be summarized as follows:

- Cardiovascular effects
- Pulmonary effects
- Central nervous system (CNS) effects
- Delayed gastric emptying
- Drug–drug interactions

Cardiovascular Effects

Cardiovascular effects of cocaine are largely due to the sympathetic stimulation resulting from inhibition of the peripheral uptake of norepinephrine and other sympathomimetic neurotransmitters. Central sympathetic stimulation has been suggested as an alternative mechanism to explain the exaggerated sympathetic response.[9,10] The resulting hypertension, tachycardia, and coronary artery vasospasm are responsible for the myocardial ischemia seen with cocaine toxicity.[11,12] In addition, there is evidence that cocaine activates platelets, increases platelet aggregation, and promotes thrombus formation.[13] Knowledge of the mechanism of myocardial ischemia in patients with cocaine abuse is key for effective treatment. Classically, beta-blockers are avoided because their use may lead to unopposed alpha-mediated coronary vasoconstriction.[14-16] This concept has been recently challenged, and there is some evidence to support the use of beta-blockers in cocaine-related myocardial ischemia.[17] Esmolol is used for treatment of cocaine-induced myocardial ischemia because of its short duration of action and the ability to titrate the dose to a target heart rate.[18,19] Labetalol offers some advantage in that regard because of its combined alpha- and beta-receptor blocking effect.[20,21] Alpha-blockers and nitroglycerin have been used effectively for symptomatic treatment.[22-24]

A major concern in the anesthetic management of the cocaine-abusing patient is the occurrence of cardiac arrhythmias. These include ventricular tachycardia, frequent premature ventricular contractions, or torsades de

TABLE 7-1 **Pharmacokinetics of Cocaine According to the Route of Administration**

Route of Administration	Onset of Action	Peak Effect	Duration of Action
Inhalation (smoking)	3-5 sec	1-3 min	5-15 min
Intravenous	10-60 sec	3-5 min	20-60 min
Intranasal/intramucosal	1-5 min	15-20 min	60-90 min
Gastrointestinal	Up to 20 min	Up to 90 min	Up to 180 min

pointes.[25] Myocardial ischemia has been suggested as the underlying mechanism for these arrhythmias[26]; however, cocaine-induced sodium and potassium channel blockade is currently believed to be more important. This cation channel blockade results in QRS and QTc prolongation,[27] which is considered to be the primary mechanism for induction of these cocaine-induced arrhythmias.[12,28]

Aortic dissection[29] and ruptured aortic aneurysm[30,31] have been reported with short-term abuse. Peripheral vasoconstriction may mask the picture of hypovolemia in the setting of acute cocaine toxicity.

Long-term use of cocaine can cause left ventricular hypertrophy, systolic dysfunction, and dilated cardiomyopathy.[32] Repetitive cocaine administration is associated with the development of early and progressive tolerance to systemic, left ventricular, and coronary vascular effects of cocaine. The mechanism of tolerance involves neither impaired myocardial nor coronary vascular responsiveness to adrenergic stimulation but rather attenuated catecholamine responses to repetitive cocaine administration.

Pulmonary Effects

Approximately 25% of individuals who smoke crack cocaine develop nonspecific respiratory complaints.[33] Within 1 to 48 hours, the smoking of cocaine may produce a combination of diffuse alveolar infiltrates, eosinophilia, and fever that has been termed *crack lung*.[34,35] Long-term cocaine exposure can produce diffuse alveolar damage, diffuse alveolar hemorrhage, noncardiogenic pulmonary edema, and pulmonary infarction.[36]

Central Nervous System

Stimulation in acute toxicity can lead to euphoria, psychomotor agitation, violence,[37] hyperthermia,[38] and seizures.[39-41] Cocaine-induced psychomotor agitation can cause hyperthermia when peripheral vasoconstriction prevents the body from dissipating the heat being generated from persistent agitation. The resulting fever has to be differentiated from other causes of hyperthermia in the setting of general anesthesia. Cocaine is associated with both focal neurologic deficits and coma. Possible causes include vasoconstriction (i.e., transient ischemic attack or ischemic stroke) and intracerebral hemorrhage.[42-44] Minimum alveolar concentration (MAC) of halothane and other inhalational agents is increased with the long-term use of cocaine.[42-44] Cocaine was found to delay gastric emptying via a central mechanism.[45] This effect becomes more relevant in the setting of trauma and obstetrics. Cocaine and amphetamine–regulated transcript (CART) is a chemical that acts in the CNS to inhibit gastric acid secretion via brain corticotropin–releasing factor system.[46,47]

Drug–Drug Interactions

Even though cocaine is a known inhibitor of the enzyme cytochrome P450 2D6,[48] pharmacokinetic drug–drug interactions (DDIs) are generally unlikely to be clinically relevant. However, pharmacodynamic DDIs need to be taken into account in the perioperative period. Cocaine's potent sympathomimetic effects may act synergistically with other drugs (e.g., stimulants, anticholinergic agents, and noradrenergic reuptake inhibitors) to produce an array of undesirable side effects (e.g., blurred vision, constipation, tachycardia, urinary retention, arrhythmias, and other effects). Synergistic pressor effects can produce vascular compromise that can precipitate cardiac ischemia or cerebrovascular accidents. Ketamine may exacerbate the sympathomimetic effect of cocaine.[49] Halothane and xanthine derivatives sensitize the myocardium to the arrhythmogenic effect of epinephrine and should be avoided as well.[50] Cocaine has been reported to alter the metabolism of succinylcholine because they both compete for metabolism by plasma cholinesterases.[51,52] However, Birnbach[53,54] found that succinylcholine can be used safely in standard doses. Cigarette smoking was found to enhance cocaine-induced coronary artery vasospasm in the atherosclerotic segments when compared with the vasoconstriction produced by cocaine alone.[55] This effect was not evident in normal coronary arteries.

OPTIONS

The anesthesiologist has to answer the following questions during perioperative management of the cocaine-abusing patient: How safe is it to anesthetize patients with short-term cocaine abuse? How much time should lapse after the last positive toxicology screening test or self-reported use before it is "safe" to proceed? Should we rely on the results of the urine drug screen alone, or should we also consider clinical signs and symptoms of acute toxicity before making the decision about whether to proceed with or delay an elective surgery? Many anesthesia practitioners would prefer to delay such surgery until the patient tests negative for cocaine or has not been using cocaine for 72 hours. In a recent survey of the chiefs of the anesthesia departments in the Veterans Administration (VA) health system,[56] more than 60% of the VA

facilities would cancel and/or delay scheduled elective surgery if patients tested positive for cocaine in their urine drug screen. This decision is more difficult nowadays because of the increased costs and wastage of resources associated with routine cancellation of these cases.

EVIDENCE

Evidence to Support Perioperative Risk of General Anesthesia with Acute Cocaine Toxicity

The risk of acute myocardial infarction (MI) is increased by a factor of 24 in the 60 minutes after the use of cocaine in persons who otherwise are at relatively low risk of myocardial ischemia.[57] A meta-analysis, done in 1992, reported a total of 92 cases of cocaine-related MI.[58] Two thirds of patients had their MI within 3 hours of the use of cocaine (with a range of 1 minute to 4 days). Data from the third National Health and Nutrition Examination Survey (NHANES III) found that 1 of every 20 persons ages 18 to 45 years reported regular use of cocaine.[59] This survey demonstrated that the regular use of cocaine was associated with an increased likelihood of nonfatal MI. One of every four nonfatal MI in young patients was attributable to the frequent use of cocaine in this survey. No increased risk of nonfatal stroke was seen in this population associated with frequent or infrequent use of cocaine. The focus of research in this area is to determine risk factors for developing MI in cocaine-abusing patients. A recent study suggested that age, pre-existing coronary artery disease (CAD), hyperlipidemia, and smoking are associated with the diagnosis of MI among patients hospitalized with cocaine-associated chest pain.[60] Cocaine-induced myocardial ischemia can occur regardless of whether CAD was pre-existing. However, it has been shown that coronary artery vasospasm tends to be more severe in the diseased segments of the coronary vessels when compared with the normal coronary arteries in response to intranasal cocaine in a dose of 2 mg/kg of body weight.[61]

Most of the cases of cocaine-related myocardial ischemia are reported in the emergency medicine and internal medicine literature after recreational use of cocaine. Seven case reports of cocaine-induced myocardial ischemia were in the setting of the use of cocaine for topical anesthesia for ear, nose, and throat (ENT) procedures.[62-68] In some of these cases, the patients were under general anesthesia. Two more cases of myocardial ischemia were reported with patients under general anesthesia after recreational use of cocaine.[69,70] Other cardiac events reported with patients under general anesthesia with short-term use of cocaine include prolonged QT interval,[71] ventricular fibrillation,[72] and acute pulmonary edema.[73,74] One case report described a patient coming to the operating room after a motor vehicle accident with a white foreign body in the back of the oropharynx that proved to be crack cocaine.[75] This case goes on to report wide swings of blood pressure, patient agitation, and hypotension resistant to treatment with ephedrine.

One of the few studies that demonstrated the interaction between cocaine and general anesthesia was that by Boylan and colleagues.[76] They found that increasing the depth of anesthesia with isoflurane from 0.75 MAC to 1.5 MAC in their swine model was not associated with reversal of, or decrease in, the hemodynamic responses to cocaine infusion.[76] The observed responses were increase in systemic vascular resistance, ventricular arrhythmias, diastolic hypertension, and reversal of the endocardial/epicardial blood flow. Immediate administration of cocaine at a dose equivalent to doses abused by cocaine abusers decreased cerebral blood flow (CBF), cerebral blood volume (CBV), and tissue hemoglobin oxygenation StO_2 in rats anesthetized with isoflurane[77]; cocaine-induced changes in CBF followed the peak uptake of cocaine in the brain.

Airway management may require special attention in acute cocaine toxicity. Supraglottic edema has been reported in this setting.[78]

The half-life of cocaine ranges from 60 to 90 minutes.[79] A reasonable assumption would be that most of the cocaine-related cardiac events in the perioperative period will happen at a time when the level of the metabolites, not the parent drug, is high in the circulation. The questions now are, "How active are the metabolites of cocaine, and can they affect the coronary vessels to the same extent as cocaine itself?" Brogan and colleagues[80] randomly assigned 18 patients undergoing coronary artery catheterization for evaluation of chest pain to receive either intranasal cocaine or normal saline. They estimated the diameter of the coronary arteries and measured different hemodynamic variables at 30, 60, and 90 minutes. They found that coronary vasospasm happened twice, once at 30 minutes and the second at 90 minutes. The initial coronary artery vasospasm correlated with peak levels of cocaine in the blood. The recurrent vasospasm occurred at 90 minutes, when cocaine was hardly detected in the blood. The levels of the main metabolites of cocaine (benzoylecgonine and EME) were at their peak at this point. Although this study was able to document a temporal relation between recurrent coronary vasospasm and peak levels of cocaine metabolites, it did not prove that these metabolites were the cause of the vasoconstriction. Such proof will come only from assessment of coronary vasoreactivity after direct administration of each metabolite.

Recent studies have suggested that various metabolites of cocaine may exert a substantial influence on a variety of tissues, including the heart, brain, and arterial smooth muscle. In rats, norcocaine, another pharmacologically active metabolite of cocaine, was found to be equipotent to cocaine in inhibiting norepinephrine uptake and in causing tachycardia, convulsions, and death.[81] In feline cerebral arteries in vitro, benzoylecgonine is a more potent vasoconstrictor than cocaine.[82,83]

Evidence to Support the Relative Safety of General Anesthesia in Cocaine-Abusing Patients

The interaction between cocaine and general anesthesia is not well studied. Most of the information is derived

from clinical case reports or animal studies. The few studies that looked into this interaction demonstrated that general anesthesia is probably safe in cocaine-abusing patients if certain conditions are met,[84] especially in the absence of clinical signs of toxicity. Barash and colleagues[85] studied 18 patients undergoing coronary artery surgery to examine whether cocaine in a clinically used dose exerts sympathomimetic effects during general anesthesia. Eleven patients received cocaine hydrochloride as a 10% solution (1.5 mg/kg) applied topically to the nasal mucosa. The other group received a placebo treatment. There were no important differences in cardiovascular function between groups. The rise in plasma cocaine concentration bore no relationship to any changes in cardiovascular function. Administration of topical cocaine did not exert any clinically significant sympathomimetic effect and appeared to be well tolerated in anesthetized patients with CAD. The results of this study should be interpreted cautiously because the doses used for recreational use may well exceed the doses used during this study.

A more recent study by Hill and colleagues[84] studied 40 American Society of Anesthesiologists (ASA) physical status I and II patients between 18 and 55 years of age and demonstrated that individuals undergoing elective surgery requiring general anesthesia who test urine positive for cocaine but who do not show clinical toxicity are at no greater risk than drug-free patients of the same ASA physical status. The authors of this study caution that these results may not be applicable to the cocaine-abusing patient with a QT interval of 500 ms or more on a preoperative electrocardiogram or to those patients whose vital signs indicate acute cocaine toxicity. Another study looked into maternal morbidity in cocaine-abusing parturients undergoing cesarean section with general or regional anesthesia.[86] Cocaine-abusing parturients were at higher risk of peripartum events such as hypertension, hypotension, and wheezing episodes. However, when the analysis was done in a multivariate model, cocaine abuse was not an independent risk factor. There was no increase in the rates of maternal morbidity or death in the cocaine-abusing group. Patients in the two referenced studies[84,86] were relatively young and healthy. Based on the results of these two studies alone, it would be difficult to predict how anesthesia would interact with cocaine in the presence of multiple comorbidities.

Some authors[87] proposed that patients who test positive for cocaine in their urine may undergo necessary surgical and anesthetic care, after an 8-hour period without cocaine, if they are hemodynamically stable and show no clinical signs of acute toxicity. This proposal was based on a survey of oral surgery and anesthesiology training programs in the United States.[87] In the trauma setting, mortality rates and neurologic and cardiac complications during the first 24 hours after admission were not increased among patients testing positive after having a urine cocaine drug screen.[88] Another study did not show a difference in mortality or length of intensive care unit stay between patients with cocaine-positive results and patients with cocaine-negative test results.[89]

Regional Anesthesia and Cocaine-Abusing Patients

Any advantage of regional anesthesia over general anesthesia is controversial. The argument in favor of regional anesthesia, when possible, includes having an awake patient who will be able to communicate chest pain as a sign of myocardial ischemia. If regional anesthesia is selected, potential complications include combative behavior, altered pain perception, cocaine-induced thrombocytopenia, and ephedrine-resistant hypotension. Abnormal endorphin levels and changes in the mu and kappa receptors in the spinal cord may be responsible for pain sensation despite an adequate sensory level with regional anesthesia.[90] The duration of action of spinal narcotics (sufentanil) in labor is shorter in cocaine-abusing parturients relative to control subjects.[91] Many theories have been proposed to explain cocaine-induced thrombocytopenia. These include bone marrow suppression, platelet activation, and an autoimmune response with induction of platelet-specific antibodies. Gershon and colleagues[92] challenged this concept. They concluded that obtaining a routine platelet count before epidural or spinal analgesia in cocaine-abusing parturients is not necessary.

AREAS OF UNCERTAINTY

The "safe" length of time that a surgeon should wait after a patient's last use of cocaine before proceeding with elective surgery is uncertain. In addition, whether the metabolites of cocaine are active and result in effects similar to the parent drug is controversial. Another area of uncertainty is the difference between occasional users and long-term regular users of cocaine in their susceptibility to adverse events under general anesthesia.

GUIDELINES

Currently, no guidelines for perioperative management of cocaine-abusing patients are available. Of the anesthesia chiefs in the VA health system, 65% thought that having guidelines in place would be helpful.[56]

AUTHOR'S RECOMMENDATIONS

- The decision-making process involving anesthetic care of cocaine-abusing patients should be individualized. History and associated comorbidities have to be considered before the decision is made to proceed with elective cases in the setting of known recent cocaine abuse by either self-reporting or urine testing.
- The level of invasive monitoring for each patient should be made on a case-by-case basis.
- Routine testing for cocaine is not necessary if the patient is not showing any signs of clinical toxicity.
- Typically, an elective case should not be delayed if the patient is clinically nontoxic, does not have an

Continued on following page

AUTHOR'S RECOMMENDATIONS (Continued)

extensive cardiac history, and has a normal QT interval on electrocardiography.

- The issue of the interaction between cocaine and general anesthesia remains controversial. Until conclusive clinical trials address this subject, anesthesiologists should continue to individualize the decision of whether to proceed with surgery according to the setting of the practice and their level of comfort in dealing with these cases.

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CHAPTER 8

Should All Antihypertensive Agents Be Continued before Surgery?

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INTRODUCTION

Hypertension affects about 1 billion people and is a leading cause of death worldwide.[1-2] This global prevalence is likely to increase further as the population ages. The relationship between systemic hypertension and cardiovascular risk is continuous and independent of additional risk factors.[1-2] The classification of adult blood pressure in the seventh report of the Joint National Committee recognized this important relationship by introducing the classification of prehypertension to signal a patient cohort at increased future cardiovascular risk who would benefit from early intervention (Table 8-1).[1] This guideline has also classified hypertension as either stage 1 or stage 2, depending on systolic or diastolic pressure profiles (see Table 8-1).[1] Furthermore, there are multiple oral antihypertensive medications that are used alone or in combination for pharmacologic control of hypertension (Table 8-2 and Box 8-1). The cumulative evidence from multiple clinical trials demonstrates that successful ambulatory management of hypertension significantly reduces cardiovascular mortality and morbidity rates.[1,2] Furthermore, it is estimated that about 25% to 50% of surgical patients take long-term medications, in which antihypertensives as a group feature prominently.[3,4] Given all these considerations, it follows that hypertensive patients with various medication regimens will commonly undergo surgical procedures and hence be a common and important part of daily anesthetic practice.[5,6]

OPTIONS

Hypertensive patients undergoing surgery may or may not require adjustment of their antihypertensive regimen to optimize their perioperative management. This decision about perioperative continuity of antihypertensives depends on a risk–benefit analysis (Box 8-2). The possible risks from continuation or discontinuation of ambulatory antihypertensive medication may be categorized as follows:

1. The risk of inadequate control of hypertension with possible increased perioperative cardiovascular risk, if a particular agent is discontinued before surgery
2. The risk of a clinically important withdrawal syndrome or increased perioperative cardiovascular risk if a particular agent is discontinued before surgery
3. The risk of an adverse perioperative cardiovascular event such as hypotension, if a particular agent is continued until surgery

EVIDENCE

What Is the Perioperative Risk of Hypertension?

In the absence of concomitant cardiovascular disease or hypertensive end-organ damage (e.g., left ventricular hypertrophy [LVH] or renal dysfunction), stage 1 hypertension (systolic blood pressure < 160 mm Hg or diastolic blood pressure < 100 mm Hg) does not increase perioperative risk in noncardiac surgery. In a study of 4315 adults older than 50 years undergoing elective major noncardiac surgery, hypertension was not an independent predictor of postoperative cardiac complications.[7] A meta-analysis of more than 30 observational studies found no clinically significant association between hypertension and perioperative complications.[8]

However, the perioperative risk associated with hypertension appears to be significant in cardiovascular procedures and pheochromocytoma resection. Recent trials in adult cardiac surgery have demonstrated that systolic hypertension (defined as a systolic blood pressure > 140 mm Hg), systolic hypervariability (defined as a systolic blood pressure > 140 mm Hg and/or < 80 mm Hg), and pulse pressure hypertension (defined as a pulse pressure > 80 mm Hg) are significant risk factors for perioperative death, stroke, left ventricular dysfunction, and renal failure.[9-16]

With respect to vascular procedures, perioperative hypertension was a significant risk factor for neurologic deficit in not only carotid endarterectomy but also carotid stenting.[15-17] Furthermore, in 128 adults undergoing carotid endarterectomy, hypertension was a significant predictor of perioperative myocardial ischemia ($p < 0.05$).[18] In a recent study of 10,081 adults undergoing vascular surgery, hypertension was significantly associated with perioperative cardiac complications ($p < 0.005$).[19]

TABLE 8-1 Classification and Suggested Management of Blood Pressure in Adults

Blood Pressure Classification	Systolic Blood Pressure		Diastolic Blood Pressure	Lifestyle Modification	Drug Therapy
Normal	<120 mm Hg	and	<80 mm Hg	Encourage	None
Prehypertension	120-139 mm Hg	or	80-89 mm Hg	Yes	None
Stage 1 hypertension	140-159 mm Hg	or	90-99 mm Hg	Yes	Yes
Stage 2 hypertension	≥160 mm Hg	or	≥100 mm Hg	Yes	Yes

Adapted from Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. JAMA 2003;289:2560–72.

TABLE 8-2 Oral Antihypertensive Agents

Antihypertensive Drug Class	Clinical Examples
Thiazide diuretics	Chlorothiazide; indapamide; metolazone
Loop diuretics	Bumetanide; furosemide
Potassium-sparing diuretics	Amiloride; triamterene
Aldosterone-receptor blockers	Spironolactone; eplerenone
Beta-blockers	Atenolol; bisoprolol; metoprolol; nadolol; propranolol; timolol
Beta-blockers with intrinsic sympathomimetic activity	Acebutolol; penbutolol; pindolol
Combined alpha- and beta-blockers	Carvedilol; labetalol
Angiotensin-converting enzyme inhibitors	Benazepril; captopril; enalapril; fosinopril; quinapril; ramipril; trandolapril
Angiotensin receptor blockers	Candesartan; eprosartan; irbesartan; losartan; valsartan
Calcium channel blockers (non-dihydropyridines)	Diltiazem; verapamil
Calcium channel blockers (dihydropyridines)	Amlodipine; felodipine; nicardipine; nifedipine; nisoldipine
Alpha-blockers	Phenoxybenzamine; doxazosin; prazosin; terazosin
Centrally acting agents	Clonidine; methyldopa; reserpine
Direct vasodilators	Hydralazine; minoxidil

Adapted from Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. JAMA 2003;289:2560–72.

BOX 8-1 Classes of Combination Drugs for Hypertension

Angiotensin-converting enzyme inhibitors and calcium channel blockers
Angiotensin-converting enzyme inhibitors and diuretics
Angiotensin receptor blockers and diuretics
Beta-blockers and diuretics
Centrally acting antihypertensives and diuretics
Diuretic and diuretic

BOX 8-2 Considerations for Deciding to Continue or Discontinue Antihypertensive Medications before Surgery

Is discontinuation of the antihypertensive agent associated with a clinically significant withdrawal syndrome?
Is discontinuation of the antihypertensive agent associated with improved perioperative hemodynamics?
Is discontinuation of the antihypertensive agent associated with increased perioperative cardiovascular risk?

In this massive trial, long-term beta-blocker therapy (frequently a surrogate for hypertension) was independently associated with perioperative cardiac complications (odds ratio [OR], 1.4; 95% confidence interval [CI], 1.0 to 1.8; $p = 0.036$).[19] With respect to pheochromocytoma, progressive reduction in perioperative cardiovascular complications has been attributed to contemporary perioperative management of hypertension.[20-22]

The presence of LVH adds significant additional perioperative cardiovascular risk in noncardiac surgery. In the absence of aortic outflow obstruction or hypertrophic cardiomyopathy, LVH typically is a result of systemic hypertension. In a prospective observational study of 405 patients undergoing major vascular surgery, LVH on preoperative electrocardiogram significantly predicted myocardial infarction and/or cardiac death (OR, 4.2; $p = 0.001$).[23] In a study of 474 men with coronary artery disease undergoing major noncardiac surgery, LVH significantly predicted perioperative myocardial ischemia.[24]

In the presence of severe baseline hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg), the relationship to perioperative cardiovascular risk is less clear. A recent meta-analysis demonstrated that these patients may be at more risk but that there was no evidence that delaying surgery reduces this risk.[8] Despite the lack of evidence, expert opinion recommends that, when possible, surgery be delayed for medical control of baseline severe hyperetension.[25-27]

Furthermore, "white coat hypertension" (short-term blood pressure elevation on the day of surgery due

to anxiety) also confers no additional perioperative cardiovascular risk. This entity was the subject of a randomized controlled trial of 989 surgical patients with well-controlled baseline hypertension with diastolic blood pressures greater than 110 mm Hg on the day of surgery, despite anxiolysis with midazolam.[28] Study patients were then randomly assigned to surgery after intranasal nifedipine or delayed surgery with further medical control of hypertension. No outcome difference was detected between groups. However, an important qualifier is that all patients in this study had no previous hypertensive end-organ damage, symptomatic atherosclerotic arterial disease, aortic stenosis, conduction system disease, or pregnancy-induced hypertension.

In summary, perioperative cardiovascular risk due to baseline hypertension alone is significant in the setting of LVH, cardiovascular procedures, pheochromocytoma resection, and possibly when persistently severe. Thus, for surgical patients without these qualifiers, there is minimal additional cardiovascular risk due to worsening hypertension from discontinuing their antihypertensive medications before surgery. Therefore, for most hypertensive patients, perioperative decisions about their antihypertensive regimen are not based on the intrinsic risk due to hypertension but rather on the considerations that follow.

Which Agents Decrease Risk If Continued Perioperatively?

Beta-Blockers (see Chapter 39)

Perioperative beta-blockade has been extensively reviewed in multiple recent multisociety guidelines.[27,29,30] Their consensus is that hypertensive patients receiving beta-blockers should continue to receive beta-blockade perioperatively (Class I recommendation; that is, this recommendation should be followed because the benefit far outweighs the risk). The evidence supporting this recommendation was ranked as level C; that is, the evidence is limited to expert opinion and case reports, mainly about beta-blocker withdrawal.[27,29,30,31]

The beta-blocker withdrawal syndrome was first recognized with propranolol, the first widely available beta-blocker introduced into clinical practice in the 1970s.[31] In a case series, perioperative withdrawal of propranolol was associated with significant myocardial ischemia.[31] A recent prospective observational cohort study of 2588 adult outpatients found that the risk of myocardial infarction was further significantly increased by withdrawal of cardioselective beta-blockade.[32] Because it is already clear that perioperative beta-blockade withdrawal is dangerous, this question is unlikely to be further studied in a prospective trial.

Perioperative beta-blockade in certain at-risk populations is associated with significant reduction in cardiovascular risk. The indications for beta-blockade in perioperative cardiovascular protection in patients with and without hypertension are explored in recent guidelines.[27,29,30]

Given their cardiovascular risk of withdrawal and their perioperative cardiovascular benefit, existing beta-blockade in hypertensive surgical patients should be continued up to the day of surgery and throughout the perioperative period.[27,29,30,33]

Alpha-2 Agonists (Clonidine)

Clonidine is a centrally acting alpha-agonist. It is available in oral, transdermal, and parenteral formulations. Recent high-quality evidence has demonstrated its significant perioperative cardiovascular benefit. In a 2003 meta-analysis of 23 trials (total $N = 3395$), perioperative alpha-2 agonists reduced mortality rate (relative risk, 0.76; 95% CI, 0.63 to 0.91), and myocardial infarction (relative risk, 0.66; 95% CI, 0.46 to 0.94).[34] A subsequent randomized trial ($N = 190$) showed that perioperative clonidine significantly reduced myocardial ischemia (from 31% to 14%; $p = 0.01$) and long-term mortality rate (relative risk, 0.43; 95% CI, 0.21 to 0.89).[35] In a 2009 meta-analysis of 31 trials (total $N = 4578$), perioperative alpha-2 agonists reduced mortality rate (relative risk, 0.66; 95% CI, 0.44 to 0.98; $p = 0.04$) and myocardial infarction (relative risk, 0.68; 95% CI, 0.57 to 0.81; $p < 0.0001$).[36]

The recent multisociety perioperative care guidelines have recommended alpha-2 agonists for control of hypertension in surgical patients with coronary artery disease (Class IIb recommendation, that is, benefit outweighs risk; level of evidence B, that is, evidence from trials that have evaluated limited populations).[27,29] The perioperative cardiovascular benefits of alpha-2 agonists are reviewed comprehensively in a dedicated chapter in this textbook (see Chapter 32).

Perioperative discontinuation of alpha-2 agonists such as clonidine is, however, dangerous in hypertensive patients who have taken this drug class on a long-term basis. Perioperative clonidine withdrawal is associated with severe delirium, hypertension, and myocardial ischemia.[37-38] Recent expert consensus has recommended careful supervision of perioperative clonidine therapy to avoid the deleterious effects of its withdrawal.[6,39-41] Given the risks of withdrawal and the potential cardiovascular benefit, expert consensus recommends that existing therapy with alpha-2 agonists such as clonidine in hypertensive surgical patients should be continued up to the day of surgery and throughout the perioperative period.[39-41]

Calcium Channel Blockers

Calcium channel blockers, including the dihydropyridines, are widely used for the pharmacologic management of hypertension.[1,2,42,43] There are no described withdrawal syndromes related to perioperative discontinuation of calcium channel blockade. Furthermore, a recent meta-analysis (11 studies: total $N = 1007$) has demonstrated that in noncardiac surgery perioperative calcium channel blockade, especially diltiazem, significantly reduced myocardial ischemia (relative risk, 0.49; 95% CI, 0.30 to 0.80), supraventricular tachycardia (relative risk, 0.52; 95% CI, 0.37 to 0.72), and mortality and major morbidity rates (relative risk, 0.35; 95% CI, 0.15 to 0.86).[44] A similar meta-analysis (41 studies: total

$N = 3327$) in cardiac surgery demonstrated that perioperative calcium channel blockade significantly reduced myocardial infarction (OR, 0.58; 95% CI, 0.37 to 0.91; $p = 0.02$), myocardial ischemia (OR, 0.53; 95% CI, 0.39 to 0.72; $p < 0.001$), and supraventricular tachycardia (OR, 0.62; 95% CI, 0.41 to 0.93; $p = 0.02$).[45] Calcium channel blockade was also associated with a trend toward reduced perioperative mortality after coronary artery bypass grafting (OR, 0.66; 95% CI, 0.26 to 1.70; $p = 0.4$).[45] A recent meta-analysis (13 studies: total $N = 724$) has also demonstrated that in kidney transplantation, perioperative calcium channel blockade may significantly reduce the risk of postoperative acute tubular necrosis (relative risk, 0.62; 95% CI, 0.46 to 0.85) and delayed graft function (relative risk, 0.55; 95% CI, 0.42 to 0.73).[46] These nephroprotective effects of calcium channel blockers for kidney transplant recipients were confirmed in a second larger meta-analysis (36 studies: total $N = 2667$), which demonstrated significantly reduced graft loss (risk ratio, 0.75; 95% CI, 0.57 to 0.99) and improved glomerular filtration (mean difference in glomerular filtration rate, 4.5 mL per minute; 95% CI, 2.2 to 6.7).[47]

Therefore, because of the net perioperative outcome benefit, it follows that existing calcium channel blockade in hypertensive surgical patients should be continued throughout the perioperative period. This is the current recommendation from the American College of Physicians, as outlined in their physicians' information and education resource.[41]

Alpha-Blockers

Alpha-blockers are a mainstay of preoperative preparation of patients with pheochromocytoma and are credited with improved perioperative survival in resection of this tumor.[20,21] Preoperative alpha-blockade, including that with the long-acting phenoxybenzamine, is titrated to control hypertension by peripheral catecholamine blockade.[48] Frequently, beta-blockade is added subsequently for control of tachycardia and arrhythmia in the setting of epinephrine-secreting tumors. It is recommended to continue the antihypertensive regimen up to and including the day of surgical resection to minimize preoperative catecholamine-related adverse events.[48,49] This is the current recommendation from the American College of Physicians, as outlined in their physicians' information and education resource.[41]

Regardless of the preoperative antihypertensive regimen, alpha-blockade and/or beta-blockade will persist after tumor resection, depending on the half-life of the agents chosen. Consequently, severe intraoperative hypotension may ensue after tumor removal due to significantly reduced catecholamine secretion, as well as residual alpha- and beta-blockade. This severe hypotension may require aggressive volume resuscitation and support of systemic vascular resistance with vasopressin adminstration.[50,51] Because this intraoperative hypotension is readily managed, it is not an indication to recommend discontinuation of preoperative alpha-blockade on the morning of surgery for resection of pheochromocytoma. The resulting net perioperative benefit is the rationale for the expert recommendation to continue aggressive catecholamine blockade up to the morning of surgery.[41]

Which Agents May Increase Risk If Continued Perioperatively?

Angiotensin System Inhibitors

Pharmacologic blockade of the angiotensin system may be associated with significant intraoperative hypotension, whether due to angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers.[52] This hypotensive risk may be significantly reduced by preoperative discontinuation of these agents. In a randomized trial of 51 vascular surgical patients, discontinuation of ACE inhibitors 12 to 24 hours before anesthetic induction significantly protected against hypotension ($p < 0.05$).[53] In a prospective case-controlled clinical trial of 72 vascular surgical patients, preoperative angiotensin receptor blockade significantly increased hypotension ($p < 0.05$) and vasopressor requirement ($p < 0.001$).[54] A retrospective study of 267 hypertensive patients receiving both types of angiotensin inhibition demonstrated that discontinuation of the angiotensin blockade at least 10 hours before surgery was significantly associated with a reduced risk of intraoperative hypotension.[55] Furthermore, recent randomized trials have demonstrated that intraoperative hypotension due to angiotensin inhibition may be treated effectively with ephedrine, norepinephrine, and/or vasopressin analogs such as terlipressin.[56-59] Therefore, based on the cumulative evidence, the expert recommendation is that angiotensin blockade in hypertensive surgical patients be discontinued on the morning of surgery.[6,41]

Diuretics

Hypokalemia is common in hypertensive patients receiving long-term diuretic therapy. In a randomized trial of 233 hypertensive adults managed with chronic diuretic therapy, the prevalence of hypokalemia (defined as a serum potassium level less than 3.5 mEq/L) was 25%.[60] Perioperative hypokalemia, especially in cardiac surgery, is associated with an increased risk of arrhythmia. In a prospective multicenter trial of 2402 cardiac surgical patients, a serum potassium level less than 3.5 mEq/L significantly predicted serious arrhythmia (relative risk, 2.2; 95% CI, 1.2 to 4.0), intraoperative arrhythmia (relative risk, 2.0; 95% CI, 1.0 to 3.6), and postoperative atrial flutter/fibrillation (relative risk, 1.7; 95% CI, 1.0 to 2.7).[61] Furthermore, a recent large observational trial ($N = 65043$) demonstrated that in noncardiac surgery, diuretic therapy in combination with angiotensin blockade was significantly associated with intraoperative hypotension ($p < 0.05$).[62]

Therefore, because long-term diuretic therapy for hypertension perioperatively may aggravate hypokalemia, risk of arrhythmia, and risk of hypotension, it is reasonable to discontinue this therapy perioperatively, including the day of surgery. This is the current expert recommendation.

TABLE 8-3 **Recommended Preoperative Management of Antihypertensive Medications**

Antihypertensive Drug Class	Recommendation for Morning of Surgery	Sequelae with Discontinuation of Perioperative Therapy	Sequelae with Continuation of Perioperative Therapy
Beta-blockers	Continue	Withdrawal syndrome	Cardiovascular risk reduction
Clonidine	Continue	Withdrawal syndrome	Cardiovascular risk reduction
Calcium channel blockers	Continue	None described	Cardiovascular risk reduction
Alpha-blockers in association with pheochromocytoma	Continue	Severe preoperative and intraoperative systemic hypertension	Systemic hypotension, especially after tumor excision (readily treatable)
Angiotensin blockers (ACEI or ARB)	Discontinue	Significant reduction in risk of intraoperative hypotension	Significant risk of intraoperative hypotension
Diuretics	Discontinue	None described	Possible aggravation of hypokalemia with adverse outcome

ACEI, angiotensin-converting enzyme inhibitors; *ARB,* angiotensin receptor blockers.

AREAS OF UNCERTAINTY

The first area of uncertainty is whether intraoperative hypotension associated with long-term ambulatory angiotensin blockade can be improved with modification of the induction technique. In the referenced prospective trials, the anesthetic induction technique (propofol and narcotic) was highly vagotonic, confounding the observed hypotension with the hypotensive effects due to bradycardia.[53-55] Perhaps vagolysis with preinduction glycopyrrolate would ameliorate hypotension associated with propofol induction in the setting of angiotensin blockade.[63,64] A recent trial documented a significant reduction in hypotension associated with etomidate induction in this setting.[65] Furthermore, it remains to be determined how variations in angiotensin genotype affect the perioperative hypotensive response associated with angiotensin blockade.[66]

The second area of uncertainty is the perioperative effects of the following antihypertensives: direct-acting vasodilators such as hydralazine and centrally acting vasodilators such as reserpine and methyldopa.[67] These antihypertensive drugs are less commonly used, and consequently there is a paucity of published evidence about their perioperative applications. There are no clear indications to stop or continue these agents on the morning of surgery. In the author's opinion, it is reasonable to stop or continue these agents before surgery, depending on clinical circumstances.

GUIDELINES

The current guidelines for perioperative management of antihypertensive therapy are available from the American College of Physicians, as outlined in their physicians' information and education resource.[41] Furthermore, the American and European multisociety guidelines complement the perioperative approaches outlined in the guideline from the American College of Physicians.[27,29,30] Lastly, the overall guidelines for hypertension management (both inpatient and outpatient) are specified in the referenced American and European multisociety guidelines.[1,2]

AUTHOR'S RECOMMENDATIONS

The final recommendations are summarized by agent class in Table 8-3. This chapter is in full agreement with all current guidelines, including those from the American College of Physicians and the American Heart Association/American College of Cardiology. Perioperative management of ambulatory antihypertensives must account for the particular antihypertensive agents, the planned surgical procedure, the overall risk–benefit profile, and current guidelines; the anesthetic plan should then be adjusted accordingly.

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CHAPTER 9

What Is the Optimal Timing for Smoking Cessation?

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INTRODUCTION

Cigarette smoking is the most important avoidable cause of mortality in the United States. The long-term effects of cigarette smoking in causing cardiac disease, vascular disease, pulmonary disease, and a variety of cancers has been recognized for many years now.[1-4] The benefits of smoking cessation in reducing future risk of these diseases compared with those who continue to smoke are also well documented.[5] Despite this body of knowledge and its wide dissemination, approximately 20% of the adult population continue to smoke.[6] Thus the anesthesiologist is faced with providing preoperative advice and perioperative care to many current smokers. The questions that then arise are whether the smoker is at increased risk of perioperative complications and whether cessation of smoking in the short-term before surgery influences these risks.

There are short-term effects of inhaling cigarette smoke that could cause intraoperative complications. Nicotine causes dose-related increases in heart rate and both systolic and diastolic blood pressure,[7] is a peripheral vasoconstrictor, and increases coronary artery resistance in diseased vessels.[8] Carbon monoxide (CO) inhaled in cigarette smoke combines with hemoglobin to form carboxyhemoglobin (COHb); levels of COHb in smokers' blood are reported from 5% up to a peak of 20% depending on smoking practice.[9] Smokers under anesthesia have been demonstrated to have higher CO concentrations than nonsmokers.[10] The high affinity of CO for hemoglobin interferes with the oxygen carrying capacity of hemoglobin and moves the oxygen dissociation curve to the left,[11] thus decreasing overall oxygen content and oxygen availability to tissues.

The long-term effects of smoking on the cardiovascular and respiratory systems might also cause perioperative problems. Cigarette smoking is a leading cause of atherosclerotic disease and a major risk factor for coronary artery disease.[12] It is also the leading cause of chronic obstructive pulmonary disease.[13] In addition, of particular relevance to anesthesia, smokers have a significantly greater upper airway sensitivity than nonsmokers.[14]

OPTIONS/THERAPIES

When presented with a current smoker scheduled for surgery, the options are to advise quitting or not to do so.

EVIDENCE

Relationship between Smoking and Perioperative Complications

This section will provide an overview of the literature linking smoking with perioperative complications. These studies are almost exclusively observational in nature. The literature pertaining to smoking cessation in the perioperative period is addressed in the subsequent section. Smoking is an important contributor to perioperative morbidity: In 2003 Moller and colleagues[15] identified smoking as the single most important risk factor for cardiopulmonary and wound-related complications after arthroplasty. Two large database studies have confirmed current smoking as a risk factor for adverse perioperative events. Using a propensity matched analysis of 520,242 patients undergoing noncardiac surgery, Turan and colleagues[16] found that current smokers had significantly greater odds of pneumonia, unplanned intubation and mechanical ventilation, cardiac arrest, myocardial infarction, and stroke. Wound infections, organ space infections, and septic shock were also increased.[16] In a similar study of 393,741 surgeries using a Veterans Affairs database, Hawn and colleagues[17] found that although current smokers were younger and healthier than nonsmokers, they experienced significantly more postoperative pneumonia, surgical site infections, and death.

Pulmonary Complications

An increased incidence of postoperative pulmonary complications in smokers has been recognized since 1944 when Morton[18] reported in a prospective series of 1257 patients undergoing abdominal surgeries that the incidence of pulmonary complications was approximately 60% in smokers versus 10% in nonsmokers. In the subsequent years the finding of increased pulmonary complications in smokers has been replicated in numerous studies, although the reported rates are lower. Smokers have an increased rate of all pulmonary complications,[19,20] infective pulmonary complications,[21,22] a higher rate of admission to the intensive care unit after surgery,[23] and a higher rate of prolonged mechanical ventilation.[24] The mechanism behind these increased complication rates is suggested by the multivariate analysis carried out by Mitchell and colleagues[25] on 40 patients

undergoing nonthoracic procedures. They found that although smokers had a higher rate of pulmonary complications, smoking per se was not an independent predictor of these complications but that sputum production was. A similar finding was reported by Dilworth and White,[21] who found that the risk of postoperative chest infection in a prospective study of 127 patients undergoing abdominal surgery was markedly higher at 83% if a smoker had evidence of chronic bronchitis compared with 21% in its absence. Nonsmokers had a 7% rate of chest infection.

Airway Complications

Schwilk and colleagues[26] reviewed the occurrence of perioperative airway and respiratory events (re-intubation, laryngospasm, bronchospasm, hypoventilation) in 26,961 anesthesia procedures. They found an incidence of 5.5% in smokers compared with 3.1% in nonsmokers. Interestingly, the risk of all such events was higher in smokers younger than 35 years and particularly in such patients with chronic bronchitis. Smoking was also identified as an independent predictor of bronchospasm in an analysis of a randomized trial of anesthetic agents involving 17,201 patients.[27]

Cardiovascular Complications

John and colleagues,[28] in an analysis of a database of 19,224 patients who underwent coronary artery bypass graft (CABG) surgery, identified smoking as an independent predictor of stroke. Smoking was also identified as an independent predictor of operative mortality in patients undergoing internal mammary artery grafting.[29] In patients undergoing abdominal aortic surgery, smoking was found to be an independent predictor of postoperative complications, of which the most common was a deterioration in renal function.[30] In a prospective investigation of the short-term effects of smoking, Woehlck and colleagues[31] reported that patients younger than 65 years with no history of ischemic heart disease undergoing noncardiac, nonvascular surgery who smoked shortly before surgery had a higher rate of ST segment depression than those who did not; however, postoperative outcomes were not reported.

Surgical Complications

Smoking has been identified as a significant risk factor for a number of postoperative surgical complications. Postoperative smoking has been identified as increasing not only the nonunion rate after spinal fusion in orthopedic surgery[32] and the need for reoperation after ankle arthrodesis[33] but also the infection rate after amputation[34] and resource consumption after joint replacement, despite the smokers being younger and with less identified comorbidities than the nonsmokers.[35] Anastomotic leaks after colorectal surgery are more common in smokers than in nonsmokers,[36] and smokers have more complications after plastic surgery to the extent that it has been suggested that plastic surgeons refuse to operate on those who fail to abstain.[37]

Smoking Cessation and Perioperative Complications

The influence of preoperative smoking cessation on perioperative outcomes had been addressed in a number of observational studies, randomized controlled trials (RCTs), and systematic reviews or meta-analyses. These are discussed now.

Observational Studies

In 1984 Warner and colleagues[38] reported a retrospective analysis of 500 randomly selected patients who had undergone CABG in one year. A history of smoking was noted for 456 patients. The rates of perioperative respiratory complications were reported in relation to the reported period of smoking cessation before surgery. Those who continued to smoke up to the time of surgery had a complication rate of 48%; nonsmokers had a rate of 11%. Smokers who reported stopping 8 weeks or more before surgery had a complication rate of approximately 17%, which was not statistically different from that of nonsmokers. Those who stopped smoking for less than 8 weeks before surgery had complication rates not statistically different from those who continued to smoke. When analyzed in 2-week blocks, the rate of complications rose slightly for those who stopped up to 4 weeks before surgery before falling toward that of nonsmokers.

A prospective study followed up 200 consecutive patients undergoing CABG of whom 150 were current or ex-smokers.[39] The findings were similar to the previous study: respiratory complications occurred in 33% of continuing smokers and in 11% of nonsmokers. Of those who had ceased smoking, complications occurred in 57% of those who stopped 8 weeks or less before surgery but in only 15% of those who stopped more than 8 weeks before surgery. Those who had stopped smoking for more than 6 months had a complication rate similar to that of those who had never smoked.

Brooks-Brunn[40] reported on the development of a predictive model for postoperative pulmonary complications after abdominal surgery using a prospective sample of 400 patients. Previously reported risk factors for postoperative pulmonary complications were collected, including length of smoking cessation before surgery. A history of smoking in the 8 weeks before surgery was one of six risk factors in the final model.

A further prospective series reported postoperative pulmonary complications in 410 patients undergoing noncardiac surgery.[41] This group again reported that current smokers had a higher complication rate (odds ratio [OR], 5.5) than nonsmokers or past smokers (OR, 2.9) and that smoking was an independent risk factor.

Nakagawa and colleagues[42] reported similar findings in a retrospective study of 288 patients undergoing thoracic surgery, again focusing on pulmonary complications. The incidence of complications was 24% in nonsmokers, 43% in current smokers (here including those who smoked within 2 weeks of surgery), 54% in those who stopped smoking between 2 and 4 weeks

preoperatively, and 35% in those who stopped more than 4 weeks before surgery. These differences persisted with the same ranking when the results were corrected for possible confounding factors. Four-week moving averages showed that the rate of complications in smokers who stopped before surgery reached approximate equivalence with that of nonsmokers at an abstinence period around 8 weeks.

The results of the aforementioned articles raised concerns that pulmonary complications may be increased if patients were to undergo surgery within 4 weeks of quitting; however, subsequent studies indicate that this is not the case. Reporting on pulmonary complications in 300 patients undergoing thoracotomy, Barrera and colleagues[43] found more complications for smokers versus nonsmokers but no significant difference between groups of smokers (quit > 2 months, quit < 2 months and ongoing) nor an increase in recent quitters. Similar findings were reported by Groth and colleagues[44] in 213 patients undergoing pulmonary resection; no difference was seen in overall or specific postoperative complications, including pulmonary complications, among current, recent (quit < 1 month), and distant (quit > 1 month) smokers. In a similar study of 7990 patients from a thoracic surgery database, Mason and colleagues[45] reported that smokers had a 6.2% rate of major pulmonary complications compared with 2.5% in those who had never smoked. ORs for smoking categorized by timing of preoperative quitting (versus never-smokers) were 1.8 for current smokers, 1.62 for those who had quit 14 days to 1 month prior, 1.51 for those who had quit 1 month to 12 months before surgery, and 1.29 for those who had quit more than 12 months prior.

The influence of smoking cessation on wound complications was investigated by Kuri and colleagues[46] in a retrospective study of 188 patients who underwent reconstructive head and neck surgery. They divided patients into five groups based on preoperative smoking history: smokers (smoked within 7 days of surgery), late quitters (abstinence 8 to 21 days before surgery), intermediate quitters (abstinence 22 to 42 days before surgery), early quitters (abstinence 43 days or longer), and nonsmokers. Impaired wound healing was assessed by the need for subsequent surgical intervention. Impaired wound healing was significantly less frequent in the intermediate quitters (55%), early quitters (59%), and nonsmokers (47%) than in the smokers (85%). After multivariate analysis to control for other factors known to influence wound healing, intermediate and early quitters and nonsmokers continued to have a significantly lower risk of impaired healing than smokers. Late quitters had a lower incidence of impaired wound healing (68%) than smokers and a lower risk on multivariate analysis, but these changes were not statistically significant. The authors' conclusion was that 3 weeks of abstinence is required to reduce wound complications, but a moving average of impaired wound healing incidence they present suggests that this begins declining with 1 week of abstinence.

Taken together, these studies indicate that the risk of complications declines the longer the period of preoperative abstinence. All of the studies can be criticized for being observational in nature and for relying on patient-reported information. In none of the studies is it clear whether any advice to cease smoking was given to the patients involved or whether the observed changes in smoking behavior reflected the patients' own assessment of the appropriate course of action, which could potentially result in a self-selected patient group. The clinician is then left asking whether advice and interventions to quit smoking before surgery would, firstly, be effective and, secondly, result in fewer complications.

Randomized Studies

Several RCTs have addressed these issues. In an experimental study, Sorensen and colleagues[47] compared wound healing in never-smokers and smokers randomly assigned to either continued smoking or abstinence (with nicotine patch or placebo). Sacral wounds were made at 1, 4, 8, and 12 weeks after randomization. Continued smokers had greater rates of infection than abstinent smokers (and never-smokers) in wounds made 4 or more weeks after randomization. The use of a nicotine patch did not affect outcome.

In a clinical trial, Moller and colleagues[48] performed a multicenter study randomly assigning 120 smokers scheduled for elective hip or knee arthroplasty 6 to 8 weeks preoperatively to either a standard care group or a smoking intervention group. Those in the smoking intervention group were offered weekly meetings with a nurse where they were strongly encouraged to stop smoking. Nicotine replacement was provided along with smoking cessation education. Results were analyzed on an intention-to-treat basis. Thirty-six of the intervention group stopped smoking, and 14 reduced consumption. In the control group only four patients stopped smoking. Postoperative complications were significantly less frequent in the intervention group (18% versus 52%), and the largest effect was seen for wound-related complications. Cardiovascular complications were also more common in the control group (10% versus 0%), but this was not statistically significant. In a comparison of those who reduced their consumption versus those who stopped smoking, the reduction in complications was significant only for those who stopped; those who reduced consumption had the same complication rate as those who continued smoking.

In a similar study, also conducted in Denmark, Sorensen and Jorgensen[49] investigated the influence of a preoperative smoking intervention in patients undergoing colorectal surgery. Sixty patients were randomly assigned to 2 to 3 weeks of either continued smoking or a smoking intervention program similar to that just described. The intervention was successful in decreasing preoperative smoking (89% in the intervention group either quit or decreased consumption versus 13% in the control group). However, no difference in any postoperative complication rates was found.

Lindstrom and colleagues[50] randomly assigned 117 patients scheduled for orthopedic or general surgery to either an intervention group (counseling and nicotine

TABLE 9-1 **Systematic Reviews/Meta-analyses of Preoperative Smoking Cessation**

Study	Included Trials	Total Patients	Findings
Wong et al, 2012[56]	2 RCTs 23 obs	21,318	Quit > 4 wk less pulmonary, wound comps Quit < 4 wk no effect
Myers et al, 2011[53]	2 RCTs 9 obs	441	No detrimental impact if quit within 8 wk
Mills et al, 2011[52]	6 RCTs 15 obs	648 14,262	RCTs: intervention RR reduction 41% for comps > 4 wk cessation larger treatment effect than < 4 wk Obs: cessation decreased total, pulmonary, wound comps. Longer cessation more effective.
Thomsen et al, 2010[55]	8 RCTs	1156	Intervention decreased smoking Intervention decreased all, wound comps
Thomsen et al, 2009[54]	11 RCTs	1194	Intervention decreased comps Intensive intervention more effective than less intensive

comps, postoperative complications; *obs,* observational trials; *RCTs,* randomized controlled trials; *RR,* relative risk.

replacement) or standard care 4 weeks preoperatively. The intervention group had significantly less postoperative complications overall.

In a study of brief preoperative intervention (one counseling session 2 to 10 days before surgery) in 130 patients scheduled for breast cancer surgery, randomization to the intervention group had no effect on perioperative complications.[51]

Overall, these studies suggest that smoking intervention in the preoperative period is effective in reducing tobacco consumption and can reduce complications, although possibly only if initiated early enough and if it is of sufficient intensity. One caveat is that, in reported studies, approximately 25% of patients who were invited to participate refused, which may influence the generalizability of the findings.

Systematic Reviews and Meta-Analyses

Five systematic reviews or meta-analyses surveying the literature on smoking cessation in the perioperative period have been published.[52-56] These are summarized in Table 9-1. Despite differences in methodology, similar findings are reported. Quitting smoking before surgery decreases total postoperative complications, and complication rates decrease with longer periods of abstinence. Quitting within 4 weeks of surgery did not increase pulmonary complications. Regarding interventions to promote preoperative cessation, the most recent meta-analysis reports that both intensive and brief interventions are effective.[55]

AREAS OF UNCERTAINTY

- Does smoking in the immediate preoperative hours lead to a demonstrable effect on clinically relevant outcomes?
- What is the minimum time period required for a formal smoking intervention program to reduce postoperative complications? What should such a program consist of?

GUIDELINES

Recommendations to quit smoking preoperatively are virtually universal. The American Society of Anesthesiologists has a useful Stop Smoking for Surgery initiative.[57]

AUTHOR'S RECOMMENDATIONS

All smokers should be identified before surgery and quit at least 4 weeks preoperatively but earlier is better. Because this is not always possible,

- all smokers scheduled for surgery are strongly encouraged to quit. Formal support to quit smoking including nicotine therapy should be made available.
- no smoking should occur on the day of surgery for any patient.
- all smokers seen for surgery should be advised to quit permanently.

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CHAPTER 10

Which Patient Should Have a Preoperative Cardiac Evaluation (Stress Test)?

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INTRODUCTION

Preoperative cardiovascular risk assessment attempts to prospectively identify at-risk patients, allowing targeted perioperative management so that event rates can be reduced.[1] Perioperative cardiac events include both "demand" events, in which perioperative stress increases myocardial oxygen requirements to a level that cannot be met because of fixed obstructive coronary artery disease (CAD) or low perfusion pressure,[2,3] and true "acute coronary syndromes" (ACSs) with occlusive plaque rupture,[4-6] likely due in part to perioperative inflammation/cytokine response and an associated prothrombotic state.[2] Epicardial obstructive CAD sufficient to cause demand-related biomarker release can be reliably identified by cardiac stress testing and coronary angiography. Consequently, preoperative cardiovascular assessment evolved from risk factor identification to ischemia evaluation, using risk factors to identify at-risk patients and cardiovascular stress testing (with or without angiography) to identify hemodynamically significant CAD in those patients, who could then undergo revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery.

Retrospective and observational data support the concept of risk reduction by preoperative revascularization,[7] but those data predate modern medical management. Revolutionary changes in cardiovascular medical management, particularly the advent of perioperative beta-blockade,[8-13] together with advances in surgical and anesthetic techniques, have significantly reduced operative morbidity and mortality rates: event rates have decreased from approximately 10% to 15% in intermediate-risk patients three decades ago[1] to approximately 5% in contemporary "at-risk" patients (i.e., with risk factors for or known CAD) and to approximately 1.5% in unselected noncardiac surgery patients.[2] This reduction in risk likely attenuates the benefit of preoperative revascularization. The power of modern medical management has been demonstrated in multiple trials, with both single study[14] and aggregate data[15] demonstrating that revascularization provides no incremental benefit over maximal medical management in patients with stable, symptomatic CAD. Moreover, surgical outcomes continue to improve, such that the mortality rate of major surgeries is so low[16] as to make the risk of revascularization prohibitive. Consequently, the role of preoperative cardiac stress testing has been reduced to the identification of extremely high-risk patients, for example, those with significant left main (LM) disease, for whom preoperative revascularization may provide a benefit independent of the operation.

Historically, preoperative cardiovascular risk assessment has lacked widespread standardization or consensus, despite published guidelines. Perceived goals have varied, adherence to recommendations has been poor,[17] and many assessments resulted in no formal recommendations.[18] Furthermore, differing opinions occurred in a majority of cases, and opinions contradicted consensus guidelines in a significant minority.[19] With increasing data to guide the evolution of consensus guidelines into evidence-based guidelines, greater consensus and adherence among practitioners will, it is hoped, follow.

OPTIONS/EVALUATION STRATEGIES

As we integrate the available data into our standard practice, the following key issues emerge:

1. Understanding risk factor implications as well as absolute contraindications to elective/urgent surgical procedures
2. Understanding treatment options independent of revascularization that can significantly affect patient outcome
3. Understanding the risks and benefits of revascularization in the preoperative period
4. Appropriate testing: which patients to test and how to test them

EVIDENCE FOR A ROLE OF PERIOPERATIVE RISK STRATIFICATION AND RISK MODIFICATION

Early studies of risk stratification focused primarily on the identification of risk factors predictive of increased event rates,[20] enabling construction of risk indices to prospectively quantify perioperative cardiovascular risk.[21] Current guidelines focus on the Lee Revised Cardiac Risk Index (RCRI; Table 10-1), which divides patients

TABLE 10-1 **Revised Cardiac Risk Index (RCRI)***

RCRI Class	RCRI Score	Cardiovascular Event Rate†
Class I	0	0.5 (0.2, 1.1)
Class II	1	1.3 (0.7, 2.1)
Class III	2	3.6 (2.1, 5.6)
Class IV	<2	9.1 (5.5, 13.8)

*RCRI indicates the number of the following risk factors present: high-risk surgery, ischemic heart disease, history of cerebrovascular disease, history of congestive heart failure, presence of insulin-requiring diabetes, preoperative serum creatinine exceeding 2.0 mg/dL.
†Cardiovascular event rates from the derivation patient cohort.
From Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100(10):1043–9.

into quartiles of predicted risk.[22] The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for preoperative cardiac assessment also define four "major" risk factors that preclude nonemergent surgical procedures: active/recent unstable coronary syndrome, decompensated heart failure, significant arrhythmia, and severe valvular disease.[23]

EVIDENCE THAT SPECIFIC HIGH-RISK MARKERS DEMAND PREOPERATIVE ASSESSMENT AND INTERVENTION

Acute Coronary Syndrome

An active unstable coronary syndrome is, until proved otherwise, an ACS reflecting erosion or rupture of an atherosclerotic plaque. Patients with an ACS are at increased perioperative risk, and in such cases, surgery should be delayed when possible. Retrospective electrocardiogram analysis from the GUSTO-IIb (Global Use Of Strategies To Open occluded arteries in ACSs) study demonstrated that mortality rates rise for 20 to 30 days after presentation, after which mortality rates stabilize.[24] As such, current guidelines identify 30 days as the cutoff for a "recent" ACS[23]; further delay in surgery would not be expected to alter risk, in the absence of other confounding issues.

Decompensated Congestive Heart Failure

Although treatments for congestive heart failure have advanced significantly in the past decade, survival benefits have been more prominent in patients with mild to moderate disease than in those with advanced heart failure.[25] The annual mortality rate in randomized trials of Class III/IV heart failure ranges from 18.5% to 73%,[26] whereas the Acute Decompensated Heart Failure National Registry (ADHERE) of decompensated heart failure admissions found an overall in-hospital mortality rate of 4%; subgroup mortality rates ranged from 2.1% to 21.9%.[27] These rates, which exceed the expected cardiovascular event rates for the vast majority of elective surgical procedures, would almost certainly increase significantly with the hemodynamic and systemic stress of surgery. Early multivariate risk factor analyses confirmed that decompensated heart failure was associated with increased perioperative morbidity and mortality risk.[1] As such, decompensated congestive heart failure must be treated before surgery.

Arrhythmia

In the perioperative context, "significant" arrhythmia refers to hemodynamically significant rhythm disturbances. However, ventricular arrhythmias are of sufficient threat that even hemodynamically tolerated sustained ventricular arrhythmias should delay anything but emergent surgery. There is no literature characterizing the level of risk that can be ascribed to a preoperative sustained ventricular arrhythmia; given the life-threatening nature of such arrhythmias, to seek to obtain such data would be unethical. In contrast, there is evidence that nonsustained ventricular arrhythmias do not preclude surgical procedures and do not increase perioperative cardiovascular risk.[28,29]

Uncontrolled atrial arrhythmias (i.e., with ventricular response rates exceeding approximately 100 beats per minute) place patients at increased risk of demand ischemia. Accordingly, rate control should be established before surgery. Although rate-controlled atrial arrhythmias do not preclude surgery, they are associated with an unmodifiable increase in perioperative risk and identify a sicker cohort of patients. For patients undergoing CABG, preoperative atrial fibrillation (AF) increases the length of stay, rehospitalization rate, and long-term mortality rate but not the operative mortality rate.[30] Preoperative AF is associated with an increased perioperative cardiovascular mortality rate (adjusted odds ratio, 4.0) in noncardiac surgery,[31] but this may reflect unidentified comorbidities that increased both the prevalence of AF and cardiovascular risk or an inadequate perioperative rate control.

With atrial arrhythmias, there is the ancillary issue of anticoagulation. Rapid postoperative reinstatement of anticoagulation to minimize thromboembolic risk places patients at an increased risk of postoperative bleeding[32] and may not provide significant benefit.[33] Although patients with AF are, in general, at relatively low short-term risk of thromboembolic events, having age-dependent stroke rates of 1% to 5% per year,[34] the potentially devastating nature of these events makes risk–benefit assessment challenging. In the current ACC/AHA guidelines, a Class IIb recommendation is given to "bridging" patients for whom oral anticoagulants must be held for more than a week, but notes that the efficacy of both unfractionated heparin and subcutaneous low-molecular-weight heparin in this setting is uncertain.[35] Modern oral anticoagulants offer the benefit of predictable bioavailability and effect, relative to unfractionated heparin, and avoid the risk of heparin-induced thrombocytopenia. However, the inability to reverse these agents may limit their use in the perioperative setting.

Symptomatic bradycardia and high-grade atrioventricular conduction abnormalities are also considered significant arrhythmias in the context of preoperative risk assessment. For these rhythms, the primary consideration is whether temporary or permanent pacemaker implantation should be considered. The availability of reliable "semi-permanent" devices enables protection from bradycardia perioperatively without consigning the patient to a permanent device if the bradycardia is anticipated to resolve (e.g., Lyme carditis with heart block) or is by nature transient (e.g., vagal hypersensitivity).

Valvular Disease

Valvular disease is the best studied of the four "major" risk factors. In general, regurgitant lesions are not a contraindication to elective surgery because such lesions are relatively tolerant of perioperative fluid shifts and anesthetic induction. In contrast, symptomatic or severe stenotic lesions are sensitive to changes in both preloading and afterloading, increasing the risk of perioperative hemodynamic embarrassment.

Although the decreasing incidence of rheumatic heart disease has made mitral valve stenosis a rare clinical finding, aortic stenosis (AS) remains common. Some retrospective surgical series found no increase in perioperative cardiovascular event rates in patients with significant AS,[36] but the majority of studies suggest that morbidity and mortality rates are higher in these patients.[37,38] A recent retrospective case-control analysis supports this contention, in that stenosis severity predicted a sevenfold increase in cardiovascular events.[39] Taken together, the available evidence supports the current standard of practice, in which clinically significant AS is addressed before an elective surgical procedure.[21] Although percutaneous balloon valvuloplasty was historically used in patients needing surgery who were not candidates for aortic valve replacement,[23] transcatheter aortic valve replacement may now allow a more durable intervention in such patients.[40] This novel therapy is developing rapidly, but its use perioperatively remains to be determined.

EVIDENCE FOR MODIFICATION OF PERIOPERATIVE RISK: ROLE OF MEDICAL TREATMENT

Much of our understanding of relative risk is derived from the Coronary Artery Surgery Study (CASS) registry,[41] in which perioperative cardiovascular morbidity and mortality rates varied as a function of surgical "risk," and the highest risk was associated with vascular surgeries.[41] Based on this registry, we now subdivide surgical procedures into three classes (high, intermediate, and low risk).[21] Although much of this information is intuitive, data from the CASS registry codified the stratification of procedural risk. The higher event rates associated with "high-risk" noncardiac surgery (i.e., vascular surgery) have made these procedures the ideal setting in which to explore perioperative risk reduction.

Evidence for Perioperative Beta-Blockade

The role of so-called demand perioperative ischemia[2,3] suggests that hemodynamic stress contributes to cardiovascular events. Periods of greatest risk include perinduction and the immediate postoperative period, presumably as lightened sedation allows increasing sympathetic drive and resultant tachycardia.[3] Sympatholytic therapy with beta-blockers should blunt this response, minimizing myocardial demand.

The first large-scale study of perioperative beta-blockade randomly assigned patients undergoing intermediate- to high-risk surgery to placebo versus atenolol (target heart rate, 65 beats per minute), reducing postoperative mortality rate from 8% to 0% by 3 months after surgery.[10] Three years later, the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) study group randomly assigned high-risk vascular surgery patients with positive preoperative dobutamine echocardiography to perioperative bisoprolol versus placebo, with a reduction in cardiac death rates from 17% to 3.4% and nonfatal myocardial infarction (MI) rates from 17% to 0%.[12] Subsequent work by the same group demonstrated that maximal beta-blockade dose and heart rate control optimized the perioperative protective benefit.[42]

The role, if any, of beta-blockade in low-risk patients remains unclear. In a retrospective analysis of a multicenter cohort (the Premier's Perspective database) undergoing major noncardiac surgery, the perioperative mortality rate was lower with beta-blocker use in intermediate- and high-risk patients but showed a trend toward increased mortality rates in low-risk patients.[9] These data are difficult to interpret because beta-blocker use in these patients may serve as a marker for a negative perioperative event that led to, rather than resulted from, beta-blockade. Although some studies have gone so far as to suggest that beta-blockade is not beneficial in intermediate-risk patients[43-46] or even high-risk patients,[47] these results likely reflect methodologic limitations, including underdosing and inadequate duration of beta-blockade,[44-46] abrupt initiation of a relative high dose of long-acting beta-blockade without preceding dose titration,[47] and dilution with low-risk procedures or patients.[44-46]

The DECREASE-2 study randomly assigned a relatively homogenous population of 770 intermediate-risk vascular surgery patients to preoperative stress testing versus no testing; patients with significant stress-induced ischemia could have preoperative revascularization at the discretion of their care team.[48] In this population, of which 8.8% had extensive ischemia (35% of whom underwent revascularization [50% partial, 50% complete] before vascular surgery), there were no significant differences in death or MI rates. In contrast, heart rate control was significantly correlated with morbidity and mortality rates: the event rate was 1.7% in patients with a heart rate below 50 beats per minute versus 16.5% in patients with a heart rate exceeding 65 beats per minute. These results suggest that, if adequate beta-blockade can be achieved, preoperative cardiac stress testing has no

role in intermediate-risk patients.[48] The weight of evidence supporting perioperative beta-blocker therapy prompted a focused update to the ACC/AHA perioperative guidelines,[49] which advised perioperative beta-blockade in high-risk patients (Class I recommendation for vascular surgery, Class IIa for intermediate- to high-risk surgery); beta-blockade in low-risk patients receiving a Class IIb recommendation. In the subsequent full revision of the ACC/AHA guidelines, these recommendations were broadened to a Class IIa indication encompassing all patients with at least one clinical risk factor and/or with known CAD who are scheduled for intermediate- or high-risk procedures.[23]

Evidence for Other Perioperative Medical Interventions

Invasive monitoring (e.g., pulmonary artery catheters [PACs] and arterial lines), cardiac telemetry, and an intensive care unit (ICU) setting have all been proposed to decrease perioperative morbidity. Although there are no randomized controlled trial data examining their role in perioperative cardiovascular risk reduction, cardiac telemetry and ICU admission are widely accepted as cost-effective and beneficial in at least a subset of patients, particularly high-risk patients, as well as those requiring invasive monitoring or frequent titration of hemodynamically active medications.[50] In contrast, the perioperative role of the PAC has decreased in recent years. Observational studies suggest that PAC use *increases* morbidity and mortality rates.[51,52] Although prospective studies of PACs in the perioperative setting have a number of methodologic limitations,[53] the largest randomized controlled study suggests that PACs have insufficient benefit.[54] The PAC has no role in current routine perioperative care, although we cannot exclude the possibility that there does exist a specific subpopulation for which use of the device may be beneficial.

A number of pharmacologic agents, including alpha agonists, nitroglycerin, and diltiazem, have been studied but have shown only limited evidence of perioperative benefit.[7,55-57] More recently, 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors ("statins"), drugs with recognized pleiotropic therapeutic effects on the cardiovascular system,[58] have been examined. Observational retrospective studies suggest that perioperative statin use is protective,[8,59] and a growing body of evidence supports statin use in vascular surgery patients[60-62] and patients undergoing abdominal surgery.[63] In the current ACC/AHA guidelines, statin initiation receives a Class IIa recommendation for patients undergoing vascular surgery and a Class IIb recommendation for patients with at least one clinical risk factor scheduled to undergo an intermediate risk procedure; patients already taking a statin should continue the medication perioperatively (Class I).[23]

A medication of ongoing consideration is aspirin. Although antiplatelet agents were traditionally discontinued perioperatively to minimize bleeding, observational trials demonstrated decreased morbidity and mortality rates in cardiac surgery patients who received perioperative aspirin.[64-66] Limited evidence in noncardiac surgery suggests aspirin may be beneficial[67] in this setting, although other researchers have found no clinical benefit.[68] The need to continue antiplatelet therapy after drug-eluting stent (DES) placement is an additional driver for continuing aspirin: data suggest that the risks of antiplatelet-associated bleeding are less than the risks associated with antiplatelet withdrawal after stenting.[69] Research into intravenous "bridge" therapies is ongoing,[70] but to date, the clinical benefits of such a strategy are unclear. Given the continuing evolution of available agents for and considerations inherent in antiplatelet therapy management after stenting, a cardiologist should be consulted before discontinuation of antiplatelet therapy for any procedure in a patient with a coronary artery stent. Consensus guidelines from the European Society for Cardiology underscore the need for multidisciplinary consultation and care of these patients.[71]

EVIDENCE FOR MODIFICATION OF PERIOPERATIVE RISK: ROLE OF PREOPERATIVE REVASCULARIZATION

Data defining the role of perioperative revascularization can be temporally stratified by the means of revascularization (CABG, angioplasty, stent, and DES). The CASS database provided the first retrospective evidence of risk reduction with revascularization; it showed reduced cardiovascular morbidity and mortality rates for at least 6 years after CABG.[41] Importantly, these data predate the use of the left internal mammary artery (LIMA) conduit, which has greater longevity,[72] which suggests that protective effects could be more durable in the current era.

By the mid-1980s, percutaneous transluminal coronary angioplasty (PTCA) was a viable alternative to CABG. Retrospective review suggested that, compared with procedures used in historical controls, PTCA reduced perioperative cardiovascular morbidity and mortality rates,[73,74] and prospective randomized evaluation found that PTCA was as effective as CABG in lowering perioperative risk.[75,76]

PCI, employing coronary stents to scaffold open lesions, was examined in the preoperative setting in the Coronary Artery Revascularization Prophylaxis (CARP) trial.[77] CARP was the first prospective randomized trial to study preoperative revascularization in patients with stable obstructive CAD, enrolling patients scheduled for elective major vascular surgery (abdominal aortic aneurysm [AAA] repair or lower extremity revascularization) in whom angiography revealed significant CAD amenable to revascularization. Significant (greater than 50%) stenosis of the LM artery was an exclusion criterion, as was a left ventricular ejection fraction (EF) less than 20% or severe AS. The patients, a very high-risk population (67% with multivessel disease; RCRI score of 2 or more in 49% and 3 or more in 13%), were randomly assigned to preoperative revascularization (PCI or CABG) or medical management. There were no significant differences in short-term (30-day MI rate, approximately 13%) or long-term (mortality rate at 2.7 years, approximately 22%) morbidity and mortality rates. These moderate

rates in such a high-risk population illustrate the significant improvement in medical therapy and attendant reduction in mortality rate since the CASS era.

Interestingly, a revascularization-related delay in the planned vascular procedure actually resulted in a trend toward increased vascular-related mortality.[77] This is troubling in the context of PCI, particularly with DESs. With balloon angioplasty, retrospective analysis found increased event rates for 2 weeks after intervention, which suggests that surgery should be delayed for at least 2 weeks after angioplasty.[78] Although a similar period of increased risk was observed in retrospective and observational analysis with bare-metal stents (BMSs), the recommendation with BMSs was that surgery be delayed for at least 4 weeks after PCI,[79] although there was some evidence that event rates could be increased for at least 3 months after PCI.[80,81] With the advent of DESs, the issue became complicated by the need for longer obligate dual antiplatelet therapy. Although initial guidelines recommended dual antiplatelet therapy for 3 months for a CYPHER (Johnson & Johnson sirolimus-coated) stent and 6 months with a TAXUS (Boston Scientific paclitaxel-coated) stent, current recommendations advise at least 1 year of dual antiplatelet therapy after DES placement.[82] Current data suggest that extension of dual antiplatelet therapy beyond a year does not reduce cardiovascular event rates relative to aspirin monotherapy.[83] Retrospective analysis of perioperative event rates after BMS or DES placement reveal no significant differences,[84] but the prolonged antiplatelet regimen for DESs is a significant issue for surgeons. Importantly, discontinuation of antiplatelet therapy is the strongest risk factor for cardiovascular events after PCI,[84] underscoring the necessity of cardiologist input before discontinuing antiplatelet therapy in a patient who has had prior PCI.

ASSESSMENT OF ISCHEMIA: WHO AND HOW TO TEST

Functional capacity is predictive of both perioperative and long-term cardiac events[23]: Increased morbidity and mortality rates are seen in patients with less than 4-MET (metabolic equivalent) capacity.[85] A simple marker for 4-MET capacity is the ability to walk up two flights of stairs. Patients who can, by history or example, exert themselves to this level do not require stress testing. Surgery can proceed with best medical therapy.

In patients with unclear or poor functional capacity, cardiac stress testing can provide relatively accurate identification and quantification of ischemia, regardless of the mechanism of stress (i.e., exercise, pharmacologic stress, or vasodilation) and/or the metric of assessment (i.e., electrocardiogram, myocardial perfusion imaging, or echocardiography). Sensitivity and specificity for the detection of significant CAD are on the order of 70% to 88% across modalities.[86] Modality selection should be guided by local expertise and patient-specific factors, and the preference should be for exercise over pharmacologic stress whenever possible given the additional functional and hemodynamic information that is obtained with exercise.[23]

For perioperative patients, stress-induced reversible perfusion defects have a positive predictive value of 2% to 20% for perioperative death or MI; negative predictive value is on the order of 99%.[23] In general, prognostic information is limited to that subset of patients with elevated clinical risk, extensive ischemia, or both.[87,88] Thus, although they have adequate sensitivity and specificity, all modalities have an unacceptably low positive predictive value and, as such, require a very restrictive criterion for the degree of ischemia that triggers further evaluation. Positive predictive value is expected to further decline with widespread implementation of perioperative beta-blockade, which should further reduce perioperative event rates.

The overarching emphasis of the ACC/AHA guidelines has long been that preoperative ischemia evaluation is no different than in other elective settings.[21] The fact that a patient is scheduled for surgery, regardless of the degree of surgical risk, does not affect the patient's relative need for assessment and possible revascularization. The recent Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial demonstrated that, for stable CAD, event rates do not differ with the addition of PCI to best medical therapy.[14] This is underscored by the aforementioned CARP trial,[77] which demonstrated that revascularization had no perioperative survival benefit, even in patients with clinically stable multivessel disease undergoing high-risk surgery.

Taken together, the available evidence suggests that cardiac catheterization is best employed for two purposes: (1) to exclude life-threatening/critical CAD (e.g., critical LM disease) and (2) for relief of refractory symptoms. The former indication is more challenging, as it is difficult to know how broad a net to cast in order to identify those rare patients with critical disease. This was partially addressed by the aforementioned DECREASE-2 study, which demonstrated that, with adequate beta-blockade, no interval benefit was seen from stress testing with or without revascularization in intermediate-risk vascular surgery patients.[48] These results suggest that preoperative cardiac testing has no role in intermediate-risk patients (RCRI, 1-2) for whom adequate perioperative beta-blockade can be provided.[48]

CONTROVERSIES

The role of elective/nonurgent percutaneous revascularization remains a matter of some controversy. As noted previously, COURAGE[14] and a subsequent meta-analysis[15] found no survival benefit to PCI. Most cardiologists believe that the symptom relief provided by PCI warrants its use in patients with symptoms refractory to best medical therapy. Furthermore, available data suggest practice patterns have been slow to change post-COURAGE: many patients undergo PCI without receiving optimal medical therapy.[89] As such, PCI will remain prominent in ischemia management, bringing with it an increase in the difficulty of perioperative care.

Stent selection (BMS versus DES) has significant perioperative implications. When the first-generation DESs were approved by the U.S. Food and Drug

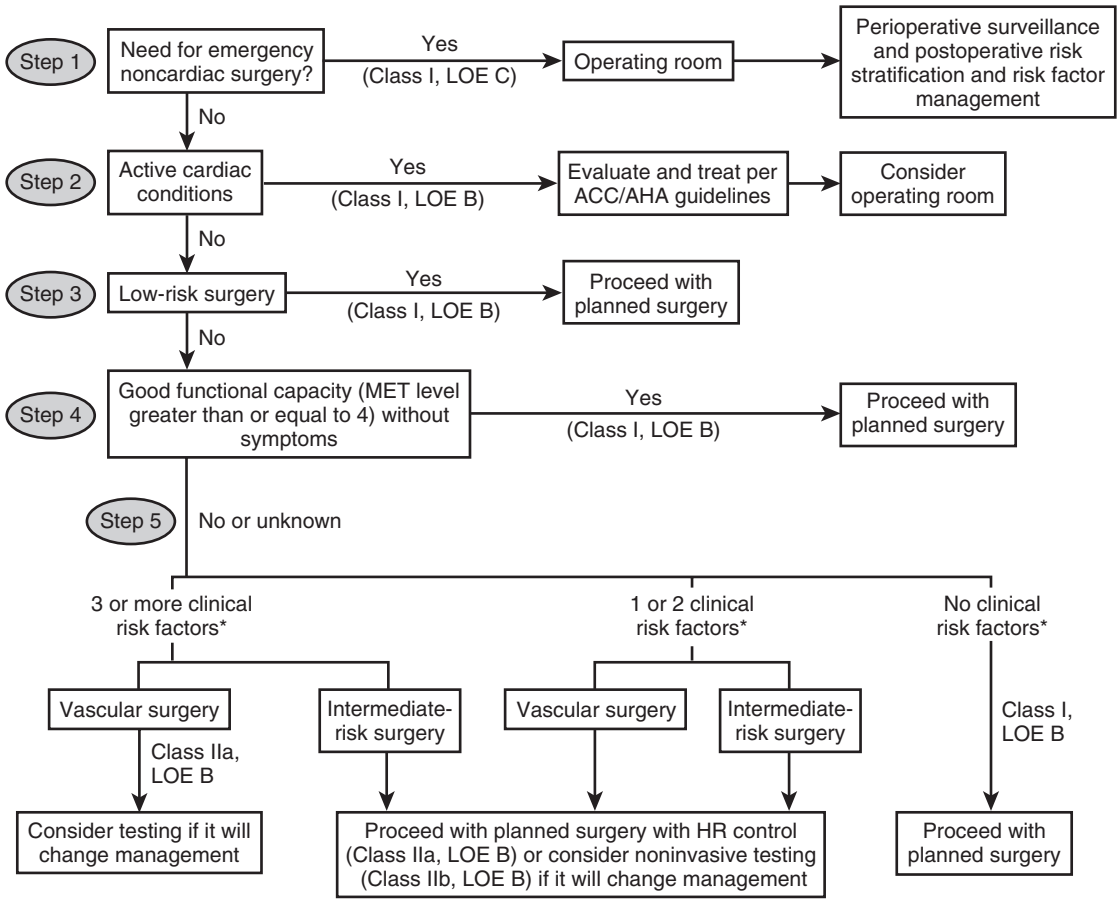

FIGURE 10-1 ■ Cardiac Evaluation and Care Algorithm for Noncardiac Surgery Based on Active Clinical Conditions, Known Cardiovascular Disease, or Cardiac Risk Factors for Patients 50 Years of Age or Greater. *Risk factors include heart failure, diabetes mellitus, ischemic heart disease, cerebrovascular disease, and renal insufficiency. *ACC/AHA,* American College of Cardiology/American Heart Association; *HR,* heart rate; *LOE,* level of evidence; *MET,* metabolic equivalent. (Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al: ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery—Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 2007;116:1971–96.)

Administration, their use rapidly supplanted that of BMSs,[90] including off-label use, which, by 2007, made up more than half the DES recipient population.[82] With the release of BASKET-LATE (Basel Stent Kosten-Effektivitäts Late Thrombotic Events Trial) and subsequent trials,[91,92] however, it became clear that the first-generation DES platform had intrinsic weaknesses; the in-stent restenosis reduction was counterbalanced in part by a small increase in (potentially fatal) late in-stent thrombosis. Overall, on-label use of first-generation DESs did provide superior outcomes to BMSs,[93-94] and subsequent developments in DESs have resulted in lower in-stent thrombosis rates than were seen with first-generation stents.[95] However, given the antiplatelet considerations, BMSs are preferred for patients with anticipated surgical procedures. Unfortunately, it is easy to see how one's ability to peer into the future may not stretch out to the limits of patients' 1-year required clopidogrel therapy with DESs. Consequently, arguments regarding the safety of perioperative antiplatelet therapy will almost certainly continue. It is essential that both prospective randomized trials and registry data examine this issue, particularly in patients with prior coronary artery stents so that an evidence base can be provided on which consensus can be reached.

AREAS OF UNCERTAINTY

The evidence base for cardiovascular risk assessment has developed through the increasing willingness of investigators to randomly assign patients with an increasing burden of disease. Patients with a significantly reduced EF or LM disease are the two populations perceived to be too high risk for randomization; revascularization in these patients was presumed to be beneficial. Until the CARP trial, however, many investigators would have argued that revascularization of stable multivessel disease was beneficial. The DECREASE-V pilot study may herald the next generation of preoperative studies. In it, the previously excluded populations of LM disease and low EF were included in randomization of vascular surgery patients to preoperative revascularization or standard medical management.[96] Of note, 8% of randomly assigned patients had LM disease, and 67% had three-vessel disease. Not surprisingly, given the high-risk

characteristics of this population, event rates were high: 30-day mortality rates were approximately 5% to 10%, and 30-day MI rates were approximately 16%. Revascularization had no statistically significant effect.

DECREASE-V raises more questions than it answers and will almost certainly lead to a new generation of studies in extremely high-risk patients. If preoperative revascularization in patients with LM or critical three-vessel disease proves ineffective at reducing cardiovascular risk, the role of preoperative stress testing will need to be redefined, if not eliminated.

As the field moves from revascularization toward conservative medical therapy, noninvasive imaging strategies will offer an attractive alternative to the historical stress test/catheterization approach. In particular, computed tomography (CT) can noninvasively evaluate CAD. For technical reasons, at present, CT can exclude significant obstructive disease but cannot accurately quantify the degree of disease when present,[97] making it inadequate for preoperative ischemia evaluation, in which the issue is the exclusion of critical disease. Future technical developments will allow CT coronary angiography to provide more physiologically relevant information, which may in turn allow these studies to serve an expanded role in preoperative ischemia evaluation.

GUIDELINES

The ACC/AHA has released new perioperative risk assessment and management guidelines for patients at risk of CAD.[23] These evidence-based guidelines, which reflect the state of our current knowledge base, reserve preoperative cardiac stress testing for patients who meet the following criteria (Figure 10-1):

1. The patient has poor or unknown functional capacity. Adequate functional capacity is a good prognostic indicator. For patients who are able to achieve 4 METS (the equivalent of walking up two flights of stairs), revascularization is unlikely to affect their risk of cardiovascular events.
2. The patient is being considered for a nonemergent surgical procedure of at least intermediate risk. Emergent procedures, by definition, do not have the luxury of time to allow ischemia evaluation. Low-risk procedures do not require preoperative evaluation.
3. The patient does not have an absolute contraindication or "red flag." Patients with active arrhythmia, unstable coronary syndrome, decompensated heart failure, or significant stenotic valvular lesions should be evaluated and managed by a cardiologist before consideration of surgery.
4. The patient has sufficient clinical risk factors (at least three) to cause concern for LM/multivessel disease.
5. Revascularization would be performed preoperatively if ischemia evaluation were positive (i.e., the patient's management will potentially be altered by the evaluation).

As noted previously, the current ACC/AHA guidelines have also broadened the perioperative beta-blockade recommendations.[23] Although the Class I indication remains unchanged (patients with a nonsurgical beta-blocker indication and high-risk patients scheduled for vascular surgery), the Class IIa indication has been expanded to all patients with at least one clinical risk factor or with known CAD who are scheduled for intermediate- or high-risk procedures.

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CHAPTER 11

Should Patients with Stable Coronary Artery Disease Undergo Prophylactic Revascularization before Noncardiac Surgery?

Santiago Garcia, MD • Edward O. McFalls, MD, PhD

INTRODUCTION

The preoperative assessment of a patient in need of elective noncardiac surgery is often a difficult task. There has been enormous controversy regarding the appropriate strategy for diagnosing and managing coronary artery disease before elective noncardiac surgery because of the paucity of clinical trial data. Overall, elective surgical procedures in a population of general medical patients are associated with a very low risk of perioperative cardiac complications; the incidence of either myocardial infarction (MI) or death is less than 1%.[1,2] Although the risk increases with the age of the patient, the low risk of perioperative complications does not justify widespread cardiac testing among all groups of surgical patients.

Among patients undergoing vascular surgery, however, the perioperative risk of cardiac complications is high. Although the reasons relate, in part, to the hemodynamic stresses associated with aortic procedures, the prevalence of atherosclerotic heart disease in patients undergoing vascular surgery exceeds 50%[3] and therefore may require special attention in the preoperative period. Coronary artery disease remains the major cause of death after any vascular operation[4]; therefore consideration for preoperative coronary artery revascularization has been a justifiable endeavor.

OPTIONS

As outlined by the American College of Cardiology/American Heart Association (ACC/AHA) Task Force recommendations before noncardiac operations,[5] the approach to assessing the potential cardiac risk associated with any patient scheduled for an elective noncardiac operation includes the nature of the operation, the risk of associated coronary artery disease, and the functional capacity of the patient (Figure 11-1). Determining the probability that a patient has severe obstructive coronary artery disease is one key ingredient of the preoperative risk assessment and should be based initially on the clinical history coupled with the nature of the operation. This entails the understanding that patients with vascular and orthopedic operations have the highest risk of postoperative cardiac complications compared with other noncardiac operations.[6-9] Specifically, individuals in need of a vascular operation involving an abdominal approach for either an expanding abdominal aortic aneurysm or advanced claudication have the highest risk.[2] Although urgent and emergent vascular operations occur in at least 20% of screened patients undergoing vascular operations,[10] these individuals are rarely considered candidates for preoperative coronary angiography and their preoperative risk management will not be addressed. The initial evaluation requires an assessment of a prior history of cardiac problems or risk factors along with either classic angina or unusual symptoms such as shortness of breath or atypical chest pains. Attention should be given to clinical risk variables[2,11] and include age greater than 70 years, angina, history of congestive heart failure, prior MI, prior stroke or transient ischemic attack (TIA), history of ventricular arrhythmias, diabetes mellitus (particularly insulin dependent), and abnormal renal function (creatinine level greater than 2.0 mg/dL). The physical examination also provides insight into high-risk variables,[5,10] including a chronic debilitated state, increased jugular venous distention, edema, S_3 gallop, and significant aortic stenosis, and the 12-lead electrocardiogram (ECG) provides prognostic information related to the presence of abnormal Q waves or heart rhythms. Although select clinical variables do predict perioperative cardiac morbidity and mortality risk, the optimal risk stratification tool for prediction of all complications in the postoperative period is controversial.[9] The final approach, therefore, is to determine whether, despite the absence of unstable clinical variables, there is sufficient concern to justify provocative stress testing preoperatively. Assessing the functional capacity of patients undergoing elective operations is an important ingredient in determining whether a patient can withstand the rigors of a prolonged operation. In those patients who are unable to achieve a 4-MET demand, a level compatible with routine daily activities, there is increased risk of postoperative events, and additional testing may be warranted.[12] Among patients with sufficient exercise capacity and an interpretable ECG, stress testing with an ECG alone may be a

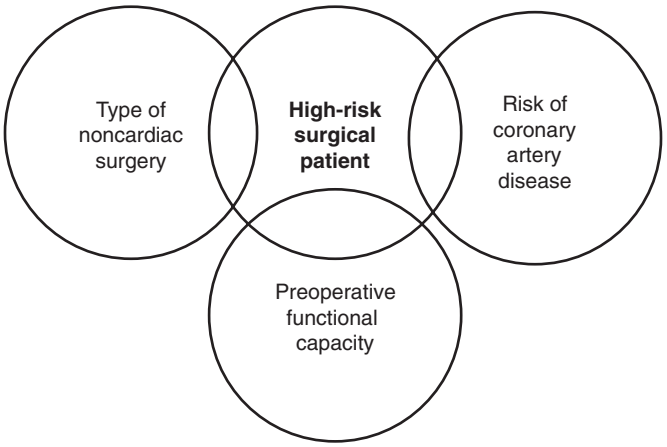

FIGURE 11-1 ■ Preoperative Assessment.

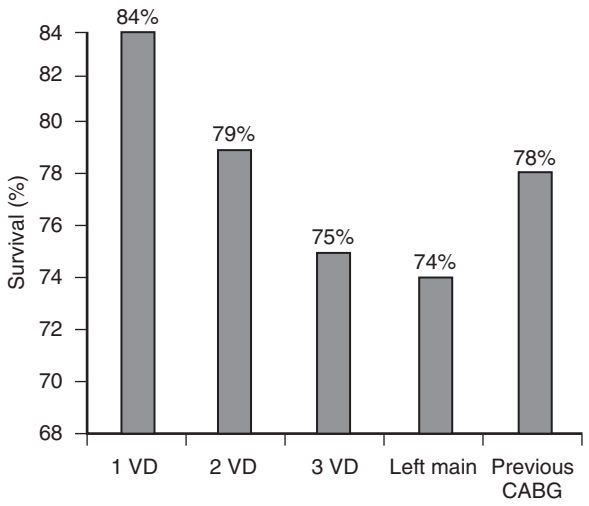

FIGURE 11-2 ■ Extent of Coronary Artery Disease and Survival 2.5 Years after the Vascular Operation. *CABG,* coronary artery bypass graft; *VD,* vessel disease.

cost-effective means of risk stratification for low-risk patients who do not need additional cardiac workup.[13,14] Among those patients who cannot exercise or who have baseline ECG abnormalities, stress imaging tests have been recommended as the standard alternative for the preoperative detection of multivessel coronary artery disease.[6] The presence of multiple ischemic segments indicative of either multivessel coronary artery disease or left main disease is considered high risk and is associated with an increased risk of perioperative cardiac complications and reduced long-term survival.[15,16] Ultimately, a combined approach of using clinical variables associated with stress imaging tests is most cost-effective.[17] The role of adjuvant pharmacologic therapies cannot be overemphasized[18] and will be addressed in other chapters.

EVIDENCE

Role of Coronary Revascularization

Severe coronary artery disease is common among patients undergoing vascular surgery[3] and is a major determinant of long-term survival after vascular surgery.[4] Thus the role of coronary revascularization in the preoperative management of patients with stable coronary artery disease has been one of the most debated issues in the field of perioperative medicine. As part of the Coronary Artery Revascularization Prophylaxis (CARP) trial, we have learned from the registry and randomized cohorts undergoing preoperative coronary angiography that the extent and severity of coronary artery disease is an identifier of long-term survival after vascular surgery (Figure 11-2).[19] This observation, coupled with outcome data from the Coronary Artery Surgery Study (CASS), which suggested better outcomes in patients with vascular disease who underwent coronary artery bypass surgery,[20] would support a plausible hypothesis that widespread identification and treatment of coronary artery disease should be an essential part of preoperative management. The paucity of prospective randomized data, however, made it difficult for physicians to reach a consensus on the optimal strategy for those patients with coronary artery disease who are scheduled for elective noncardiac surgery. A survey conducted before the publication of the CARP trial showed that recommendations for preoperative revascularization deviated from the guidelines 40% of the time, and the chance of widely disparate opinions among the participating cardiologists was 26%.[21] Clearly, a large-scale trial was needed to test the long-term benefit of preoperative coronary artery revascularization before major noncardiac operations.

The CARP trial was the first randomized, multicenter study designed to assess the role of prophylactic revascularization in patients with coronary artery disease undergoing elective vascular operations.[10] Over a 4-year period involving 18 university-affiliated Veterans Affairs medical centers, 510 (9%) of 5859 screened patients were enrolled and randomly assigned to a preoperative strategy of either coronary artery revascularization or no revascularization before elective vascular surgery. The surgical indications were an abdominal aortic aneurysm in 169 (33%) or symptoms of lower extremity arterial occlusive disease including severe claudication in 189 (37%) and rest pain in 152 (30%). Among the patients randomly assigned to a strategy of preoperative coronary artery revascularization, percutaneous coronary intervention (PCI) was performed in 141 (59%) and bypass surgery was performed in 99 (41%). The results of the study showed that procedural-related deaths associated with coronary artery revascularization occurred in only 1.7% of the patients, and no complications were related to cerebrovascular events, loss of limbs, or dialysis. The median times (interquartiles) from randomization to vascular surgery were 54 (28, 80) days in the coronary revascularization group, however, and 18 (7, 42) days in the no-revascularization group ($p < 0.001$). Within 30 days after vascular surgery, the mortality rate was 3.1% in the coronary revascularization group and 3.4% in the no-revascularization group ($p = 0.87$). An MI, defined by any elevation in troponins after vascular surgery, occurred in 11.6% of the revascularization group and in 14.3% of the no-revascularization

group ($p = 0.37$). At a median time of 2.7 years after randomization, the mortality rates were 22% in the revascularization group and 23% in the no-revascularization group ($p = 0.92$; relative risk, 0.98; 95% confidence interval, 0.70 to 1.37). The conclusions from the CARP study are that, among patients undergoing elective vascular surgery, a strategy of preoperative coronary artery revascularization before elective vascular surgery does not improve outcome but rather may delay or even prevent the needed vascular procedure. Based on these data, coronary artery revascularization before elective vascular surgery among patients with stable ischemic heart disease is not supported.[10] Since the CARP trial was published, three other studies have reported outcomes in patients with coronary artery disease undergoing noncardiac surgery (Table 11-1).[22,23]

Landesberg and colleagues[24] have accumulated enormous experience over the past decade and have shown that preoperative stress imaging tests with thallium can identify patients with a worse postoperative outcome. They have also shown the utility of a clinical scoring system that, in conjunction with a high-risk preoperative thallium test, suggests improved outcomes with preoperative coronary artery revascularization.[23] The authors have implied that the CARP results are not generalizable because the trial was underpowered for high-risk coronary anatomy because of the low prevalence of patients with triple-vessel coronary artery disease and the exclusion of unprotected left main stenoses from randomization.[23] To address this potential limitation, however, Poldermans and colleagues[22] tested the benefit of a strategy of preoperative coronary artery revascularization in patients with high-risk stress imaging test results who were scheduled for vascular surgery. Their preliminary results showed a borderline unfavorable outcome with revascularization 1 year after vascular surgery (mortality rate at 1 year: revascularization, 26.5%, no revascularization, 23.1%; $p = 0.58$). In a subgroup analysis of the CARP trial, we found no evidence of clinical benefit among patients with multivessel coronary artery disease randomly assigned to prophylactic revascularization.[25] More recently, Monaco and colleagues[26] randomly assigned 208 high-risk patients undergoing vascular surgery to a "selective strategy" consisting of coronary angiography based on high-risk findings on noninvasive imaging or a "systematic strategy" that consisted of routine preoperative coronary angiography with coronary revascularization as needed. As expected, the revascularization rate was higher in the systematic strategy arm of the study (58% versus 40%). Although in-hospital cardiac complications were similar in the two groups, a reduction in major cardiac events (MACE), including mortality, was reported during long-term follow-up in favor of a systematic strategy (86% versus 69%). The authors presumed this was due to higher utilization rates of coronary revascularization in the systematic strategy arm.

So how should a clinician integrate the findings from these three studies into a unified approach in the preoperative period? Although the findings from Landesberg and colleagues[24] are informative for prognosis, the potential selection bias that favors any decision to undergo coronary artery revascularization in some patients is an important limitation on predicting late outcomes on retrospective analyses. Likewise, in the study by Monaco and colleagues, the decision to perform coronary revascularization was not randomized, and this could explain the disproportionate magnitude of the benefit (20% absolute and 50% relative risk reduction in MACE at 8 years) with only modest differences in utilization rates of coronary revascularization.

Although the final study results of the DECREASE-V pilot study are unknown, together with the CARP trial results, they do not support an aggressive strategy in the vast majority of patients with stable cardiac symptoms. One important exception to this general

TABLE 11-1 **Clinical Studies Assessing the Role of Coronary Revascularization before Major Vascular Surgery**

	CARP Trial	DECREASE-V Pilot	Landesberg Study	Monaco Study
Study design	Multicenter, prospective	Multicenter, prospective	Single center, retrospective	Multicenter, prospective
Treatment allocation	Randomized	Randomized	Nonrandomized	Randomized
Endpoint	Mortality rate at 2.7 yr	Mortality rate at 1 yr	Mortality rate at 3 yr	Major adverse cardiac events
Treatment effect	No benefit	No benefit, possible harm	Benefit in intermediate risk	Benefit
Total patients screened	5859	1880	624	672
Total patients randomized	510	101	N/A	208
Patients with three-vessel or left main disease	93	37	73	55
Mortality rate: no revascularization group	23%	23.1%	21.8%	Not reported
Mortality rate: revascularization group	22%	26.5%	14.6%	Not reported

CARP, Coronary Artery Revascularization Prophylaxis; *DECREASE,* Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography.

rule is worth mentioning. Patients with left main coronary artery disease were excluded from the randomization process in CARP, but their management and outcomes after vascular surgery were captured in the CARP registry.[19] This subset of patients consisted of 48 of 1048 patients undergoing preoperative coronary angiography before their intended vascular surgery (4.6%). Although their long-term survival rate appears to be improved with preoperative coronary artery revascularization (survival at 2.5 years for surgically and medically treated left main disease was 84% and 52%, respectively; $p < 0.01$), it is uncertain that the prevalence of such a small cohort before vascular surgery warrants widespread screening with expensive stress imaging tests.

AREAS OF UNCERTAINTY

To improve the outcomes of high-risk patients undergoing elective operations, we must shift the paradigm from widespread identification and treatment of coronary artery disease in the preoperative phase to a more comprehensive identification and modification of risk factors in the postoperative phase. Among patients undergoing noncardiac operations, postoperative MI occurs primarily in those individuals with a prior history of coronary artery disease,[27] and the highest risk is related to surgery for an expanding abdominal aortic aneurysm.[2] Serial troponin assays have become the standard means of surveillance in the postoperative period because only a minority of patients with a documented MI will have symptoms,[28,29] The cost-effectiveness of widespread measurements of biochemical markers after noncardiac surgery is unclear but potentially provides a beneficial effect in targeting those individuals with advanced coronary artery disease in need of revascularization. The incidence of perioperative MI among individuals undergoing a vascular operation approaches 20% and can be predicted by abnormalities on preoperative stress imaging with thallium.[29] Among those individuals with a perioperative MI, the mortality rate is increased nearly fourfold during a 6-month postoperative follow-up period[30,31] and may predict the long-term mortality rate, although this is not certain beyond the first postoperative year.[32] Among those patients undergoing their intended vascular operation within the CARP trial, a perioperative elevation of troponin I above the 99th percentile of normal was most common in patients undergoing abdominal aortic cross-clamp procedures and was associated with a worse long-term outcome.[33] The causative factors that relate to a new MI in the postoperative phase are not necessarily related to a severe stenosis within a coronary artery that has not been revascularized. Instead, postoperative ischemic myocardium can be a result of coronary arteries that have been completely occluded and have insufficient collateral flow or a new unstable coronary artery lesion.[33] Alternatively, the perioperative phase can be associated with increased myocardial supply–demand mismatch, leading to subendocardial hypoperfusion without any change in the severity of the coronary artery stenoses.[34] Based on pathologic analysis from patients who have died of a perioperative MI, advanced coronary artery disease is present in the majority of patients; only a minority of individuals show intracoronary artery thrombus.[35,36] Clearly, more studies are needed to not only understand the biology of acute coronary artery syndromes after noncardiac surgery but also determine the optimal timing of revascularization, if that is deemed necessary. After the operations, it is imperative that therapies directed at secondary prevention be vigorously administered in suitable patients and should include antiplatelet agents, statins, beta-blockers, and possibly angiotensin-converting enzyme inhibitors. Within the CARP study, the vast majority of patients in both treatment arms were using these medications 2 years after randomization, and this may have contributed to an improved outcome in patients not undergoing an initial strategy of coronary artery revascularization.[9] Other than ischemic heart disease, patients with other modifiable risk characteristics, including congestive heart failure, ventricular arrhythmias,[37] and diabetes, need to be targeted in the postoperative period. Among the nonrandomized patients in the registry of the CARP study, these clinical variables were independent clinical variables that predicted the long-term mortality rate.[38]

GUIDELINES

Guidelines published by the ACC/AHA on perioperative cardiovascular evaluation and care define recommendations as follows.

Recommendations for Preoperative Coronary Revascularization with Coronary Artery Bypass Grafting or Percutaneous Coronary Intervention

All of the following Class I indications are consistent with the ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery.

Class I

Coronary revascularization before noncardiac surgery is

- Useful in patients with stable angina who have significant left main coronary artery stenosis. (level of evidence [LOE]: A)
- Useful in patients with stable angina who have three-vessel disease. (Survival benefit is greater when the left ventricular ejection fraction is less than 0.50.) (LOE: A)
- Useful in patients with stable angina who have two-vessel disease with significant proximal left anterior descending stenosis and either an ejection fraction less than 0.50 or demonstrable ischemia on noninvasive testing. (LOE: A)
- Recommended for patients with high-risk unstable angina or non–ST-segment elevation MI. (LOE: A)
- Recommended in patients with acute ST-segment elevation MI. (LOE: A)

Class IIa

1. In patients in whom coronary revascularization with PCI is appropriate for mitigation of cardiac symptoms and who need elective noncardiac surgery in the subsequent 12 months, a strategy of balloon angioplasty or bare-metal stent placement followed by 4 to 6 weeks of dual antiplatelet therapy is probably indicated. (LOE: B)
2. In patients who have received drug-eluting coronary stents and who must undergo urgent surgical procedures that mandate the discontinuation of thienopyridine therapy, it is reasonable to continue aspirin if at all possible and restart the thienopyridine as soon as possible. (LOE: C)

Class IIb

The usefulness of preoperative coronary revascularization is not well-established

- In high-risk ischemic patients (e.g., abnormal dobutamine stress ECG with at least five segments of wall-motion abnormalities). (LOE: C)
- For low-risk ischemic patients with an abnormal dobutamine stress ECG (segments 1 to 4). (LOE: B)

Class III

1. It is not recommended that routine prophylactic coronary revascularization be performed in patients with stable coronary artery disease before noncardiac surgery. (LOE: B)
2. Elective noncardiac surgery is not recommended within 4 to 6 weeks of bare-metal coronary stent implantation or within 12 months of drug-eluting coronary stent implantation in patients in whom thienopyridine therapy or aspirin and thienopyridine therapy will need to be discontinued perioperatively. (LOE: B)
3. Elective noncardiac surgery is not recommended within 4 weeks of coronary revascularization with balloon angioplasty. (LOE: B)

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AUTHORS' RECOMMENDATIONS

- To improve the outcomes of high-risk patients, clinicians must shift the paradigm of widespread screening and treatment of coronary artery disease before the operation to a comprehensive strategy for modification of risks in the postoperative period.
- The optimal strategy for identifying and treating high-risk patients before elective noncardiac surgery should underscore the value of a conservative strategy that includes proceeding with a timely operation, if deemed appropriate. It also should ensure use of medical therapies that reduce secondary outcomes in patients with coronary artery disease, particularly regarding therapeutic doses of beta-blockers.
- Patients with an unprotected left main stenosis may be the only subset of patients with multivessel coronary artery disease that need special consideration before a vascular operation. This subset consists of less than 5% of individuals undergoing noncardiac operations and does not justify widespread stress imaging tests preoperatively so that such a small subset can be identified.
- Those individuals with evidence of a perioperative myocardial infarction, congestive heart failure, ventricular arrhythmias, and diabetes should be targeted and appropriately treated in the postoperative period.

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CHAPTER 12

What Are the Role and Management of Percutaneous Coronary Intervention for Noncardiac Surgery?

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INTRODUCTION

Percutaneous coronary intervention (PCI) has revolutionized the management of coronary artery disease (CAD), initially with balloon angioplasty (BA) and subsequently with coronary stenting both with bare-metal stents (BMSs) and with drug-eluting stents (DESs).[1] The high incidence of coronary restenosis from neointimal coronary endothelial growth after BA prompted the clinical development and introduction of BMS placement. Although they represented a significant therapeutic advance, BMSs were still associated with coronary restenosis rates in excess of 10%.[1,2] The second major significant reduction in coronary restenosis after PCI resulted from DESs that pharmacologically retard stent endothelialization and neointimal growth with antimitotic agents such as sirolimus, paclitaxel, everolimus, and zotarolimus.[1-3] Because of slow release of these cytostatic agents, the risk of coronary restenosis with DESs has been significantly reduced to less than 10%.[1,2] The newer generations of DESs have extended the outcome benefits even further as compared with the first generation of DESs with a 38% lower risk of clinically significant coronary restenosis, a 43% lower risk of stent thrombosis (ST), and a 23% lower risk of death.[3]

Since the introduction of DESs, millions of these devices have been implanted worldwide.[4] The prevention of coronary ST is of paramount importance because this complication has a high mortality rate.[5] The risk of ST is particularly high before the coronary stent has been coated with endothelium (approximately 4 to 6 weeks for BMSs and at least 1 year for DESs).[4,5] As a result, dual antiplatelet therapy with aspirin and clopidogrel has been recommended for at least 1 month after BMS placement and for at least 12 months after DES placement.[1,4] Although premature discontinuation of antiplatelet therapy is a major risk for ST, there are multiple identified clinical and angiographic risk factors for ST (Table 12-1).[4-8]

The perioperative period qualifies as a major risk factor for ST because noncardiac surgery (NCS) activates platelets and induces hypercoagulability.[1,4,9] The significant risk of perioperative ST for BMSs was highlighted in a small case series that documented a 20% mortality rate in NCS within 6 weeks after BMS deployment.[10] Furthermore, NCS after recent BA is not without risk of myocardial ischemia and perioperative mortality. In a case series of 350 patients who had NCS within 2 months after BA, the perioperative mortality rate was 0.9% (95% confidence interval [CI], 0.2% to 2.5%).[11]

Given that up to 20% of patients with coronary stents require NCS within 3 years after PCI, the perioperative management of patients with recent PCI (BA, BMSs, DESs) is important because it concerns millions of patients who may be at significant perioperative risk of major adverse cardiovascular events.[12,13] This chapter reviews the options, latest evidence, and current expert recommendations concerning the perioperative risk of recent PCI in NCS.

OPTIONS TO MINIMIZE STENT THROMBOSIS AFTER RECENT PERCUTANEOUS CORONARY INTERVENTION AND NONCARDIAC SURGERY

The perioperative options for limiting coronary thrombosis after recent PCI are presented in Table 12-2.[1,4,14] The evidence for each option will be reviewed. Recent expert recommendations will be presented according to the schema of the American Heart Association (AHA) and American College of Cardiology (ACC), as outlined in Tables 12-3A (classes of recommendations) and 12-3B (levels of evidence). The expert recommendations and corresponding levels of evidence have been summarized in Table 12-4 (class I recommendations), Tables 12-5A and 12-5B (classes IIa and IIb recommendations), and Table 12-6 (class III recommendations).[14,15] The AHA/ACC guidelines for PCI (2011)[1] and perioperative cardiovascular care for NCS surgery (2007)[15] are available at www.americanheart.org (section on statements and practice guidelines; last accessed June 12, 2012.)

TABLE 12-1 **Identified Risk Factors for Coronary Stent Thrombosis**

Clinical Risk Factors	Angiographic Risk Factors
Cessation of platelet blockade	Thrombus-containing coronary lesions
Advanced age	Multiple coronary lesions
Diabetes	Overlapping coronary stents
Low ejection fraction	Coronary ostial lesions
Renal failure	Small-caliber coronary vessels
Acute coronary syndrome	Complicated stent deployment
Perioperative period	Coronary bifurcation lesions
Malignancy	Inflow lesion proximal to coronary stent
Peripheral arterial disease	Outflow lesion distal to coronary stent
Smoking	Development of neoatheroma within coronary stent

TABLE 12-2 **Options for Limiting Coronary Thrombosis after Noncardiac Surgery and Recent Percutaneous Coronary Intervention (PCI)**

Options	Considerations within the Option
Minimize preoperative PCI	1. Limit preoperative PCI in stable coronary disease 2. PCI for unstable coronary syndromes
Consider type of PCI	1. Balloon angioplasty 2. Bare-metal stents 3. Drug-eluting stents
Optimize platelet blockade	1. Continue aspirin and clopidogrel 2. Perioperative bridging with intravenous platelet blockade 3. Continue aspirin only
Education and collaboration	1. Surgeon 2. Cardiologist 3. Surgery at center with primary PCI availability

TABLE 12-3A **Definition of Classification Scheme for Clinical Recommendations**

Clinical Recommendations	Definition of Recommendation Class
Class I	The procedure/treatment should be performed (benefit far outweighs the risk)
Class IIa	It is reasonable to perform the procedure/treatment (benefit still clearly outweighs the risk)
Class IIb	It is not unreasonable to perform the procedure/treatment (benefit probably outweighs the risk)
Class III	The procedure/treatment should not be performed because it is not helpful and may be harmful (risk may outweigh the benefit)

Adapted from the following guidelines:

1. *Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery. Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. Circulation 2007;116:1971–96.*
2. *Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011;124:2574–609.*

TABLE 12-3B **Classification Scheme for Supporting Evidence for Clinical Recommendations**

Level of Evidence	Definition of Recommendation Class
Level A	Sufficient evidence from multiple randomized trials or meta-analyses
Level B	Limited evidence from a single randomized trial/multiple nonrandomized studies
Level C	Case studies and/or expert opinion

Adapted from the following guidelines:

1. *Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery. Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. Circulation 2007;116:1971–96.*
2. *Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011;124:2574–609.*

TABLE 12-4 Class I Recommendations for Percutaneous Coronary Intervention (PCI) and Noncardiac Surgery (NCS)

Recommendation	Class and Evidence
PCI before NCS is indicated in appropriate patients with stable angina who have two-vessel disease with significant proximal left anterior descending artery stenosis and either an ejection fraction less than 50% or demonstrable ischemia on noninvasive testing	I (level A)
PCI before NCS is recommended for appropriate patients with high-risk unstable angina or non–ST-segment elevation myocardial infarction	I (level A)
PCI before NCS is recommended in appropriate patients with ST-segment elevation myocardial infarction	I (level A)

ST, stent thrombosis.

Adapted from the following guidelines:

1. *Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery. Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. Circulation 2007;116: 1971–96.*
2. *Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011;124:2574–609.*

TABLE 12-5A Class IIa Recommendations for Percutaneous Coronary Intervention (PCI) and Noncardiac Surgery (NCS)

Recommendation	Class and Evidence
In patients who require PCI to alleviate myocardial ischemia and who require elective NCS in the following 12 mo, the recommended strategy is balloon angioplasty or bare-metal stent placement followed by 4-6 wk of dual antiplatelet therapy (aspirin and clopidogrel)	IIa (level B)
In patients who have drug-eluting coronary stents and who require emergency NCS that mandates discontinuation of clopidogrel, it is reasonable to continue aspirin therapy and restart clopidogrel as soon as clinically possible	IIa (level C)

Adapted from the following guidelines:

1. *Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery. Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. Circulation 2007;116: 1971–96.*
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TABLE 12-5B Class IIb Recommendations for Percutaneous Coronary Intervention (PCI) and Noncardiac Surgery (NCS)

Recommendation	Class and Evidence
The benefit of PCI before NCS is not established in high-risk ischemic patients (e.g., five or more wall motion abnormalities during dobutamine stress echocardiography)	IIb (level C)
The benefit of PCI before NCS is not established in low-risk ischemic patients (e.g., one to four wall motion abnormalities during dobutamine stress echocardiography)	IIb (level B)

Adapted from the following guidelines:

1. *Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery. Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. Circulation 2007;116: 1971–96.*
2. *Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011;124:2574–609.*

TABLE 12-6 **Class III Recommendations for Percutaneous Coronary Intervention (PCI) and Noncardiac Surgery (NCS)**

Recommendation	Class and Evidence
Routine PCI in patients with stable coronary artery disease is not recommended before NCS	III (level B)
Elective NCS that requires perioperative discontinuation of clopidogrel or aspirin and clopidogrel is not recommended within 4-6 wk of bare-metal coronary stent deployment	III (level B)
Elective NCS that requires perioperative discontinuation of clopidogrel or aspirin and clopidogrel is not recommended within 12 mo of drug-eluting coronary stent deployment	III (level B)
Elective NCS is not recommended within 4 wk of coronary revascularization with balloon angioplasty	III (level B)

Adapted from the following guidelines:

1. *Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery. Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. Circulation 2007;116:1971–96.*
2. *Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011;124:2574–609.*

EVIDENCE

Minimize Preoperative Percutaneous Coronary Intervention

Patients with CAD will often not benefit from coronary revascularization with PCI before NCS. The Coronary Artery Revascularization Prophylaxis (CARP) trial randomly assigned 510 patients with angiographically proved CAD to coronary revascularization or medical management before elective major vascular surgery (33% abdominal aortic aneurysm repair; 67% infrainguinal vascular bypass).[16] The exclusion criteria included significant left main coronary stenosis, unstable CAD syndromes, aortic stenosis, and severe cardiomyopathy (defined as a left ventricular ejection fraction < 20%). Coronary revascularization was achieved surgically in 41% and with PCI in 59% of enrolled subjects. Patients with or without preoperative revascularization had a similar incidence of postoperative myocardial infarction (8.4% versus 8.4%, $p = 0.99$) and a similar 27-month survival rate (78% versus 77%, $p = 0.98$).[16] Therefore this landmark study suggests that preoperative PCI for stable CAD may not be required before NCS. Of all patients screened for the CARP trial, 4.6% had clinically important left main coronary disease.[17] Even though this subset was excluded from the CARP trial, it was the only subset who demonstrated a survival benefit from preoperative coronary revascularization.[17] Further analysis of the CARP dataset has also revealed that although postoperative cardiac complications are accurately predicted by the revised cardiac risk index (odds ratio [OR], 1.73; 95% CI, 1.26 to 2.38; $p < 0.001$), preoperative coronary revascularization was unable to reduce these complications in high-risk subgroups identified by the revised cardiac risk index (OR, 0.86; 95% CI, 0.50 to 1.49; $p = 0.60$).[18] Interestingly, patients in the CARP trial who underwent preoperative revascularization had better protection from subsequent myocardial infarction from surgical revascularization as compared with PCI (6.6% versus 16.8%; $p = 0.024$).[19]

The DECREASE-II trial evaluated preoperative cardiac testing in major vascular surgical patients who had intermediate cardiac risk factors and who received adequate beta-blocker therapy.[20] This trial demonstrated that preoperative coronary revascularization did not significantly improve the 30-day outcome in patients with extensive ischemia (OR, 0.78; 95% CI, 0.28 to 2.1; $p = 0.62$).[20]

The DECREASE-V pilot study randomly assigned 101 vascular surgical patients with extensive ischemia (defined as five or more ischemic segments during dobutamine stress echocardiography or at least three ischemic segments identified by dipyrimadole perfusion scintigraphy) to preoperative coronary revascularization versus best medical therapy.[21] Coronary revascularization was achieved surgically in 35% and with PCI in 65% of enrolled subjects. The composite primary outcome (perioperative death and myocardial infarction) was similar between study groups (43% for revascularization versus 33% for medical therapy; OR, 1.4; 95% CI, 0.7 to 2.8; $p = 0.30$). The incidence of death and myocardial infarction at 1 year was high at 47% but similar in both groups (49% for revascularization and 44% for medical therapy; OR, 1.2; 95% CI, 0.7 to 2.3; $p = 0.48$).

Taken together, these three important clinical trials (CARP, DECREASE-II, and DECREASE-V) point to a more limited role for PCI in stable CAD before NCS. Their cumulative evidence forms the basis of the expert recommendations relating to PCI before elective NCS in stable CAD (see Tables 12-4 to 12-6).

In unstable angina or myocardial infarction, PCI is indicated in appropriate patients for management of the acute coronary syndrome in its own right. Firstly, PCI before NCS is recommended for appropriate patients with high-risk unstable angina or non–ST-segment elevation myocardial infarction (class I recommendation; level A evidence). Secondly, PCI before NCS is also recommended in appropriate patients with ST-segment elevation myocardial infarction (class I recommendation; level A evidence).

In the setting of stable CAD, PCI has a more limited role, as explained earlier. Routine PCI in patients with stable CAD is not recommended before NCS (class III recommendation; level B evidence). The benefit of PCI before NCS is not established in high-risk ischemic patients, for example, with five or more wall motion abnormalities during dobutamine stress echocardiography (class IIb recommendation; level C evidence). The benefit of PCI before NCS is also not established in low-risk ischemic patients, for example, with one to four wall motion abnormalities during dobutamine stress echocardiography (class IIb recommendation; level B evidence). PCI before NCS surgery, however, is indicated in appropriate patients with stable angina who have two-vessel disease with significant proximal left anterior descending (LAD) artery stenosis and either an ejection fraction less than 50% or demonstrable ischemia on noninvasive testing (class I recommendation; level A evidence).

Type of Percutaneous Coronary Intervention

Balloon Angioplasty

Seven retrospective studies have examined cardiovascular outcome after coronary BA before NCS. The main features of these studies are summarized in Table 12-7.[11,22-27] Five of the seven studies are limited by factors such as a small sample size, a long interval between coronary angioplasty and surgery, or a control group with coronary stents.[22-24,26,27] The remaining two studies suggest that NCS after BA is safe, particularly if surgery occurs at least 2 weeks after coronary intervention.[11,21] This minimum time period allows the coronary injury at the BA site to heal and thus not be at risk for perioperative thrombosis.

Thus it appears that the 2- to 4-week period after BA minimizes the incidence of an acute coronary syndrome after NCS. However, if surgery occurs more than 8 weeks after coronary BA, significant restenosis at the angioplasty site might cause perioperative myocardial ischemia. The expert recommendation specifies that elective NCS after BA should be performed within a narrow window of 4to 8 weeks after coronary revascularization with BA (class III recommendation; level B evidence). Daily aspirin therapy should be maintained perioperatively, unless the bleeding risk is deemed too high.

Recently, drug-eluting BA has emerged as a new technique in PCI.[28] This technique was introduced as a possible solution for selected de novo coronary lesion subsets and in-stent restenosis. The exact clinical niche of this novel technology has yet to be determined. This new technique in PCI has not been addressed in recent guidelines because of its developing role.[1-15]

Bare-Metal Coronary Stents

The retrospective study by Kaluza and colleagues[10] (n = 40) documented a 20% perioperative mortality rate in patients who had NCS less than 6 weeks after coronary stenting with BMSs. A second retrospective study by Wilson and colleagues[29] (n = 207) demonstrated a 3% perioperative mortality rate in patients with BMSs who underwent NCS within 6 weeks of coronary stenting. A third report by Reddy and Vaitkus[30] (n = 56) revealed a 38% incidence of ST or cardiovascular death in patients who had undergone NCS within 14 days of BMS deployment. No patient who had NCS more than 6 weeks after BMS placement had cardiovascular complications. In a fourth study by Sharma and colleagues[31] (n = 47), perioperative mortality rate was 26% in the setting of NCS less than 3 weeks after BMS placement as compared with a 5% mortality rate in the setting of NCS more than 3 weeks after BMS placement. This study also documented in the early surgery group an 85.7% (6 of 7) mortality rate in patients who had stopped thienopyridine therapy.

TABLE 12-7 **Outcomes with Coronary Balloon Angioplasty (CBA) before Noncardiac Surgery**

Clinical Study	Sample Size	Time from CBA to Surgery	Mortality Rate	Myocardial Infarction	Comment
Allen et al (1991)[22]	148	Mean of 338 days	2.7%	0.7%	Long interval to surgery
Huber et al (1992)[23]	50	Mean of 9 days	1.9%	5.6%	Small study; no control group
Elmore et al (1993)[24]	14	Mean of 10 days	0%	0%	Very small study
Gottlieb et al (1998)[25]	194	Mean of 11 days	0.5%	0.5%	Only vascular surgeries
Posner et al (1999)[26]	686	Median of 1 yr	2.6%	2.2%	Long interval to surgery
Brilakis et al (2005)[11]	350	Within 2 mo	0.3%	0.6%	All events occurred after surgery within 2 wk after CBA
Leibowitz et al (2006)[27]	216	Early (0-14 days) Late (15-62 days)	11% 20%	7.2% 16.8%	56% CBA; 44% stents Similar outcomes

Adapted from the following guideline: Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery. Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. Circulation 2007;116:1971–96.

The collective findings from this set of studies can be interpreted with respect to the cellular process that lines BMSs with coronary endothelium. Endothelialization of BMSs takes about 4 to 6 weeks, after which the risk of BMS thrombosis is extremely unlikely. During the process of stent endothelialization, dual antiplatelet therapy with aspirin and clopidogrel is recommended to minimize the risk of ST. The clopidogrel is no longer required after 6 weeks when endothelialization is typically adequate. Thereafter, aspirin therapy is recommended indefinitely and should be continued perioperatively, unless the bleeding risk is judged to be prohibitive.

As a result, the expert recommendation is that elective NCS, which requires perioperative discontinuation of clopidogrel, is not recommended within 4 to 6 weeks of bare-metal coronary stent deployment (class III recommendation; level B evidence).

Drug-Eluting Stents

DESs revolutionized PCI because they have significantly reduced the rate of coronary restenosis because of retardation of coronary endothelial growth from slow release of antimitotic agents.[32] As a consequence, ST with DES remains an ongoing risk because of lack of endothelialization. A systematic review of perioperative ST included 10 studies (1995 to 2006) for a sum total of 980 patients who had NCS after placement of either a BMS or DES.[33] The median interval between stent deployment and NCS was 13 to 284 days, and the majority of the pooled cohort had BMS. The perioperative rates of death and myocardial infarction ranged from 2% to 28% and 3% to 20%, respectively. Despite the limitations of the included studies, two perioperative factors significantly increased perioperative cardiovascular risk: (1) discontinuation of dual antiplatelet therapy (i.e., aspirin and clopidogrel) and (2) surgery within 6 to 12 weeks after stent deployment. These collated findings from the literature were confirmed in a subsequent study by the same investigators ($n = 192$).[34]

These findings from systematic review do not specifically apply to DESs because the pooled study population included BMSs as well as DESs. The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) studied 6033 patients treated with DESs and 13,738 patients treated with BMSs with a 3-year follow-up.[35] The relative rate of clinical coronary restenosis was 60% lower in the DES group. However, in the DES group, there was an incremental absolute risk of death of 0.5% per year and an incremental absolute risk of death or myocardial infarction of 0.5% to 1.0% per year after the initial 6 months. The adverse long-term events with DESs are principally related to the risk of ST. The multiple risk factors for ST are summarized in Table 12-1.

A new generation of DESs has been developed that was designed to address the weaknesses of first-generation DES. The first-generation stents have a higher risk of ST than newer generation DESs due to hypersensitivity from the stent polymer, thicker strut design, and antimitotic drug kinetics.[36-39] The newer generation of DESs has greater biocompatibility, thinner struts, and better antiproliferative drug platforms.[3,40-41] Recent data from the Swedish coronary stent registry demonstrated a 43% lower risk of ST with the latest DES in the first 2 years after implantation.[3] In a large observational cohort study, newer DESs were associated with a 58% to 68% reduction in overall risk of ST.[41]

The persistent risk of ST with DESs is reviewed in a multisociety expert guideline that focuses on the prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents, especially DESs.[42] The expert recommendation is that elective NCS which requires perioperative discontinuation of clopidogrel is not recommended within 12 months of DES deployment (class III recommendation; level B evidence). Furthermore, in patients who have DESs and who require emergency NCS that mandates discontinuation of clopidogrel, it is reasonable to continue aspirin therapy and restart clopidogrel as soon as clinically possible after surgery (class IIa recommendation; level C evidence). Currently, there are no differences in recommendations for perioperative platelet blockade based on the stent generation.[1,15,42]

CURRENT RISK OF STENT THROMBOSIS IN NONCARDIAC SURGERY

Patients with coronary stents frequently require NCS. In a recent single center study, 22% of patients required NCS within 3 years of DES implantation and had a perioperative cardiac complication rate of 2%.[13] In a large multicenter study, 4.4% of patients required major NCS in the first year after DES placement and had a major cardiac complication rate of 1.9%.[43] In this sizeable study, the cardiac risk was 27 times higher in the week after NCS (hazard ratio, 27.3; 95% CI, 10.0 to 74.2; $p < 0.001$).[43] A large tertiary care center documented a 2.0% risk of perioperative ST in surgical patients with DESs; the risks of ST ($p < 0.0001$) and major adverse cardiovascular events ($p < 0.014$) decreased significantly in the first 6 months after surgery.[44] A recent multicenter French observational study documented a 1.5% incidence (95% CI, 0.79 to 2.21) of perioperative ST, noting that the ST risk was 2.5% when NCS was performed in the first year after stent insertion, but declined to 1.3% thereafter.[45] Interestingly, the risk of ST did not correlate with stent type, although cessation of oral platelet blockade more than 5 days before NCS independently predicted cardiovascular complications (OR, 2.11; 95% CI, 1.23 to 3.63; $p = 0.007$).[45] The mortality rate due to ST in this contemporary study was 29.4%, highlighting the concern about the prevention of this perioperative complication.[45]

Perioperative Antiplatelet Therapy

In the presence of a BMS or DES, early withdrawal of antiplatelet therapy is a major risk factor for perioperative ST (see Table 12-1).[1,15,42] The options for perioperative platelet blockade to maintain stent patency and to minimize perioperative ST include the following:

1. Continue dual antiplatelet therapy during and after surgery.
2. Discontinue clopidogrel but bridge the patient to surgery by using short-acting intravenous platelet blockade; then restart clopidogrel as soon as possible after surgery.[46]
3. Continue aspirin perioperatively but discontinue clopidogrel preoperatively; restart it as soon as possible after surgery.

Option I: Dual Antiplatelet Therapy during and after Surgery

This option maintains standard dual platelet blockade perioperatively and has a very low incidence of ST. The perioperative team must weigh the risks of bleeding associated with the particular surgical procedure versus the life-threatening consequences of ST. In procedures such as dental extractions,[47] cataract surgery,[48] and routine dermatologic surgery,[49] bleeding can almost always be controlled locally even in the presence of dual platelet blockade. In surgical procedures with a higher bleeding risk, surgeons can often be persuaded to continue both aspirin and clopidogrel when reminded that ST often results in death or significant myocardial infarction.[50] However, this strategy must be adapted in the setting of closed space surgery such as in the brain, the spinal cord, and the eye.[51-53]

Option II: Discontinue Clopidogrel and Bridge with Intravenous Platelet Blockade

Platelet inhibition due to clopidogrel is irreversible. Clopidogrel must be discontinued for 5 to 10 days before normal hemostasis is achieved from the production and release of new platelets. If NCS is required early after stent placement and clopidogrel must be stopped (e.g., craniotomy for tumor resection), it is not unreasonable to bridge the patient with short-acting intravenous anticoagulation.[54] Because ST is primarily due to platelet aggregation, it is logical that an intravenous antiplatelet agent such as a short-acting platelet receptor IIb/IIIa blocker would be important. Tirofiban and eptifibatide are two IIb/IIIa blockers that have been demonstrated to be well tolerated. In concept, short-acting anticoagulant infusion bridging therapy already has a clinical precedent in the preparation of a patient with a mechanical heart valve for NCS. The patient at risk of valve thrombosis is admitted to the hospital for discontinuation of warfarin with interim heparinization as a bridge to surgery.

This bridging approach was first exemplified in a study of 30 patients with DESs undergoing NCS.[55] Clopidogrel was discontinued 5 days before surgery. Each patient was admitted to the hospital 3 days before surgery for commencement of tirofiban and heparin infusions. These dual anticoagulant infusions were discontinued 6 hours before surgery. On the first postoperative day, a loading dose of clopidogrel was started followed by maintenance dosages thereafter. Aspirin therapy was continued throughout the perioperative period. Although these patients had no perioperative ST, this case series is proof-of-concept only.

Since this initial case series, there have been multiple trials validating the safety and efficacy of perioperative bridging with intravenous platelet blockade in high-risk patients with BMSs or DESs.[54,56-59] The thoracic surgery team at Duke has developed an algorithm for patients taking clopidogrel who will be undergoing lung resection; it is summarized in Figure 12-1.[59] Their patient cohort required lung resection due to lung cancer but were also at high risk of bleeding complications. In their study, a patient's risk of ST was evaluated preoperatively. Risk factors for ST included DES implantation less than 12 months before the current surgery or DES implantation longer than 12 months ago but associated with renal insufficiency, critical stent location, or off-label placement of a coronary stent. High-risk patients stopped clopidogrel 5 days before surgery, and were admitted 2 to 3 days preoperatively for bridging with an eptifibatide infusion. The eptifibatide infusion was stopped 8 hours before surgery, and clopidogrel was restarted 12 to 48 hours after surgery. This protocol was implemented successfully with close cooperation between the thoracic surgeons, anesthesiologists, and cardiologists.[59]

The approach to perioperative management of platelet blockade in the setting of coronary stents has recently been systematically reviewed in two separate multisociety guidelines.[60-61] These guidelines highlight the importance of the bridging approach in high-risk settings with multidisciplinary collaboration. This perioperative teamwork is essential to optimize the balance between coronary stent patency and surgical hemostasis.[60-61]

A novel option for antiplatelet bridging therapy is the short-acting intravenous $P2Y_{12}$ blocker cangrelor. Cangrelor has an extremely short half-life (3-6 minutes), which gives it a very rapid offset of effect and return to baseline platelet function within an hour.[62] This is in contrast to the glycoprotein IIb/IIIa inhibitors which have an offset time of 4-6 hours. Cangrelor was recently evaluated in a randomized placebo-controlled study to bridge patients on clopidogrel to coronary artery bypass surgery.[63] Patients were randomly assigned to receive cangrelor or placebo for 48 hours after discontinuation of clopidogrel. Cangrelor was stopped 1 to 6 hours before surgery. Cangrelor exposure blocked platelet activity (relative risk, 5.2; 95% CI, 3.3 to 8.1; $p < 0.001$) and did not increase surgical bleeding risk (relative risk, 1.1; 95% CI, 0.5 to 2.5; $p = 0.763$).[63] This study was underpowered to evaluate cangrelor's ability to reduce ST.

Option III: Discontinue Clopidogrel Preoperatively and Restart after Surgery

This approach is logical if the coronary stent is fully endothelialized with a low risk of perioperative ST (4 to 6 weeks for BMSs and 12 months for DESs). However, there is variability in the rate of stent endothelialization, especially for DESs. Consequently, the risk for ST may persist in a subset of patients beyond 1 year.[64-65] When clopidogrel is begun postoperatively, it is reasonable to give a loading dose as there is post-surgical platelet activation and many patients are hyporesponsive to clopidogrel.[66]

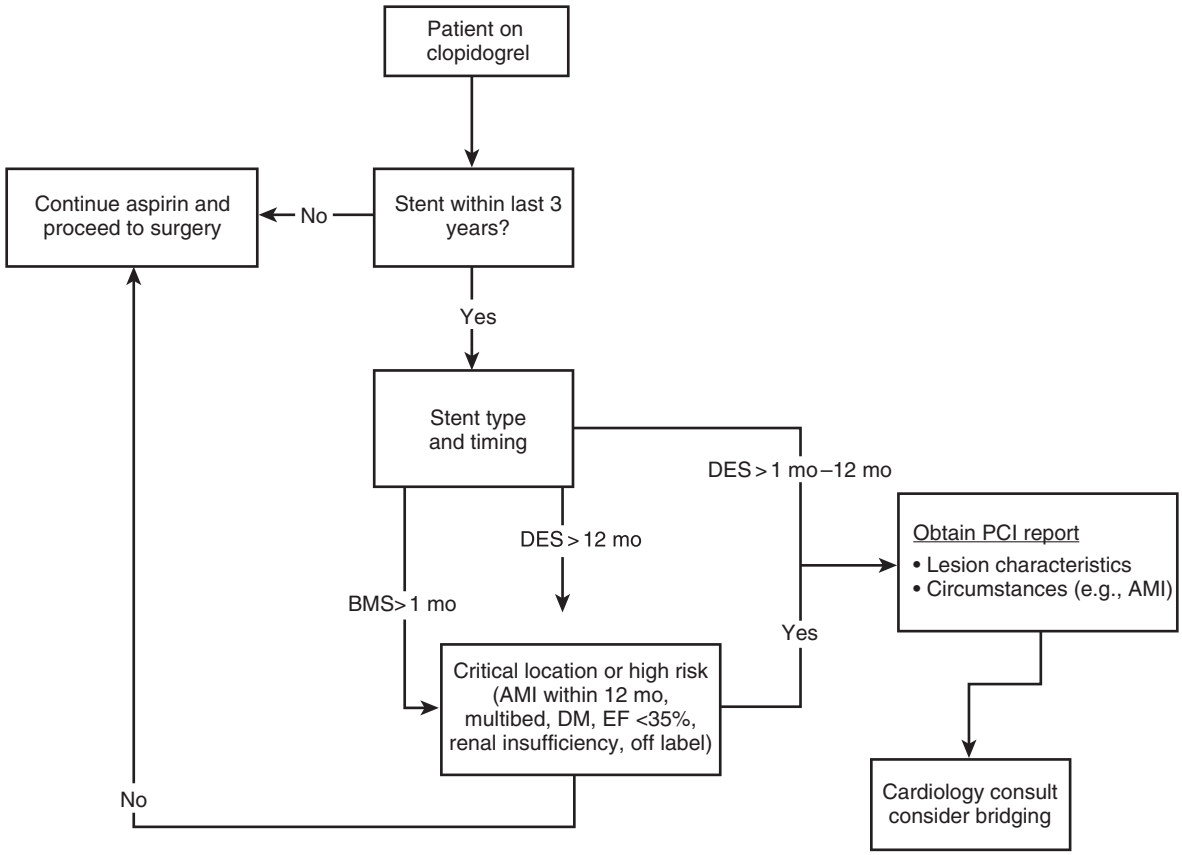

FIGURE 12-1 ■ Algorithm for Evaluation of Patients Receiving Clopidogrel Undergoing High-Risk Surgery. *AMI,* acute myocardial infarction; *BMS,* bare-metal stent; *DES,* drug-eluting stent; *DM,* diabetes mellitus; *EF,* ejection fraction; *PCI,* percutaneous coronary intervention. (Adapted from Ceppa DP, Welsby IJ, Wang TY, Onaitis MW, Tong BC, Harpole DH, et al. Perioperative management of patients on clopidogrel (Plavix) undergoing major lung resection. Ann Thorac Surg 2011;92:1971–6.)

Aspirin therapy should be continued throughout the perioperative period.[67] For patients who have DESs and who require emergency NCS that mandates discontinuation of clopidogrel, it is reasonable to continue aspirin (class IIa recommendation; level C evidence).[1,15]

EDUCATION AND COLLABORATION

The severe morbidity and mortality rates associated with perioperative ST mandate a collaborative approach among surgeons, anesthesiologists, and cardiologists.[1,15,60-61]

In a survey of anesthesiologists, 63% were not aware of recommendations about timing of NCS after BMS or DES placement.[68] Anesthesiologists and surgeons should have a collaborative approach to patients with coronary stents.[1,15,60-61,69] This approach could include the following aspects:

1. Determination of all stent details such as stent type(s), coronary locations, date(s) of implantation, and duration and type of antiplatelet therapy
2. Consultation with a cardiologist, preferably the patient's cardiologist
3. A joint decision with input from the anesthesiologist, surgeon, and cardiologist about the timing of NCS and the perioperative anticoagulation plan with special emphasis on platelet blockade
4. Performance of the NCS in a medical center that has 24-hour interventional cardiology coverage for prompt therapy of ST, if it occurs

MANAGEMENT OF PERIOPERATIVE STENT THROMBOSIS

ST most often manifests as an ST-segment elevation myocardial infarction and requires early reperfusion. Thrombolytic therapy is contraindicated in this setting because of the risk of severe bleeding after recent surgery. Furthermore, it is less effective than primary PCI. An early invasive strategy for acute myocardial infarction after NCS was still associated with a 35% mortality rate ($n = 48$).[70] Although this is a high perioperative mortality rate, it was in patients who often were treated after cardiac arrest or who were in cardiogenic shock. Despite advances in coronary stent design, perioperative ST still has a high mortality rate.[45]

AREAS OF UNCERTAINITY

The natural history of perioperative ST after BMS and DES implantation still requires further investigation to confirm incidence, determine contemporary

perioperative outcomes, and assess the best perioperative practice of platelet blockade, including the novel blocker cangrelor. Furthermore, the current problem of ST with DESs has prompted the development of bioabsorbable DESs in an effort to deal effectively with not only restenosis but also thrombosis.[71] Although this next generation of coronary stents has demonstrated clinical equivalency in initial clinical evaluation, long-term large-scale studies are required to assess their efficacy and safety compared with current DESs, including that in the perioperative period.[71] The recent approval of the novel oral $P2Y_{12}$ blocker, prasugrel, has introduced an alternative to clopidogrel for dual oral platelet blockade.[1,72] Further trials are indicated to assess the effects of this agent on perioperative outcome and management of platelet blockade.

GUIDELINES AND AUTHORS' RECOMMENDATIONS

The options and evidence concerning the perioperative risks and management of recent percutaneous coronary intervention (PCI) before noncardiac surgery (NCS) have been discussed. This topic is important because it is common and serious. We support the expert recommendations on this topic from the recent guidelines for PCI as well as perioperative cardiovascular evaluation and care for NCS.[1,15] These recommendations are summarized for rapid review and quick reference in Tables 12-4 through 12-6.

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CHAPTER 13

How Should We Prepare the Patient with a Pacemaker/Implantable Cardioverter-Defibrillator?

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INTRODUCTION

Battery-operated pacemakers (PMs) revolutionized the treatment of fatal electrical conduction abnormalities in 1958, just a few years after the invention of the transistor. As this science has matured, PMs have been designed to provide atrioventricular synchronization, improve the quality of life for the chronotropically incompetent patient, prevent and treat atrial fibrillation, and reduce ventricular contractile dyssynchrony in the presence of cardiomyopathy. The development of implantable cardioverter-defibrillators (ICDs), capable of antitachycardia pacing or high-energy shock, extended this science to patients who experience ventricular tachyarrhythmias. ICDs were first demonstrated in 1980 and approved by the U.S. Food and Drug Administration (FDA) in 1985. Current ICDs represent advancements of PM technology, so every ICD implanted today, in addition to high-energy therapy for ventricular arrhythmias, can provide the entire functional set of antibradycardia-pacing capabilities found in a conventional PM.

These devices are no longer confined to keeping the heart beating between a minimum rate (pacing function) and a maximum rate (ICD functions); they are now employed as therapy to improve the failing heart (biventricular [BiV] pacing, also called cardiac resynchronization therapy [CRT]). Electronic miniaturization of PMs and ICDs has permitted the design and use of sophisticated electronics in patients who need artificial pacing or automated cardioversion/defibrillation of their heart (or both).

Coupled with population aging, continued enhancements and new indications for implantation of PMs or ICDs will lead to increasing numbers of patients with these devices. Safe and efficient clinical management of these patients depends on our understanding of implantable systems, indications for their use, and the perioperative needs that they create.

However, the increasing specialization, the proprietary nature of hardware and software developments, and the complexity of cardiac generators limit generalizations that can be made about the perioperative care of these patients. Additionally, the absence of published trials, the incorrect interpretation of adverse events in published literature, and the economic and technical challenges involved in appropriately evaluating these devices preoperatively and postoperatively add to the difficulties in properly managing these patients.

These issues led the American Society of Anesthesiologists (ASA) to publish a Practice Advisory for these patients in 2005, which was updated in 2011.[1] In addition, the Heart Rhythm Society (HRS) and ASA, in collaboration with the American Heart Association and the Society of Thoracic Surgeons, recently published an Expert Consensus Statement.[2] Other recommendations have been published as well,[3-6] although not all authors advocate routine disabling of ICD high-energy therapy in the perioperative period.[7]

OPTIONS/THERAPIES

Information contained herein applies to the perioperative management of patients with PMs and ICDs. It does not address the management of patients for whom these therapies might become necessary nor instances when these devices might no longer be needed.

EVIDENCE

Whether PM or ICD patients have increased perioperative morbidity or mortality risk remains an area ripe for investigation. Levine and colleagues[8] reported increases in pacing thresholds (i.e., the amount of energy required to depolarize the myocardium) in some thoracic operations. In 1995, Badrinath and colleagues[9] retrospectively reviewed ophthalmic surgery cases in one hospital in Madras, India, from 1979 through 1988 (14,787 cases) and found that the presence of a PM significantly increased the probability of a mortal event within 6 weeks postoperatively, regardless of the anesthetic technique. Pili-Floury and colleagues[10] reported that two of 65 PM patients (3.1%) undergoing significant noncardiac surgery died postoperatively of cardiac causes over a 30-month study period. They also reported that 12%

of patients required preoperative and 7.8% required postoperative modification of PM programming. In abstract form, Rozner and colleagues[11] reported a 2-year retrospective review of 172 PM patients evaluated at a preoperative anesthesia clinic, showing that 27 of 172 (16%) needed a preoperative intervention (nine of 27 were generator replacement for battery depletion). Additionally, follow-up of the 149 patients who underwent an open surgical procedure showed five ventricular pacing threshold increases, one atrial pacing threshold increase, and one PM electrical reset, all of which took place in patients undergoing nonthoracic surgery. All of these cases involved electromagnetic interference (EMI) from a monopolar electrosurgical unit (ESU), and one large ventricular pacing threshold was observed after a significant fluid and blood resuscitation after the loss of 2500 mL of blood in a 45-year-old woman. Finally, Cheng et al[12] prospectively evaluated 57 patients with ICDs (17% not evaluated in the past 3 months) and 35 with PMs (23% not evaluated in the past 6 months) for a variety of cases. There was no change in pacing or sensing thresholds but significantly decreased lead impedance in all chambers. One ICD reported an elective reset because of battery depletion during the case. At postoperative evaluation, several devices reported EMI but no ICDs delivered therapy.

For the patient with ventricular tachycardia or ventricular fibrillation, ICDs clearly reduce deaths, and they remain superior to antiarrhythmic drug therapy.[13] Further, studies suggesting prophylactic placement in patients without evidence of tachyarrhythmias (Multicenter Automatic Defibrillator Implantation Trial–II [MADIT-II], which studied ischemic cardiomyopathy and patients with an ejection fraction less than 0.30,[14] and Sudden Cardiac Death–Heart Failure Trial [SCD-HeFT], which studied any cardiomyopathy and patients with an ejection fraction less than 0.35[15]) have significantly increased the number of patients for whom ICD therapy is indicated.

ICD features and advancements can present consequences particularly relevant to the perioperative practitioner. First, all ICDs have bradycardia-pacing capability, and the presence of pacing artifacts on an electrocardiogram (ECG) might lead a practitioner to mistake an ICD for a conventional PM. Second, ICD bradycardia-pacing is *never* converted to asynchronous mode with magnet placement; thus, for many ICDs, confirmation of appropriate magnet placement is absent. Third, ICDs respond to, and process, EMI differently than a PM.

This field is further complicated by the nature of electronics, as well as asymptomatic device malfunctions or outright device failure. Although PMs and ICDs are more reliable than almost any other technology, some devices fail prematurely. Maisel and colleagues[16] searched the FDA database for the years 1990-2002; they found that 4.6 PMs and 20.7 ICDs per 1000 implants had been explanted for failures other than battery depletion. For the study period, 2.25 million PMs and 415,780 ICDs were implanted, and 30 PM and 31 ICD patients died as a direct result of device malfunction. Currently, alerts exist for premature ICD lead failure, which can result in inappropriate shock or failure of shock.[17,18] A number of PMs and ICDs remain on "alert" for silent, premature battery failure, and one entire Guidant (now Boston Scientific) product line of ICDs has their magnet mode permanently disabled because of a switch malfunction.[19]

PACEMAKER AND IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR MECHANICS

PM and ICD implant indications are shown in Boxes 13-1A and 13-1B. These systems consist of an impulse generator and lead(s). Leads can have one (unipolar), two (bipolar), or multiple (multipolar) electrodes with connections in multiple chambers. In most defibrillations, as well as unipolar pacing, the generator case serves as an electrode, and tissue contact in a PM has been disrupted by pocket gas expanded by nitrous oxide.[20] Pacing in a unipolar mode (not permitted in an ICD system) produces larger "spikes" on an analog-recorded ECG, and unipolar sensing is more sensitive to EMI as well as electrical muscle artifacts. ICDs can be distinguished from conventional PMs by the presence of a shock coil on the right ventricular lead. Often, bipolar PM electrodes can be identified on the chest film because they have a ring electrode 1 to 3 cm proximal to the lead tip (Figure 13-1).

Finally, electronic devices resembling cardiac pulse generators are being implanted at increasing rates for pain control, thalamic stimulation to control Parkinson disease, phrenic nerve stimulation of the diaphragm in paralyzed patients, and vagus nerve stimulation to control epilepsy and possibly obesity.[21] These devices may be confused with a cardiac generator.

BOX 13-1A Permanent Pacemaker Indications

- Sinus node disease
- Atrioventricular (AV) node disease
- Long QT syndrome
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Dilated cardiomyopathy (DCM)

BOX 13-1B Implantable Cardioverter-Defibrillator Indications

- Ventricular tachycardia
- Ventricular fibrillation
- Postmyocardial infarction patients with ejection fraction (EF) ≤30% (MADIT II)
- Cardiomyopathy from any cause with EF ≤35% (SCD-HeFT)
- Hypertrophic cardiomyopathy
- Awaiting heart transplant
- Long QT syndrome
- Arrhythmogenic right ventricular dysplasia
- Brugada syndrome (right bundle branch block, ST segment elevation in leads V_1-V_3)

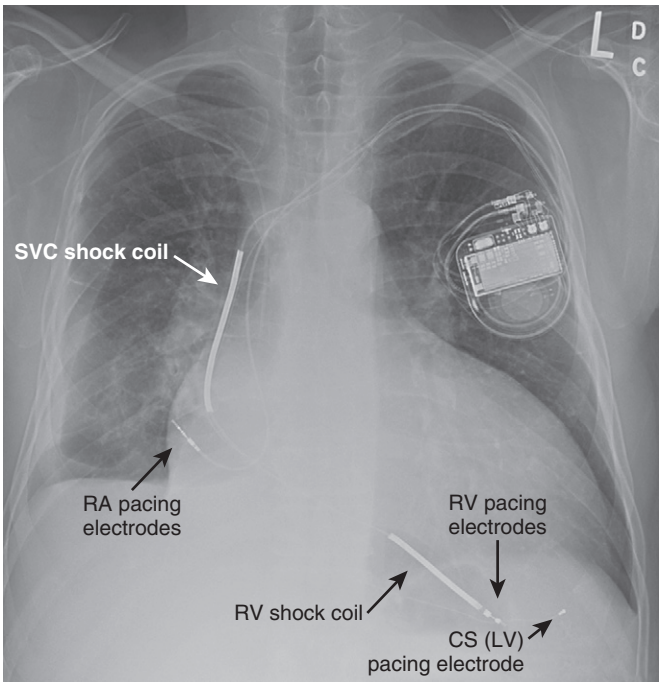

FIGURE 13-1 ■ A Defibrillator System with Biventricular Antibradycardia Pacemaker Capability. This chest film was taken from a 50-year-old man with head and neck cancer, coronary artery disease, and ischemic cardiomyopathy with ejection fraction of 15%. The implantable cardioverter-defibrillator (ICD) generator is in the left pectoral position with three leads: a conventional, bipolar lead to the right atrium *(RA),* a quadripolar lead to the right ventricle *(RV),* and a unipolar lead to the coronary sinus *(CS).* This system is designed to provide "resynchronization (antibradycardia) therapy" in the setting of a dilated cardiomyopathy with a prolonged QRS (and frequently with a prolonged P-R interval as well). The bipolar lead in the RA will perform both sensing and pacing functions. The lead in this RV is a true bipolar lead with ring and tip electrodes for pacing and sensing. The presence of a "shock" conductor (termed a *shock coil*) on the RV lead in the RV distinguishes a defibrillation system from a conventional pacemaking system. The lead in the CS depolarizes the left ventricle *(LV),* and the typical current pathway includes the anode (ring electrode) in the RV. Because of the typically wide QRS complex in a left bundle branch pattern, failure to capture the LV can lead to ventricular oversensing (and inappropriate antitachycardia therapy) in an ICD system. Many defibrillation systems (including this one) also have a shock coil in the superior vena cava *(SVC),* which usually is electrically identical to the defibrillator case (called the "can"). When the defibrillation circuit includes the ICD case, it is called an "active can configuration."

The nature of programming, which is unique to each patient and device, necessitates contact with the patient's device physician or a preoperative device interrogation to identify programmed parameters, remaining battery longevity (voltage and impedance), lead integrity (impedance), safety margins for sensing underlying rhythm signals (signal amplitude and channel sensitivity), and safety margins for pacing in each chamber (pacing threshold and pacing output). Interrogation also allows retrieval of information about the patient's rhythm behavior since the last reset of generator memory. For ICDs (and many PMs), rhythm abnormalities (atrial arrhythmias, supraventricular tachycardia, ventricular tachycardia, and ventricular fibrillation) are also stored.

PM and ICD programming is described with the use of pacemaker (NBG) or defibrillator (NBD) codes (Tables 13-1A and 13-1B). Because all ICDs perform bradycardia pacing, the most robust ICD description would include the first three characters of the NBD, followed by a dash (–), then the five character PM NBG. As an example, in Figure 13-1, the ICD was configured as VVE-DDDRV (ventricular shock capable, ventricular antitachycardia pace capable, electrogram (rate) detection for tachyarrhythmia, plus atrioventricular pacing in a dual chamber [atrial tracking] mode, with rate responsiveness, and multisite ventricular pacing). In the United States, the two most common pacing modes are VVI (single chamber ventricular pacing in the absence of a native ventricular event) and DDD (atrioventricular pacing that forces tracking of the atrial activity, whether sensed or paced).

Conventional wisdom regarding perioperative care of PM or ICD patients somehow has become "just put a magnet on it." This behavior seems to have originated with the incorrect beliefs that magnet application to a PM always produces asynchronous pacing and that a magnet application to an ICD always inhibits antitachycardia therapy. Thus many physicians mistakenly believe that magnet application will prevent signal oversensing from the "Bovie" ESU, which can result in no pacing; after all, any electrical signal on the ventricular lead is interpreted by the generator as ventricular activity, which then "inhibits" pacing output. For ICDs, the electrical noise (EMI) can precipitate shocks. However, many PMs and ICDs can have their magnet mode altered by programming, and for some PMs, the default magnet setting does not include sustained, asynchronous

TABLE 13-1A **NASPE/BPEG Generic Pacemaker Codes (NBG) (Revised 2002)**

Position I	Position II	Position III	Position IV	Position V
CHAMBERS PACED	CHAMBERS SENSED	RESPONSE TO SENSING	PROGRAMMABILITY	MULTISITE PACING
O = None	**O** = None	**O** = None	**O** = None	**O** = None
A = Atrium	**A** = Atrium	**I** = Inhibited	**R** = Rate modulation	**A** = Atrium
V = Ventricle	**V** = Ventricle	**T** = Triggered		**V** = Ventricle
D = Dual (A+V)	**D** = Dual (A+V)	**D** = Dual (T+I)		**D** = Dual (A+V)

BPEG, British Pacing and Electrophysiology Group; *NASPE*, North American Society of Pacing and Electrophysiology (now the Heart Rhythm Society).

TABLE 13-1B **NASPE/BPG Generic Defibrillator Codes (NBD)**

Position I	Position II	Position III	Position IV (or Use Pacemaker Code)
SHOCK CHAMBERS	ANTITACHYCARDIA PACING CHAMBERS	TACHYCARDIA DETECTION	ANTIBRADYCARDIA PACING CHAMBERS
O = None	**O** = None	**E** = Electrogram	**O** = None
A = Atrium	**A** = Atrium	**H** = Hemodynamic	**A** = Atrium
V = Ventricle	**V** = Ventricle		**V** = Ventricle
D = Dual (A+V)	**D** = Dual (A+V)		**D** = Dual (A+V)

BPEG, British Pacing and Electrophysiology Group; *NASPE*, North American Society of Pacing and Electrophysiology (now the Heart Rhythm Society).

TABLE 13-2 **Usual (or Default) Effects of Appropriate Magnet Placement for Most Devices**

Manufacturer	Pacemaker	ICD
Biotronik	PROGRAMMABLE • Battery OK: 10 AS events at 90 beats/min, then original programmed mode without rate responsiveness • Battery not OK: 10 AS events at 80 beats/min, then 11% below LRL	NONPROGRAMMABLE NO confirmation • Disables tachy therapies
Boston Scientific (formerly Guidant) (also CPI)	PROGRAMMABLE OFF MODE • Battery OK: AS pacing at 100 (90 at the intensified follow-up interval) beats/min • ERI: AS pacing at 85 beats/min	PROGRAMMABLE OFF MODE Confirmation: short beep at 60 Hz or with each detected heartbeat, depending on model • Disables tachy therapies [CAUTION][†]
Medtronic Corporation	NONPROGRAMMABLE • Battery OK: AS pacing 85 beats/min • ERI: AS single-chamber pacing at 65 beats/min	NONPROGRAMMABLE NO confirmation • Disables tachy detection
Pacesetter (owned by St. Jude Medical)	PROGRAMMABLE OFF (and VARIO*) MODE • Battery OK: AS pacing depends on model • ERI: AS pacing below 90 beats/min	PROGRAMMABLE OFF MODE NO confirmation • Disables tachy therapy
St. Jude Medical	PROGRAMMABLE OFF MODE • Battery OK: AS pacing 98 beats/min gradually declining over life of battery • ERI: AS pacing below 87 beats/min	PROGRAMMABLE OFF MODE NO confirmation • Disables tachy therapy
Sorin Medical (was ELA)	NONPROGRAMMABLE • AS pacing at 96 beats/min gradually declining to 80 beats/min at ERI. After magnet removal, 8 additional AS pacing cycles (the final 2 cycles are at LRL with long atrioventricular delay).	NONPROGRAMMABLE Confirmation: Pacing rate (but not mode) changes to • Battery OK: 90 beats/min • ERI: 80 beats/min • Disables tachy therapy

AS, asynchronous; *ERI*, elective replacement indicated—the device is reporting the need for generator replacement due to battery depletion; *LRL*, lower rate limit—the minimum programmed rate for the device.

CAUTION: This table is not meant to be complete. It lists the default (or out-of-box) settings for appropriate magnet placement. Only an interrogation of the generator will reveal the true settings for any programmable device. The term *PROGRAMMABLE OFF MODE* indicates that the magnet response can be eliminated in the generator by programming. For CPI/Guidant ICDs, if the magnet mode is programmed to *ON,* appropriate magnet placement immediately disables tachy detection and therapy, and tachy therapies remain disabled for as long as the magnet remains appropriately applied. If each heartbeat produces a "beep," the device will be enabled for tachy therapy on magnet removal provided it is not damaged by electromagnetic interference while the magnet is applied. If the device emits a constant tone with a magnet applied, tachy therapy is disabled regardless of whether a magnet is present.

*VARIO mode: 32 asynchronous events—the first 16 between 100 and 85 beats/min (ERI) to indicate battery performance; the next 15 at 119 beats/min with gradually declining ventricular pacing output to demonstrate capture threshold. The final pace is no output to clearly demonstrate no capture. This sequence repeats as long as the magnet is in place.

[†]Any BOS/CPI/Guidant ICD that does not beep (60 Hz for most devices with "BOS" x-ray label, otherwise beep each detected/paced R wave) when a magnet is applied or if it emits a constant tone (indicating that tachy therapy is permanently disabled) should undergo an immediate device interrogation and the patient should be electrocardiographically monitored until the interrogation is complete.

behavior. Table 13-2 shows default magnet behavior for many PMs and ICDs.

Preoperative management of the patient with a PM includes evaluation and optimization of coexisting disease(s). For the patient with cardiomyopathy, the perioperative physician(s) should ensure appropriate pharmacologic therapy (i.e., beta-blockade, afterloading reduction, diuretics when indicated, and antiarrhythmic or other special drugs for late-stage disease).[22] In fact, initiation of beta-blocker therapy produces a benefit for the cardiomyopathic patient within 10 to 14 days,[23] so delaying an elective case to institute beta-blocker therapy might be prudent. No special laboratory tests or radiographs are needed for the patient with a conventional PM. A patient with a BiV device might need a chest film to document the position of the coronary

BOX 13-2 Pacing Function Reprogramming Possibly Needed

- Any rate-responsive device—problems are well-known and have been misinterpreted with potential for patient injury; the U.S. Food and Drug Administration has issued an alert regarding devices with minute ventilation sensors
- Special pacing indication (hypertrophic cardiomyopathy, dilated cardiomyopathy, pediatrics)
- Pacemaker-dependent patient
- Major procedure with expected electromagnetic interference superior to the umbilicus
- Rate enhancements are present that should be disabled
- Special procedures
  Lithotripsy
  Transurethral or hysteroscopic resection
  Electroconvulsive therapy
  Succinylcholine use
  Magnetic resonance imaging (requires trained personnel and special monitoring equipment)

BOX 13-3 Pacemakers with Minute Ventilation Sensors

Boston Scientific (includes Guidant and CPI)
Pulsar (1172, 1272)
Pulsar Max (1170, 1171, 1270)
Pulsar Max II (1180, 1181, 1280)
Insignia Plus (1194, 1297, 1298)
Altrua

Medtronic
Kappa 400 series (401, 403)
St. Jude (includes Pacesetter and Telectronics)
Meta (1202, 1204, 1206, 1230, 1250, 1254, 1256)
Tempo (1102, 1902, 2102, 2902)

Sorin (was Ela Medical)
Brio (212, 220, 222)
Chorus RM (7034, 7134)
Opus RM (4534)
Reply DR
Rhapsody
Symphony
Talent (113, 133, 213, 223, 233)

sinus (CS) lead, especially if central line placement is planned because spontaneous CS lead dislodgment can occur.[24,25] Central line placement in the thorax should not be performed without ECG monitoring (PM or ICD), and consideration should be given to suspending ICD (if present) high-energy antitachycardia therapy because patient injury from inappropriate shock has been reported.[26]

Medicare payment guidelines allow transtelephonic (magnet) PM evaluation every 4 to 12 weeks (depending on device type and age) and a comprehensive device interrogation with a programmer at least once per year.[27] The HRS Guidelines for PM or ICD follow-up include in-office or remote monitoring of battery status every 3 to 6 months and in-office follow-up every 6 to 12 months, depending on the stability of the patient and the type of cardiac implantable electronic device (CIED).[28] Most ICD manufacturers suggest device evaluation at least every 4 months and more frequent checks for ICD and lead systems on alert or recall. Some ICDs can now be evaluated using telephonic checks; however, because pacing thresholds cannot be determined at this time, in-office evaluation with the programmer remains the test of choice.

For some patients, appropriate reprogramming (Box 13-2) remains the safest way to avoid intraoperative problems, especially if monopolar ESU will be used. Some device manufacturers will assist with this task; however, industry-employed allied professionals (i.e., the manufacturer's representatives or "reps") must be supervised by an appropriately trained physician.[29] Reprogramming the pacing function to asynchronous pacing at a rate greater than the patient's underlying rate usually ensures that no oversensing or undersensing from EMI will take place. However, setting a device to asynchronous mode has the potential to create a malignant rhythm in the patient with structurally compromised myocardium.[30-33] Reprogramming a device will not protect it from internal damage or reset caused by EMI. Consideration should be given to disabling rate responsiveness and "enhancements" (e.g., dynamic atrial overdrive, hysteresis, sleep rate, and intrinsic atrioventricular activity search) because many of these features can mimic pacing malfunction.[34-36] Because some patients undergo pacing threshold increases, pacing outputs might need to be increased in patients with pacing dependency, need for significant fluid or blood therapy, or expected prolonged surgery with likely EMI.[8,37] Pacing threshold can also be increased by some disease states.[38] Special attention must be given to any device with a minute ventilation (bioimpedance) sensor (Box 13-3)[39] because inappropriate tachycardia has been observed secondary to mechanical ventilation,[40,41] monopolar (Bovie) electrosurgery,[40,42,43] and connection to an ECG monitor with respiratory rate monitoring.[39,44-48] Sometimes, inappropriate therapy producing life-threatening results has been delivered in these settings.[41]

CONTROVERSIES

The principle issues surrounding perioperative PM and ICD patient care involve the following:

1. *Preoperative device interrogation*: According to the ASA Practice Advisory[1] and the HRS/ASA Expert Consensus Statement,[2] identification of the programmed parameters should be obtained from the patient's CIED physician or clinic or the CIED should undergo interrogation. The ASA Practice Advisory does not define *recent*, but the HRS/ASA Expert Consensus Statement states that 6 months for an ICD and 12 months for a PM should be sufficient.

2. *Perioperative reprogramming of pacing functions:* If EMI is likely (i.e., monopolar electrocautery will be used superior to the umbilicus), the ASA Practice Advisory recommends reprogramming the conventional pacing function of a PM or ICD (if possible) to an asynchronous pacing mode in pacing-dependent patients. In contradistinction, the HRS/ASA Expert Consensus Statement says that asynchronous pacing is necessary only in the presence of significant pacing inhibition, even for pacing-dependent patients. In addition, both the ASA Practice Advisory and HRS/ASA Expert Consensus documents state that consideration should be given to suspending special pacing algorithms, including rate-adaptive functions. This recommendation stems from the fact that a mechanical rate sensor might increase the paced heart rate when pressure is applied over the generator or when the chest wall is manipulated, such as during a skin preparation, and certain programming features designed to reduce ventricular pacing (such as the managed ventricular pacing mode present in many Medtronic generators) or increase battery life (such as pacing rate hysteresis) might masquerade as pacing system malfunction. The HRS/ASA statement suggests that magnet application to a PM (but not to an ICD) to achieve asynchronous pacing and disabling of rate enhancements can be appropriate therapy, provided that the magnet behavior has been verified and will not instigate untoward hemodynamics.
3. *Disabling of antitachycardia therapy for ICD patients:* The ASA Practice Advisory, HRS/ASA Expert Consensus Statement, and most experts recommend that ICD shock and antitachycardia pacing be disabled for the operating room whenever EMI is likely to occur. These documents allow for this issue to be accomplished by magnet application when deemed appropriate. However, application of a magnet to an ICD does not guarantee the deactivation of antitachycardia therapy; some ICDs have no magnet mode because of programming, and only ICDs from Boston Scientific/Guidant/CPI emit tones (provided the magnet mode is enabled) to indicate appropriate magnet placement. An old issue, permanent deactivation of a Boston Scientific ICD by magnet placement for more than 30 seconds,[49] should be rare as parameter lockouts were placed in the Boston Scientific/Guidant programmer in October 2009.
4. *Postoperative device interrogation:* EMI, regardless of the site or source, has the potential to injure a generator or cause a reset. According to both the ASA Practice Advisory and HRS/ASA Expert Consensus Statement, patients whose devices require postoperative interrogation include those that were reprogrammed before surgery, those that were potentially subjected to EMI, and those that experienced hemodynamic instability or significant intraoperative events. Nevertheless, economic, personnel, and time pressures can hinder a timely postoperative interrogation of the generator.

AREAS OF UNCERTAINTY

Recommendations in this document are based on the available literature, which is limited mostly to case reports and small patient series. Changing technology in the fields of cardiac generator design, the ability to monitor patients remotely and without need for patient action, and improvements to the perioperative equipment that might produce EMI could render many of these recommendations unnecessary. However, without robust prospectively collected scientific data and the testing of new equipment for interactions with PMs and ICDs, the approach to these patients must continue to be based largely on the data from centers that perform investigative monitoring. Much of these current data suggests that CIED patients are often seen for surgery with devices that have not been checked in a timely manner, might not work properly, might be inappropriately programmed for the perioperative period, and can be adversely affected by EMI. Until publication of rigorous bench evaluations and large clinical trials, likely in the form of a prospective registry evaluating the effects of EMI, we remain committed to the path that offers the highest degree of patient safety.

GUIDELINES

Currently, no "guidelines" exist for these patients. The ASA has published a perioperative advisory,[1] and the HRS has published an expert consensus statement in conjunction with the ASA that is also endorsed by the American Heart Association and the Society of Thoracic Surgeons.[2]

AUTHORS' RECOMMENDATIONS

Box 13-4 shows perioperative guidelines adapted from a number of sources.

Specific recommendations regarding the aforementioned controversies are summarized as an algorithm (Figure 13-2) and include the following:

Preoperative contact with the patient's cardiac implantable electronic device (CIED) physician or clinic: The Heart Rhythm Society/American Society of Anesthesiologists (HRS/ASA) advisory states that the preoperative prescription and follow-up should be determined by the patient's CIED physician.

Preoperative device interrogation: Preoperatively, all PMs and ICDs should undergo a comprehensive in-office interrogation within 6 months before the scheduled surgery/anesthetic. Particular attention should be given to patients in whom a previous problem was discovered, if a generator or lead is on alert or recall, if there is a change in patient symptomatology or condition, or if the patient gets frequent antitachycardia therapy from his or her ICD. Under these conditions, obtaining a comprehensive device interrogation immediately before surgery should be strongly considered.

Perioperative reprogramming: In general, rate enhancements, as well as rate responsiveness, should be disabled for the intraoperative period to prevent unnecessary (and possibly dangerous) therapy, especially if minute ventilation sensing is present. Consideration should be given to raising

Continued on following page

AUTHOR'S RECOMMENDATIONS (Continued)

the lower paced rate to ensure adequate oxygen delivery in patients undergoing significant surgery and to minimize the risk of R-on-T pacing if an asynchronous mode will be programmed. For the patient who demonstrates pacing system dependence undergoing surgery superior to the umbilicus in which monopolar electrosurgical unit (ESU) use or other electromagnetic interference (EMI) is likely, reprogramming to asynchronous pacing or, rarely, the placement (and testing, which will likely require reprogramming) of a temporary pacing device for surgery might be needed.

Disabling of antitachycardia therapy for ICD patients: In general, ICDs should have antitachycardia therapy deactivated for surgical procedures superior to the umbilicus whenever monopolar ESU use or EMI is likely. Deactivation by programming is more reliable than magnet placement. In fact, for scheduled cases, a magnet should be used only after consultation with an ICD expert and a stable and appropriate position of the magnet can be regularly verified during the case. Verification can include observation, audible tones (Boston Scientific/Guidant/CPI only), or the increased pacing rate (to 85 beats/min, not asynchronous) for Sorin devices. In many instances, magnet placement (assuming prior verification of magnet function) can be acceptable for preventing inappropriate ICD discharge.[50] Any patient who undergoes ICD disablement or magnet placement without prior verification of magnet behavior should be kept in a monitored environment until the ICD is interrogated and found to be working appropriately. We believe that routine ICD deactivation is unnecessary for (1) bipolar ESU use or (2) in conjunction with the HRS statement, a monopolar ESU applied inferior to the umbilicus, provided no other source of EMI is anticipated.

Postoperative device interrogation: In general, a postoperative device check ensures that no untoward issues arose during the case. It also allows any data (such as noise that gets interpreted as an arrhythmia or lead problem) to be cleared from the generator memory. It is required in any case wherein ICD tachyarrhythmia therapy was disabled by programming, and it should be the standard of care for any patient exposed to EMI. For cases in which no monopolar ESU was used, no blood was transfused, limited intraoperative fluid was administered, and no adverse issues were identified, our practice includes no postoperative generator check.[50]

The monopolar electrosurgery current return pad: Common practice among operating room personnel is to place this pad on the patient's thigh, regardless of the surgical site and pulse generator location. For monopolar ESU use superior to the umbilicus, thigh placement creates an ESU current path that can include the generator, leads, or both. Strong EMI from the ESU remains the principle enemy of an implanted generator, and the current return pad should be placed to prevent induced current in the leads. As a result, for surgery in the head and neck area, the pad should be placed on the posterior-superior shoulder contralateral to the site of the generator. This shoulder site is also acceptable for surgery on the chest wall (such as mastectomy) contralateral to the generator. For surgery on the chest wall ipsilateral to the generator, the pad should be placed on the ipsilateral arm and the return wire should be prepared into the field, if necessary, with a sterile, occlusive covering. This sterile wire can then be run superiorly along the arm to the shoulder, made stationary, and then run to the ESU generator. If the ipsilateral arm is not available, then the posterior superior aspect of the ipsilateral shoulder should be used.

BOX 13-4 Perioperative Recommendations for the Patient with a Cardiac Generator

Preoperative Key Points

- Establish preoperative contact with the patient's CIED physician/clinic to obtain appropriate records and perioperative prescription.
- Have the pacemaker or defibrillator interrogated by a competent authority before the scheduled anesthetic.
- Obtain a copy of this interrogation. Ensure that the device will pace the heart with appropriate safety margins.
- Consider replacing any device near its elective replacement period in a patient scheduled to undergo either a major surgery or surgery within 25 cm of the generator.
- Determine the patient's underlying rhythm/rate to determine the need for backup pacing support.
- Identify the magnet rate and rhythm, if a magnet mode is present and magnet use is planned.
- Program minute ventilation rate responsiveness off, if present.
- Consider programming all rate enhancements off to prevent rhythm misinterpretation.
- Consider increasing the pacing rate to optimize oxygen delivery to tissues for major cases.
- If EMI is likely, disable antitachycardia therapy if a defibrillator.
- If EMI is likely, consider programming to an asynchronous pacing mode in pacing-dependent patents.

Intraoperative Key Points

- Monitor cardiac rhythm/peripheral pulse with pulse oximeter plethysmogram or arterial waveform.
- Consider disabling the "artifact filter" on the ECG monitor.
- Whenever possible, avoid use of monopolar ESU.
- Use bipolar ESU if possible; if not possible, "pure cut" (monopolar ESU) is better than "blend" or "coag."
- Place the ESU current return pad in such a way as to prevent electricity from crossing the generator–heart circuit, even if the pad must be placed on the distal forearm and the wire covered with sterile drape.
- If the ESU causes ventricular oversensing, pacing quiescence, or inappropriate tachycardia, limit the effect by suspending the use of monopolar electrocautery, reprogramming the cardiac generator, or placing a magnet over the PM (not indicated for ICD).

Postoperative Key Points

- Have the device interrogated by a competent authority postoperatively. Some rate enhancements can be reinitiated, and optimum heart rate and pacing parameters should be determined. The ICD patient must be monitored until the antitachycardia therapy is restored.

CIED, cardiac implantable electronic device; *ECG*, electrocardiogram; *EMI*, electromagnetic interference; *ESU*, electrosurgery unit; *ICD*, implantable cardioverter-defibrillator; *PM*, pacemaker.

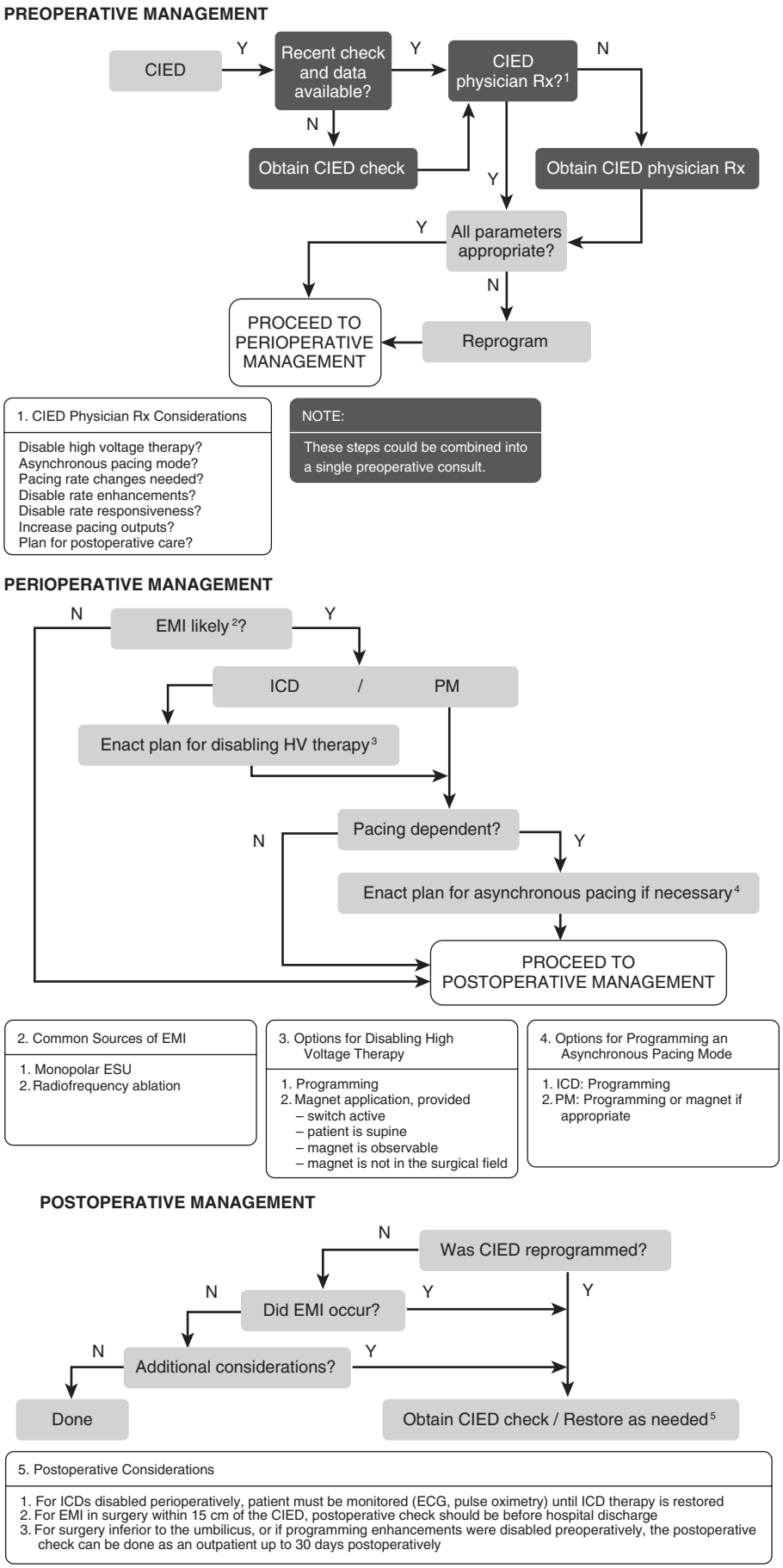

FIGURE 13-2 ■ Operative Management Considerations of a Patient with a Pacemaker *(PM)*/Implantable Cardioverter-Defibrillator *(ICD). CIED,* cardiac implantable electronic device; *ECG,* electrocardiogram; *EMI,* electromagnetic interference; *ESU,* electrosurgical unit; *HV,* high voltage.

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CHAPTER 14

When Should Pulmonary Function Tests Be Performed Preoperatively?

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INTRODUCTION

Pulmonary complications remain common after many surgical procedures, particularly those involving the upper abdomen or thorax.[1,2] Procedures that involve resection of lung tissue carry an even higher risk of pulmonary complications. Research concerning the diagnosis and prevention of perioperative cardiac complications after anesthesia and surgery has led to evidence-based interventions such as widespread implementation of perioperative beta-blocker administration.[3] The situation regarding pulmonary complications is different. Many of the preoperative factors that make pulmonary complications more likely are known. A recent comprehensive review breaks down risk factors into those associated with the patient and those associated with the surgical procedure.[4] Patient-associated risk factors include advanced age, American Society of Anesthesiologists (ASA) class 2 or higher, functional dependence, chronic obstructive pulmonary disease (COPD), smoking, and congestive heart failure. More recently, obstructive sleep apnea (OSA)[5] and pulmonary hypertension[6,7] have also been recognized as risk factors. Surgical procedures associated with increased risk of pulmonary complications include procedures in which the incision sites are close to the diaphragm such as aortic aneurysm repair, nonresective thoracic surgery, and upper abdominal surgery. Neurosurgery, emergency surgery, head and neck surgery, vascular surgery, prolonged surgery, and use of general anesthesia are also associated with increased risk.[4,8] Unfortunately, most of these risk factors are not modifiable in the preoperative period. Smoking cessation can safely be encouraged, but short-term benefits from cessation are small.[9] Preoperative screening for patients with OSA and asymptomatic pulmonary hypertension may have modest benefits. Appropriate management of OSA before elective surgery must be encouraged.[10]

Perioperative care has changed significantly in the past 10 years, in that the time between preoperative evaluation and surgery is now often very brief. Surgical interventions themselves have changed significantly, often in ways that presumably reduce the likelihood of postoperative pulmonary complications. For example, the widespread application of laparoscopic techniques for many abdominal procedures may improve postoperative pulmonary function,[11] and the introduction and widespread application of video-assisted thoracic surgery (VATS) and lung-volume reduction surgery has transformed into operative candidates patients who would have been previously told that their pulmonary function was "too bad" for surgery. In one study, impaired diffusion capacity of carbon monoxide (D_{LCO}) and reduced forced expiratory volume in 1 second (FEV_1) was not predictive of postoperative pulmonary complications (PPCs) in patients having lobectomy via VATS.[12] In addition, the move toward very rapid ambulation and discharge from the hospital has ramifications that may positively affect those patients whose pulmonary function is improved by rapid resumption of the upright posture and may have negative implications for those who clear their secretions poorly at home.

Unfortunately, there is no standard definition of what constitutes a PPC. This hinders comparison of historical case series. Reported rates of pulmonary complications vary widely depending on the patient population and the surgical intervention studied.[4,13,14] The most important complications are those that cause significant morbidity, such as pneumonia or respiratory failure. Preoperative pulmonary function tests (PFTs) have not proved to be better than clinical findings in predicting patients who go on to develop clinically significant pulmonary complications after surgical procedures that do not involve lung resection.[4]

These issues, coupled with the relative insensitivity of pulmonary function testing in identifying patients who subsequently have PPCs, have resulted in more restrictive indications for preoperative pulmonary function testing than 25 years ago. An economic analysis entitled "Blowing Away Dollars" cast significant doubt on the practice of routine spirometric analysis before abdominal surgery.[15] However, it is clear that the incidence of pulmonary complications is increased in patients with preexisting pulmonary disease.[16] It is also clear that the physical examination is not very sensitive in detecting mild to moderate pulmonary disease.[17] Likewise, clinicians are not particularly accurate in estimating the severity of an exacerbation of COPD.[18] There has been a significant shift away from ordering spirometry except in very specific circumstances (e.g., thoracic surgery that involves lung resection and severe COPD). It may be that it is too much to expect a single diagnostic test such as spirometry to result in improved outcomes when outcomes are, in reality, such complex endpoints.

Some would argue that the ready availability of therapeutic options for bronchospasm may minimize the

benefit of preoperative knowledge of the presence and severity of chronic or episodic pulmonary disease. These developments may be tied to the decline in use of preoperative PFTs, but it is more likely that as the use of spirometry to determine who was eligible or ineligible for surgical intervention went out of vogue (largely because of poor correlation between predicted postoperative FEV_1 and measured postoperative FEV_1), the enthusiasm clinicians felt toward ordering and interpreting the tests diminished.

Because there are no meta-analyses or modern randomized, placebo-controlled therapeutic trials to review concerning preoperative PFTs, the evidence that does exist will be reviewed, and a rational strategy will be suggested for the use of preoperative PFTs. The fact that a noninvasive diagnostic test such as spirometry has not been shown to improve clinical outcome does not mean that it should never be ordered.

OPTIONS/THERAPIES

Pulmonary Function Testing and Therapeutic Options

The term *pulmonary function test* is very broad. Examples of PFTs include measures of anatomic volumes, resistance to airflow, reversibility of increased airway resistance, and assessment of pulmonary reserve. Available tests include spirometry, flow volume loops, assessment of membrane surface area available for gas transport via D_{LCO}, assessment of cardiopulmonary reserve by exercise testing, ventilation-perfusion scintigraphy, and split-function lung studies. For most clinical situations an anesthesiologist encounters, the pertinent tests will be spirometry and exercise testing. Patients about to undergo pulmonary resection may require more extensive evaluation, depending on the severity of their lung disease and on the magnitude of the planned pulmonary resection.[19] Reviews of individual tests are readily available for additional detail.[20-28]

Spirometry is a very low-risk, effort-dependent test that can be performed in a physician's office. Spirometric measurements such as the FEV_1, vital capacity (VC), and forced vital capacity (FVC) are well-known to many clinicians. Spirometry is sensitive and specific for the accurate diagnosis of obstructive respiratory disease, and it may allow estimation of the effectiveness of bronchodilators in an individual patient. Diagnosis of restrictive lung disease requires measurement of lung volumes.

The second set of options that must be discussed are the therapeutic options. PFTs allow accurate categorization of a patient's pulmonary disease. Accurate diagnosis should allow for effectively targeted preoperative therapy. The therapeutic options available for pulmonary disease are well described. Antibiotics can effectively treat pulmonary infection, bronchodilators (both beta-agonists and anticholinergics) can effectively treat bronchoconstriction, and steroid therapy may be helpful for subgroups of patients with asthma and COPD. Aggressive treatment with mechanical measures such as incentive spirometry can help minimize the frequency of PPCs after abdominal surgery but perhaps not after coronary artery bypass grafting.[14,29-31] A recent review of strategies to reduce PPCs finds good evidence to support the postoperative use of lung expansion interventions (e.g., incentive spirometry, deep-breathing exercises, and continuous positive airway pressure), fair evidence to support the selective use of nasogastric tubes after abdominal surgery and the use of short-acting neuromuscular blockers intraoperatively, and conflicting evidence concerning smoking cessation, epidural analgesia or anesthesia, and the use of laparoscopic surgical techniques.[32] PPCs have, however, been shown to occur less frequently in laparoscopic than in open bariatric surgery.[33] Specific pulmonary rehabilitation programs have proved beneficial in improving cardiopulmonary capacity and may be useful in preparing patients for surgical intervention.[34]

EVIDENCE

There is no evidence of a beneficial effect from preoperative pulmonary function testing in asymptomatic patients having nonthoracic surgery. There is evidence that abnormal results on PFTs identify a group of patients who have a higher incidence of PPCs.[16,35-38] Although historically pulmonary function testing was used to identify patients who were thought to be at excessive risk, recent experience shows that some patients with chronic hypercapnia (often used as a marker signifying inoperability) can safely undergo lung-volume reduction surgery.[39] As surgical practice has become more aggressive in patients with emphysema, it has become clear that removing a nonfunctional segment of pulmonary parenchyma can be, surprisingly, well tolerated.[40] However, there is also evidence that low FEV_1, in combination with knowledge of the homogeneity of emphysema or an estimate of D_{LCO}, identifies patients at prohibitive risk of lung-volume reduction surgery.[41] Evidence has also shown that a surprisingly high percentage of patients, 37% in one series, may still be denied potentially curative lung cancer resection for non–small cell lung cancer on the basis of poor preoperative PFTs.[42]

Exercise testing is useful for examining cardiopulmonary integration and reserve, and it may allow identification of patients who are more likely to survive major thoracic surgical procedures.[28,43,44] Although formal exercise testing remains the gold standard for assessment of the maximal rate of total body oxygen consumption ($\dot{V}O_2max$) and cardiopulmonary function, it is expensive and labor intensive, and it is not necessary in patients who can give a clear history of adequate exercise tolerance. If a patient cannot walk more than 2000 feet in 6 minutes, the patient's $\dot{V}O_2max$ is likely to be less than 15 mL/kg/min.[45] Exercise oximetry also shows promise in identifying patients who are at high risk of adverse outcomes.[46] A predicted postoperative $\dot{V}O_2max$ of less than 10 mL/kg/min may be one of the few remaining contraindications to pulmonary resection because the reported mortality rate in this group of patients was 100% in one study.[47]

Additional research is necessary to refine recommendations for preoperative estimation of cardiopulmonary reserve, but it appears that physiologic testing may offer advantages over simple spirometry in identifying patients at very high risk.[46,48] A recent study suggests that poor performance on exercise testing predicts patients who will experience extended stays after thoracic surgery.[49] The overall strength of the respiratory musculature is doubtless important as well, and efforts to increase the strength of the respiratory musculature may be helpful.[50] There is now evidence that a rigorous preoperative pulmonary rehabilitation program directed at increasing exercise ability and diaphragmatic strength can improve patient well-being before surgery, may increase the number of frail patients with pulmonary disease who can reasonably undergo potentially curative thoracic surgery, and may decrease PPCs after cardiac surgery.[51-53]

AREAS OF UNCERTAINTY

There are many areas of uncertainty regarding when PFTs should be ordered preoperatively. In the absence of controlled clinical trials that demonstrate that pulmonary function testing is associated with improved outcomes, it is difficult to recommend PFTs as a necessary prerequisite for any patient or surgical procedure. However, spirometry is inexpensive to obtain, very low risk, and accurate in diagnosing what may be clinically occult pulmonary disease. Although an abnormal result on spirometry allows identification of a group of patients at elevated risk of pulmonary complications, it is poor at attempting to stratify risk among the patients at elevated risk.

GUIDELINES

The American College of Chest Physicians recommended guidelines using PFTs for physiologic evaluation of patients with suspected lung cancer being evaluated for surgery in 2007.[54] As FEV_1 and D_{LCO} progressively worsen, additional testing is recommended for prediction of postoperative pulmonary function. Very poor predicted postoperative pulmonary function is associated with an increased risk of perioperative death and cardiopulmonary complications with standard lung resection. Preoperative exercise testing is recommended for these patients, and if these test results are poor, nonstandard surgery or nonoperative treatment options for lung cancer are recommended. These guidelines are not based on prospective randomized studies that demonstrate improved outcomes; however, there is overall agreement for the use of PFTs in predicting the risk of surviving lung resection in patients with lung cancer.

In 2009, the European Respiratory Society and the European Society of Thoracic Surgeons also recommended a set of guidelines using PFTs for evaluation of the fitness of patients for radical therapy for lung cancer, including surgical resection. Their guidelines also used FEV_1, D_{LCO}, prediction of postoperative pulmonary function, and exercise testing.[55]

With regard to cardiac and upper abdominal surgery, it may be prudent to do preoperative arterial blood gas analysis and spirometry in patients with a history of tobacco use and dyspnea. However, the recent evidence-based guidelines published by the American College of Physicians (ACP) do not recommend arterial blood gas analysis.[32] For lower abdominal surgery, preoperative spirometry may be indicated for patients with uncharacterized pulmonary disease, particularly if the surgical procedure will be prolonged or extensive. For other types of surgery, PFTs might be useful for patients in whom uncharacterized pulmonary disease is present, particularly in those who might require strenuous postoperative rehabilitation programs.[56]

A set of guidelines aimed at reducing perioperative pulmonary complications in patients undergoing noncardiothoracic surgery was published by the ACP in 2006. The recommendations include screening for the patient-specific and procedure-specific risk factors listed in the introduction section of this chapter, screening for low serum albumin levels (an albumin concentration less than 35 g/L predicts an increased risk of PPCs), and the use of postoperative lung expansion maneuvers and indicated postoperative nasogastric tubes. The fifth recommendation states clearly that preoperative spirometry and chest radiography should not be used routinely for predicting postoperative pulmonary risk. The last recommendation is that right-sided heart catheterization and total parenteral nutrition should not be used solely to attempt to reduce pulmonary complications from noncardiothoracic surgery.[57]

AUTHORS' RECOMMENDATIONS

It is clear that pulmonary function tests (PFTs) are not indicated in patients with a normal history and physical examination undergoing nonthoracic surgery. At the other extreme, it is clear that a wide variety of PFTs are useful in patients with chronic pulmonary disease undergoing lung-volume reduction surgery or as risk assessment in patients with lung cancer scheduled for surgical resection. There seems to have been an excessive shift against ordering and interpreting PFTs in patients between these two extremes. After all, the only accurate way to assess blood pressure is to measure it, and the only accurate way to identify obstructive or restrictive ventilatory impairments is to measure them with PFTs.[58] When there is doubt about the presence or absence of pulmonary disease, pulmonary function testing can end the doubt with little or no risk to the patient. Clinicians should not feel compelled to avoid pulmonary function testing when there is legitimate diagnostic uncertainty present after a thorough history and physical examination (Box 14-1). In patients at high risk of perioperative pulmonary complications, results from preoperative PFTs can be compared with postoperative results to assess interventions and confirm a return to baseline levels.

BOX 14-1 Evidence on Pulmonary Function Testing

- Preoperative spirometry is not useful if the results of the preoperative history and physical examination are normal.
- Preoperative spirometry can classify undiagnosed lung disease accurately.
- Preoperative pulmonary function testing allows clinicians to accurately assess the severity of lung disease in a patient with known pre-existing lung disease.
- Preoperative pulmonary function testing is well-established in the preoperative workup of patients about to undergo pulmonary resection.
- Preoperative spirometry should not be used in isolation to declare a patient ineligible for potentially curative surgical intervention but can be used as a first step in an evaluation that includes a more global assessment of cardiopulmonary function, such as formal or informal exercise testing.
- The evaluation of patients undergoing lung-volume reduction surgery is evolving. These patients are at very high risk, and it is likely that sophisticated anatomic, radiographic, and physiologic testing will be necessary to guide medical decision making in this patient group.

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CHAPTER 15

Does the Airway Examination Predict Difficult Intubation?

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INTRODUCTION

Difficult airway management is one of the most challenging tasks for anesthesiologists. Recent data from the American Society of Anesthesiologists (ASA) Management Closed Claims Project, specifically those findings related to the difficult airway, demonstrate that the percentage of claims resulting from adverse respiratory events, although on the decline (42% in the 1980s to 32% in the 1990s),[1] continue to constitute a large source of injury. A closed claims analysis of the management of the difficult airway published in 2005 showed that of the 179 claims made between 1985 and 1999 (n = 179), 87% (n = 156) of claims came from the perioperative period. More recent closed claims analyses demonstrated that claims resulting in death and brain damage from difficult airway management were associated with induction of anesthesia but not other phases of anesthesia and decreased in the period between 1993 and 1999, as compared with the period between 1985 and 1992.[2] In 2006, a closed claims analysis of trends in anesthesia-related death and brain damage showed an overall reduction in claims for death or brain damage between 1975 and 2000 (odds ratio [OR], 0.95 per year; 95% confidence interval [CI], 0.94 to 0.96, $p < 0.01$). Of all the respiratory events (n = 503) responsible for death or brain damage, difficult intubation (n = 115), inadequate oxygenation (n = 111), and esophageal intubation (n = 66) were the top three causes.[3]

Of the three types of adverse respiratory events reported, claims for inadequate ventilation and esophageal intubation decreased significantly in the 1990s (9% as compared with 25% of claims for death and brain damage in the 1980s), possibly as a result of pulse oximetry and end-tidal carbon dioxide monitoring. Yet, the proportion of claims for difficult intubation (a technical act, uninfluenced by monitoring) and other respiratory events leading to death or brain damage remained relatively stable between the 1980s and 1990s (9% and 8%, respectively). Of the adverse respiratory events, three quarters were judged to be preventable. Thus it is possible that better prediction of and preparation for difficult airway management might lead to a reduction in these numbers.

Anesthesiologists are confronted daily with the task of determining whether endotracheal intubation will be of increased difficulty in a patient. Preoperative evaluation of the airway can be accomplished by a thorough history and physical examination, as related to the airway; in addition, various measurements of anatomic features and noninvasive clinical tests can be performed to enhance this assessment. Nonetheless, several reports have questioned whether true prediction is possible.[4-6]

The recent National Audit Project, NAP4, conducted in the United Kingdom (2008-2009) gives a point estimate of one airway related death per 180,000 general anesthetic procedures and a 1 in 22,000 incidence of adverse airway events. O'Sullivan and colleagues suggest that the real incidence of a difficult airway is likely to be more common than 1 in 5500 and may thus be experienced on a "regular" basis.[7] The data demonstrated that a formal airway assessment was conducted in only 35 of 133 cases of airway-related events occurring during anesthesia (26%). However, when an airway assessment was performed, difficulty was anticipated correctly in the majority (e.g, in 25 of 35 cases). This is suggestive that an airway examination is worthwhile. With an overall positive predictive value of 0.25, if the group identified as potentially difficult to intubate is regarded as having a "disease" and in need of some form of specialized "treatment" for airway management (e.g,. awake or sedated fiberoptic intubation), then this number needed to treat for preventing harm from failed intubation would be 4, which is acceptable.[8,9]

DESCRIPTIONS OF TERMS

Five terms are important to review and analyze in this area: failed intubation, difficult intubation, difficult laryngoscopy, difficult mask ventilation, and difficult laryngeal mask airway ventilation. The ASA Task Force on Management of Difficult Airway suggests the following descriptions:[10]

Failed intubation, or the inability to place the endotracheal tube after multiple intubation attempts, is a clear-cut endpoint. Thus there is a fairly uniform reported incidence of approximately 0.05% of surgical patients or 1:2230 and approximately 0.13% to 0.35% of obstetric patients or 1:750 to 1:280.[11,12]

Difficult tracheal intubation (DI) is described as intubation when tracheal intubation requires multiple attempts, in the presence or absence of tracheal pathology. The incidence of DI is higher than failed intubation and has been reported to be 1.2% to 3.8%.[13-16]

Difficult laryngoscopy (DL) is described as not being able to visualize any portion of the vocal cords after

Original Cormack-Lehane system	I Full view of the glottis	II Partial view of the glottis or arytenoids		III Only epiglottis visible	IV Neither glottis nor epiglottis visible
View at laryngoscopy					
Modified system Cormack-Lehane	I As for original Cormack-Lehane above	IIa Partial view of the glottis	IIb Arytenoids or posterior part of the vocal cords only just visible	III As for original Cormack-Lehane above	IV As for original Cormack-Lehane above

FIGURE 15-1 ■ Cormack-Lehane Original Grading System Compared with a Modified Cormack-Lehane System. *E,* epiglottis; *LI,* laryngeal inlet. (Reproduced with permission from Yentis SM, Lee DJH. Evaluation of an improved scoring system for the grading of direct laryngoscopy. Anesthesia 1998;53:1041–4.)

multiple attempts at conventional laryngoscopy, and many investigators include grades III and IV or grade IV alone, according to the Cormack-Lehane original grading of the rigid laryngoscopic view (Figure 15-1).[17] According to these definitions, the incidence of difficult direct laryngoscopy varies from 1.5% to 13% in patients undergoing general surgery.[11,18-24]

Difficulty in performing endotracheal intubation is the end result of difficulty in performing laryngoscopy, which depends on the operator's level of expertise, patient characteristics, and circumstances. Thus it has been suggested that the definition of DI be based on a uniform understanding of the best attempt at performing laryngoscopy/intubation and should use the number of attempts and time as boundaries only.[25] The best attempt should incorporate the effect of changing the patient's position; the effect of changing the length or type of laryngoscope blade; and the effect of simple maneuvers, such as conventional cricoid pressure, backward, upward, rightward pressure (BURP), and optimal external laryngeal manipulation (OELM).

Difficult mask ventilation (DMV) is a condition in which it is not possible for the anesthesiologist to provide adequate face mask ventilation because of one or more of the following problems: an inadequate mask seal, excessive gas leakage, or excessive resistance to the ingress or egress of gas.[26] It is clear from clinical experience that there are grades of difficulty, similar to DI. The incidence of DMV also varies in the literature from 0.01% to 5%.[15,16,27,28]

Difficult laryngeal mask airway ventilation is a situation in which providing ventilation and oxygenation to a patient with a laryngeal mask airway (LMA) is difficult. Even though not defined by ASA, researchers have defined this as an inability to place the LMA in a satisfactory position within three attempts to allow adequate ventilation and airway patency. Indices of clinically adequate ventilation are generally expired tidal volume > 7 mL/kg and leak pressure > 15 to 20 cm H_2O. Verghese and Brimacombe,[29] in their study of more than 11,000 patients, had a failure rate of 0.16%.

Descriptive Terms Used for Predicting a Difficult Airway

The following terms are commonly used to analyze the usefulness of predictive tests.[30]

Specificity: Identifies all normal intubations as being normal. A sensitivity of 90% indicates that 90% of normal intubations will be identified as normal and 10% will be falsely identified as difficult. Ideally, specificity should be 100%.

Positive predictive value (PPV): The percentage of procedures that are true DIs from all those predicted by the test to be DIs. If the test predicts 20 DIs and only four are actually difficult, the PPV for the test is 20%. Even though PPV is a useful test, it is limited by the fact that it is dependent on the prevalence of DI in the sample group.

Likelihood ratio (LR): This is a useful term and can be calculated very quickly using sensitivity and specificity only. It is the chance of a positive test if the procedure is a DI divided by the chance of a positive test if the procedure was normal. LR is sensitivity/1 – specificity. It can be seen as a factor that links pretest probability to post-test probability of a DI with the use of a nomogram.

Receiver operating characteristic (ROC) curves: These help in determining the best predictive scores. The ROC has sensitivity on the *y* axis and 1 – specificity on the *x* axis. The test with the greatest area under the curve is the better one.

PREDICTION OF THE DIFFICULT AIRWAY: THE PROBLEM

There has been a heightened awareness of and a steady rise in the amount of literature being published on the recognition and prediction of the difficult airway. Evaluation of the evidence supporting the various methods of prediction of the difficult airway involves understanding the actual endpoints and their effect on the patient

outcomes of mortality or brain death. The frequency of airway difficulty varies according to the population studied and the definition of DI used.[16] There is no universally accepted definition of DI. Most of the larger studies concentrate on DI, broadly defined by difficult rigid laryngoscopic view (Cormack-Lehane grades III and IV or grade IV only), without the best attempt used. To be useful, a classification of laryngeal view should predict difficulty (or ease) of tracheal intubation, which requires the views to be associated with increasing degrees of intubation difficulty. Nonetheless, in a study of 1200 patients, Arne and colleagues[13] found a significant difference between the incidence of Cormack-Lehane grades III and IV laryngoscopic views and the occurrence of DI in the general population, as many of the grades III and IV views were actually easy intubations. Thus one of the problems in the prediction of the difficult airway is that a DI is often not identified until laryngoscopy is performed and, as mentioned previously, there are discrepancies in the literature as to what defines difficulty.

Several authors have suggested the modification of the four-grade Cormack-Lehane scoring system (see Figure 15-1),[24,31,32] which classifies the laryngeal view during laryngoscopy. This widely adopted classification system was described to allow simulated DI, yet it is applied inaccurately by the majority.[33] Yentis and Lee[32] modified this scoring system by subdividing a grade II laryngoscope view into IIa (partial view of glottis visible) and IIb (only arytenoids visible). This five-grade classification is referred to as the modified Cormack-Lehane system (MCLS) and allows refining the definition of DL as including IIb, III, and IV (see Figure 15-1).[32] Koh and colleagues[34] found that this system better delineated the difficulty experienced during laryngoscopy and intubation than the four-grade Cormack-Lehane system. Thus the true incidence of DL may be underestimated because it excludes a subgroup of the original grade II (IIb), which may be difficult to manage.

Cook[35] further divided the Yentis and Lee modified systems into 3a (epiglottis can be seen and lifted) and 3b (epiglottis visualized but cannot be lifted); thus it consists of six grades, divided into three functional classes: easy, restricted, and difficult. Easy views were defined as when the laryngeal inlet is visible and thus suitable for intubation under direct vision (grades 1 and 2a). Restricted views were defined as when the posterior glottic structures (posterior commissure or any arytenoid cartilages) are visible or the epiglottis is visible and can be lifted (grades 2b and 3a). These views are likely to benefit from indirect intubation methods (e.g., gum elastic bougie). Difficult views were defined as when the epiglottis cannot be lifted or when no laryngeal structures are visible, which are likely to need specialist methods for intubation and may need to be performed blindly (grades 3b and 4). Cook proposed that this three-category classification system is of more practical value and had greater discrimination than Cormack-Lehane's. He found that an easy view predicts easy intubation in 95% of cases and has less than 3% need of any intubation adjuncts. A difficult view is associated with DI in three quarters of cases, and specialist intubation techniques are likely to be required. Between these extremes, a restricted view is likely to require the use of a gum bougie but no other adjuncts.

It would be useful to predict DI before it occurs, but no preoperative test has adequate sensitivity to identify most cases without substantial false-positive results.[36] Several prospective studies have identified various individual characteristics, which have significant association with laryngoscopic or intubation difficulties.[12,16,21,23,37-41] Sensitivity and PPVs of these individual variables are low, ranging from 33% to 71% for specificity. Several combinations of these variables have been shown to be more effective predictors of DI.

A meaningful evaluation of the available literature requires an assumption about a reasonable level of expectancy in terms of sensitivity and specificity of the tests used for prediction of DI. Thus if at least 9 of 10 DIs are to be predicted, a sensitivity of 90% will be required. In addition, if one assumes that one false alarm a week is acceptable, in a hypothetical practice of 10,000 cases a year, it would correspond to a specificity of 99.5%.[42] A number of investigators have attempted to achieve the goal of predicting DL or DI, or both, by combining different predictors and deriving multivariate indices so that the occurrence of false-negative results is decreased and the PPVs are increased.[13,15,28] However, to date, no single multifactorial index can be applied to all of the various surgical populations. In addition, most, with the exception of Wilson's index, have not been validated prospectively.[22,24]

New investigative modalities, including x-ray, ultrasound, and three-dimensional computed tomography (CT) scans of the airway, have been proposed to help predict a difficult airway.[35,43] A recent review performed by Sustic[44] suggests that ultrasound can be used to assess anatomy of the upper respiratory organs and possibly assist in various applications of airway management.

The Upper Lip Bite Test (ULBT),[45] a new, simple clinical bedside test performed by having the patient attempt to bite his or her own upper lip, has recently been suggested to aid in the prediction of difficulty with intubation. It is classified as follows: lower incisors can bite the upper lip above the vermilion line—Class 1; below the vermilion line—Class II; and cannot bite the upper lip—Class III. A recent external prospective evaluation of the reliability and validity of ULBT demonstrated that the interobserver reliability was better than the Modified Mallampati (MMP) score (Mallampati classification [MPT], as modified by Samsoon and Young).[12] They also found that they could not use the test on edentulous patients (11% of 1425 patients), and concluded that, like the MMP score, the ULBT was a poor predictor when used as a single screening test.[46]

Additionally, advanced computing techniques over the last decade have improved statistical analysis, allowing improved testing of variables for successful prediction of the difficult airway.[26] Nonetheless, given the low incidence of DI and the wide variation in acceptable definitions of airway terms, it is difficult to compare different studies and perform a meta-analysis of the predictors of difficult airway management.

EVIDENCE

History

After thorough review of the literature, the published evidence is not sufficient to evaluate the effect of either a bedside medical history or a review of prior medical records on predicting the presence of a difficult airway. According to the ASA task force, there is suggestive evidence (which is defined by the ASA as enough information from case reports and descriptive studies to provide a directional assessment of the relationship between a clinical intervention and a clinical outcome) that some features of both may be related to the likelihood of encountering a difficult airway.[10]

Many congenital and acquired syndromes are associated with difficult airway management. Also, certain disease states, such as obstructive sleep apnea[47] and diabetes,[48] have been suggested to correlate with an increased risk of DI. Trauma to the airway, either caused by external forces or iatrogenic from routine endotracheal intubation, may also be associated with difficult airway management. Recently, Tanaka and colleagues[49] demonstrated increased airflow resistance attributable to intraoperative swelling of the laryngeal soft tissues in patients whose airways were predicted to be normal (or easy to intubate) and who underwent routine tracheal intubation. Others have observed serious laryngeal injuries (e.g., vocal cord paralysis, arytenoid cartilage subluxation, laryngeal granulomas, and scars) after short-term intubation and anesthesia.[50] Additionally, the ASA task force found that a previous history of difficult airway management offers clinically suggestive evidence that difficulty may recur.[10]

Physical Examination

Single Predictors of Difficult Laryngoscopy/Intubation

The ability of a specific test to predict a DI is decreased by the variability of definitions of DL and DI and the inherent inaccuracy of numeric grading systems.[33] Nonetheless, several investigations have identified anatomic features that have unfavorable influences on the mechanics of direct laryngoscopy and endotracheal intubation (Table 15-1). The majority of anesthesiologists rely on predicting DI mainly as a result of several preoperative bedside screening tests.

Mallampati Classification. The MPT[51] focuses on the relative visibility of oropharyngeal structures when the patient is examined in the sitting position with the mouth fully opened, the tongue fully extended, and without phonation. Samsoon and Young[9] proposed the modified MPT (MMP) in which there are four oropharyngeal classes instead of the original three (Figure 15-2), yet Ezri et al[52] and Maleck et al[53] further suggest adding a fifth class, class 0, defined as the ability to visualize any part of the epiglottis on mouth opening and tongue protrusion. Samsoon and Young's method is by far the most widely investigated method of airway evaluation. The practical value of this method lies in its ease of application, yet practitioners often perform this examination in the supine position with or without phonation. A wide range of observations shows that this method is subject to significant interobserver variability. Overall, the literature suggests that the true sensitivity of the MMP, as modified by Samsoon and Young, is most likely between 60% and 80% and the true specificity is between 53% and 80%; the PPV is approximately 20%. A recent meta-analysis of the accuracy of MPT/MMP found substantial differences and variability in reported sensitivity and specificity values. Overall accuracy of the test was poor to good and depended on which version of the test and reference tests were used.[54] The meta-analysis also suggested that the MPT/MMP was a poor predictor of DMV.[54] Krobbuaban and colleagues[55] found that MMP Classes III and IV had a sensitivity of 70% and specificity of 60% with a PPV of 20%.

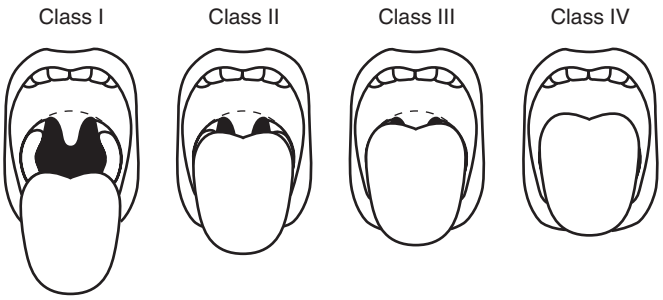

FIGURE 15-2 ■ Modified Mallampati Classification.

Additionally, a recent study suggested that the best way to perform MPT was by placing the patient in the sitting position, with the patient's head in full extension, tongue protruded, and with phonation, yet phonation did not influence the overall accuracy of this classification.[56] Mashour and Sandberg[57] evaluated 60 patients first with the MMP test and then repeated the examination with craniocervical extension. They found that by including craniocervical extension, the MMP scores were reduced. Class II MMP became Class 1.6, Class III became 2.6, and Class IV became 3.5. The sensitivity remained the same but the specificity improved from 70% to 80%. The PPV increased from 24% to 31%, and the negative predictive value (NPV) increased marginally from 97% to 98%.[57] A recent meta-analysis of 55 studies involving 177,088 patients concluded that the prognostic value of the MMP was worse than earlier estimates with a pooled sensitivity and specificity of 0.35 and 0.91 and an OR of 5.89.[58] Another recent but smaller study of 1956 patients determined that MPT is insufficient for predicting DI on its own.[59]

Thyromental Distance. The concept of thyromental distance (TMD), noted as the distance between the chin and the notch of the thyroid cartilage, was described by Patil and associates in 1983.[26] They proposed that this distance should be 6.5 cm in the healthy adult, and that if this distance is less than 6 cm, there may be intubation difficulties. Of all the morphometric measurements, TMD has been questioned the most for its value in predicting DI.[60] The sensitivity of this test is between 60%

TABLE 15-1 **Evidence of Single Predictors of Difficult Intubation**

Predictors	Study	No. of Patients	Incidence (%)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Definition of Difficult Intubation*	Best Attempt	Population
	Arne et al, 1998[13]	1200	4	78	85	19	99	4	+	General + ENT
	Savva, 1994[23]	355	1.14	64.7	66.1	8.9		1, 3, and 4	+	General + OB (10%)
	Oates et al, 1991[22]	675	1.8	42	84	4			–	General
	Butler and Dhara, 1992[18]	220	8.2	56	81	21			–	General
	Frerk, 1991[19]	244	4.5	81	82	17			–	General
Mallampatti III or IV	Rose and Cohen, 1994[16]	18,558	1.8	Relative risk, –4.5				3 > 2 attempts	–	General
	Voyagis et al, 1998[74]	1833	8.3	88.1		37.2	Original†	1	–	Obese
				86.8		50	Modified†			General
	Bergler et al, 1997[106]	91	10	60	72				–	General + ENT
	Brodsky et al, 2002[77]	100	12	58.3	70.5			1 and 3	–	Morbidly Obese
	Khan et al, 2003[45]	300	5.7	82.4	66.8	13	98.4	1	–	General
	Yamamoto et al, 1997[90]	3680	1.3	67.9	52.5	2.2		1	+	General
	El-Ganzouri et al, 1996[28]	10,507	1	44.7	89	21	96.1	1	+	General
				59.8		4.4		2		
	Wong and Hung, 1999[62]	411	1.99	85.7	62.6	3.8	99.6	1	–	Chinese ♀
IV Only	Savva, 1994[23]	355	1.14	52.9		87		1, 3, 4	+	General + OB (10%)
	Wong and Hung, 1999[62]			28.6	98.3	22.2	98.8	1	–	Chinese ♀
Thyromental Distance										
<6	Butler and Dhara, 1992[18]	220	8.2	62	25	16			–	General
<6	El-Ganzouri et al, 1996[28]	10,507	1	7	99.2	38.5	94.3	1	+	General
				16.8	99	15.4	99.1	2		
<6.5	Savva, 1994[23]	355	1.14	65	81	15		1, 3, 4	+	General + OB (10%)
<6.5	Arne et al, 1998[13]	1200	4	16	95	12	96	4	+	General + ENT
<7	Frerk, 1991[19]	244	4.5	91	82	19			–	General
<7	Schmitt, 2002[63]	270	5.9	81	73			1	+	General
Ratio of Height to Thyromental Distance										
25	Schmitt et al, 2002[63]	270	5.9	81	91			1	+	General
Sternomental Distance										
<12.5	Savva, 1994[23]	355	1.14	82.4	88.6	26.9		1, 3, 4	+	General + OB (10%)
Neck Movement										
<80°	El-Ganzouri et al, 1996[28]	10,137	1	10.4	98.4	29.5	94.4	1		General
				16.78		7.9		2		
<90°	Arne et al, 1998[13]	1200		54	85	14	98			General + ENT
Atlanto-Occipital Extension										
<35°	Wong and Hung, 1999[62]	411		85	70	4.8		1	–	Chinese ♀
Obesity										
BMI > 30 kg/m^2	Voyagis et al, 1998[74]	1833	8.3	88.9		66.7				Obese

BMI, body mass index; *ENT,* ears, nose, and throat; *OB,* obstetric; ♀, female.
*Definition of difficult intubation: (1) Cormack and Lehane grade III or IV; (2) Cormack and Lehane grade IV only; (3) No. of attempts; (4) special techniques and others.
†*Original* indicates tongue protruded by the patient; *Modified* indicates tongue actively pulled out by the anesthesiologist.

and 80% and has a specificity of 80% to 90% in some studies.[12,16,34,35] Arne and colleagues[13] and El-Ganzouri and colleagues[28] found the test to be highly insensitive (sensitivity, 16% to 17%) but very specific (specificity, 95% to 99%) with a PPV of 12% to 16%, if a more stringent definition of DI involving best attempt (with OELM) is applied.

Recently, the role of TMD has been challenged by some authors.[5,6] Chou and Wu[6] suggest that the receding mandible, one of the two components of a micrognathic mandible, is not the real cause for DL in these patients, thus TMD is irrelevant. Qudaisat and Al-Ghanem[61] suggest that TMD is a surrogate for inadequate head extension. They found that among the factors that determine TMD only the degree of head extension was significantly different between the two laryngoscopy groups. The two other factors (sagittal angulomental distance, representing mandibular growth and sagittal angulothyroid distance, representing laryngeal descent in the neck) did not differ between the two laryngoscopy groups. Wong and Hung[62] studied TMD, along with MMP and atlanto-occipital extension (AOE) and demonstrated the limitation of absolute anatomic measurements in their study involving Chinese women. The optimal TMD criterion was 5.5 cm in this study, which achieved a sensitivity of 71% and a specificity of 83%, yet the PPV was only 7.5%.[62] Schmitt and colleagues[63] attempted to adjust this measurement to the patient's size and proposed the ratio of the patient's height to thyromental distance (RHTMD). Using the ROC curve, they found a cutoff value to be 25 or greater for this ratio to predict DL with a reasonable degree of sensitivity (81%) and specificity (90%).

A recent meta-analysis performed by Shiga and colleagues[64] stated, "the diagnostic value of TMD proved unsatisfactory in their analysis." They determined that there was a wide range in the sensitivity, which could possibly be due to different cutoff points (4.0 to 7.0 cm). They also found that the positive LR of TMD improved from 3.4 to 4.1 when a more strict cutoff criterion (<6.0 cm) was applied.[64]

Recently, Krobbuaban and colleagues[55] conducted a prospective randomized study of 550 consecutive Thai patients. They found that the RHTMD had higher sensitivity (77%), higher PPV (24%), and fewer false-negative results (16%). They also found that RHTMD of 23.5 or greater, neck movement less than 80 degrees, and MMP Classes III and IV were major predictors of DL. Rosenstock and colleagues[65] found that the interobserver agreement for TMD and neck mobility was low.

Hyomental Distance. Hyomental distance (HMD), a measurement from the tip of the chin to the hyoid cartilage, has also been considered as one of the predictors of DI. Both TMD and HMD give an idea of the available space for the tongue during laryngoscopy. In an investigation involving 12 cadavers and 334 patients, Turkan and colleagues,[4] using cervical spine radiographs of patients in the neutral position, found that mean HMDs were less than the stated limit of 7 cm[66] and that HMD was the only objective variable not affected by age. However, both McIntyre[67] and Randall[60] demonstrated that radiologic measurements have not been capable of providing sensitive criteria for prediction of DI and that radiographic studies were, at best, regarded as valuable in understanding problems encountered during laryngoscopy.

Sternomental Distance. Sternomental distance (SMD), a measurement from the tip of the chin to the sternal notch, normally greater than 12.5 cm, was suggested by Savva[23] to predict DI if less than 12 cm with maximal head extension. Savva[23] found that this measurement was both more sensitive and more specific than TMD and that it may give a more accurate estimate of head extension. This measure functionally "added" the atlanto-occipital joint into the physical evaluation of the airway.[68] Ramadhani and colleagues[69] suggested that SMD was a superior measurement, compared with others, by showing that SMD had an increased sensitivity (71.1%) and specificity (66.7%) for predicting subsequent DL and that it was unaffected by age. However, the patient group in their study was limited to women of childbearing age only. Turkan and colleagues,[4] on the other hand, demonstrated that SMD measurements were affected both by age and gender, as both younger (20- to 30-year olds) and male patients had longer SMD measurements.

In their meta-analysis, Shiga and colleagues[64] found that SMD yielded moderate sensitivity and specificity. It also yielded a high positive LR and diagnostic OR.[64] The negative LR for SMD was the lowest, suggesting that it could be the best single test for ruling out DI. Nonetheless, their study was based on only three studies that included SMD.[64]

Neck Movement and Mouth Opening. Neck movement and mouth opening have also been considered as variables in predicting DI. El-Ganzouri and colleagues[28] demonstrated that three single variables, that is, restricted head and neck movement, including flexion and especially extension capability (<80 degrees[26] or <90 degrees[11]), restricted mouth opening (<4 cm[26] or <5 cm[11]), and inability to protrude the mandible, have a significant association with DI. The accuracy of the estimation of AOE with use of the Bellhouse test has been questioned and, similar to other clinical methods, is subject to wide interobserver variability.[70]

Individual examinations and tests are subject to wide interobserver variability; thus any evidence needs to be evaluated accordingly. In a study involving 59 patients, Karkouti and colleagues[71] determined that mouth opening and chin protrusion had excellent interobserver reliability, whereas seven tests (i.e., TMD, mandible subluxation, AOE and angle, profile classification, ramus length, and oropharyngeal best view) were only moderately reliable between observers. In addition, the MMP technique of assessing the oropharyngeal view has poor interobserver reliability.[72]

Rosenstock and colleagues[65] evaluated the interobserver reliability of the Simplified Airway Risk Index (SARI). The parameters used in SARI include mouth opening, TMD, ability to protrude the mandible, MMP score, head and neck mobility, and body weight. Two pairs of assessors (two specialists and two residents) performed the assessment. They used five of seven tests from

SARI and evaluated 120 patients with normal airways and 16 patients documented to have airways that were difficult to intubate. They found good interobserver agreement with mouth opening, MMP class, and mandibular protrusion, whereas TMD and neck movement had low levels of interobserver agreement.[65]

In the Yildiz and colleagues multicenter study,[73] the most sensitive criterion when used alone was mouth opening (sensitivity, 43%). In their study, the incidence of DI was significantly higher in patients with MMP Classes III and IV, a decreased average TMD and SMD, decreased mouth opening, or decreased protrusion of the mandible ($p < 0.05$). Combination of the tests did not improve their results.[73]

Rose and Cohen[16] analyzed the data regarding problems and prediction of difficult airway management in 18,500 patients and found that although the most common single abnormalities noted were restricted neck movement (3%) and decreased visualization of the hypopharynx (2.2%), with a relative risk of 3.2 and 4.5, respectively, decreased mouth opening (<2 fingers; relative risk, 10.3) and shortened TMD (<3 fingers; relative risk, 9.7) were the best predictive factors of DI.

Weight. Obesity has been studied as isolated body weight (>110 kg)[28] or body mass index (BMI; >30 kg/m^2)[74] and shown to be associated with DL, especially when accompanied with a large tongue (as assessed by MMP). Juvin and colleagues,[75] in a study involving 134 lean (BMI < 30 kg/m^2) and 129 obese patients (BMI ≥ 35 kg/m^2), determined that DI is more common among obese than nonobese patients by using the Intubation Difficulty Scale (IDS) developed by Adnet and colleagues,[76] which includes both qualitative and quantitative dimensions of DI. It is an objective scoring system involving seven variables: number of intubation attempts, skill and experience of the operators, alternative intubation techniques, glottic exposure (Cormack-Lehane), lifting force applied to the laryngoscope, application of external laryngeal pressure, and position of the vocal cords at intubation. In this study, they defined two groups of patients according to the IDS values: those with an IDS score of less than 5 (easy and slightly difficult) or 5 or greater (difficult). They found that among the classic risk factors for DI, only an MMP score of III or IV is a risk factor for DI in obese patients (OR, 12.51; specificity, 62%; PPV, 29%). They also determined that the risk of hypoxemia is higher in obese patients during anesthesia induction and that further investigation is necessary to identify the risk factors for DI in this population.[51]

Shiga and colleagues[64] found that the incidence of DI in obese patients (BMI > 30 kg/m^2) was more than three times higher than in nonobese patients. Also, Cattano and colleagues[59] found that obesity had the highest sensitivity (32%) and a PPV of 16% for predicting difficulty of intubation. The same sensitivity (32%) was found with an MMP score of Classes III and IV. Brodsky and colleagues,[77] on the other hand, studied 100 consecutive morbidly obese subjects (BMI > 40 kg/m^2) and concluded that neither absolute body weight (obesity) nor BMI is associated with intubation difficulties. Rather, they found that a large neck circumference (NC; measured at the level of the superior border of the cricothyroid cartilage) of 40 cm showed a 5% probability and an NC of 60 cm showed a 35% probability of problematic intubation; high (III or greater) MMP scores are the only predictors of potential intubation problems in this patient population. Thus whether tracheal intubation is more difficult in obese patients is debatable. Lundstrom and colleagues,[78] in a cohort study of 91,332 concluded that a BMI greater than 35 kg/m^2 is a weak (sensitivity, 7.5%; PPV, 6.4%) but statistically significant predictor of difficult and failed intubation with an OR of 1.031.

Kim and colleagues[79] demonstrated a 13.8% versus 4.8% ($p = 0.016$) incidence of DI in 123 obese patients (BMI > 27.5 kg/m^2) compared with 125 nonobese patients. Multivariate analysis showed that the MMP score, the Wilson score, and the ratio of the NC and TMD independently predicted DI (defined as intubation difficulty scale > 5) in obese patients. NC/TMD had the highest sensitivity and NPV.

NAP4 data suggest that patients with a BMI of more than 30 kg/m^2 were at least twice as likely to have serious complications of airway management as those with a BMI of 30 kg/m^2 or less. A BMI of more than 40 kg/m^2 increased the risk fourfold.[80]

Increasing knowledge of the sonoanatomy of the upper airway could potentially play a significant role in predicting difficult airways. Komatsu and colleagues[81] used ultrasound to quantify anterior neck soft tissue thickness and predict DL in 64 morbidly obese patients (BMI ≥ 35 kg/m^2). They performed an ultrasound scan of the anterior neck soft tissue and measured the distance from the skin to the anterior aspect of the airway at the level of the vocal cords. In contrast to Brodsky's findings, they concluded that the thickness of pretracheal soft tissue at the level of the vocal cords is not a good predictor of DL in either white or black obese patients. In contrast, Ezri and colleagues[52] studied Middle Eastern patients and determined that soft tissue in the neck did influence difficulty in intubation. Adhikari and colleagues,[82] in their pilot study with 5 of 51 patients having DL, found that sonographic measurements of anterior neck soft tissue thickness at the level of hyoid bone and thyrohyoid membrane can be used to distinguish difficult and easy laryngoscopies.

Additionally, Siegel and colleagues[83] demonstrated that ultrasound of the airway was a reliable, simple, and comfortable method of identifying the mechanism of airway obstruction. The role of preintubation ultrasound assessment elsewhere in the upper airway for the detection of pharyngeal or laryngeal pathology, such as tumors, abscesses, or epiglottitis, has also been studied.[84,85] Because of these discrepancies in the literature, convincing evidence to correlate soft tissue thickness of the neck with DI does not exist.[81]

Combined Predictors of Difficult Laryngoscopy and Intubation

Although no single factor has been shown to be a predictor of DI on its own, it has been widely suggested that combinations of factors improve predictability of DI. Various combinations of individual predictors have been

studied, and several multivariate indices have been proposed (Table 15-2); however, very few have been prospectively evaluated for their efficacy. In his editorial, Wilson[36] concluded that no single test is likely to be a perfect predictor of DI, and Bainton[86] suggests that the most satisfactory solution would be the "best algebraic sum" of several tests.

Shiga and colleagues'[64] recent study of bedside screening tests for predicting DI in apparently healthy people suggested that DI is predicted more accurately by combining the MPT and TMD. In their meta-analysis of 35 studies involving 50,760 patients, they found that MPT and TMD combined have the highest discriminative power. Patients with a 5% pretest probability of DI showed a 34% risk of DI after a positive result for the combination, 16% risk after a positive result for MPT alone, and 15% risk for TMD alone.[64]

Krobbuaban and colleagues[55] found that RHTMD greater than 23.5 (PPV, 24%; false-negative rate, 16%), MMP Classes III and IV (PPV, 20%; false-negative rate, 21%), and neck movement less than 80 degrees (PPV, 22%; false-negative rate, 60%) were the major factors in predicting DL. RHTMD had a higher PPV, higher sensitivity, and fewer false-negative results than the other factors. On multivariate analysis, the ORs (95% CI) of the RHTMD, MMP class, and neck movement variables were 6.72 (3.29-13.72), 2.96 (1.63-5.35), and 2.73 (1.14-6.51), respectively. The interincisor gap (<3.5 cm) and TMD (<6.5 cm) were not recognized as independent variables for DL.[55]

Matthew and colleagues[87] found all 22 patients with known DI to have a TMD less than 6 cm and MMP classifications of III or IV, whereas all 22 matched control subjects (easy intubations) had a TMD greater than 6.5 cm and MMP classifications of I or II. By prospectively testing this combination in 244 patients, Frerk[19] found a sensitivity of 80% and a specificity of 98%. Wong and Hung,[62] on the other hand, found it to be 71% and 92% in 411 Chinese women, of whom 151 were pregnant. Janssens and Hartstein[88] and Janssens and Lamy[89] recently developed a new scoring system, the Airway Difficulty Score (ADS), for predicting DI, in which a TMD less than 6 cm, MMP Class greater than I, mouth opening less than 4 cm, reduced neck mobility, and presence of upper incisors related to airway difficulty. A score between 5 and 15 is given for each patient, and a score of 8 or greater is considered to be a potential DI. When the authors compared the ADS with the IDS, they found a 75% sensitivity, 85.7% specificity, an excellent NPV of 98.7%, and a low PPV of 18.6%. This score allows the clinician to distinguish difficulty in maintaining upper airway patency, difficulty with alignment of the axes, and difficulty in visualizing the larynx. Scoring systems, such as the ADS and the IDS,[75] require further investigation and inclusion of more definitive variables.

Iohom and colleagues,[43] in a study involving 212 nonobstetric patients, found that combining MMP classification of III or IV with either a TMD of less than 6.5 cm or an SMD of less than 12.5 decreased the sensitivity (from 40% to 25% and 20%, respectively) but maintained an NPV of 93%. The specificity and PPVs increased from 89% and 27%, respectively, for MMP alone to 100%. Thus they suggest that the MMP classification, in conjunction with measurement of the TMD and SMD, may be a useful routine screening test for preoperative prediction of DI.[43]

Wilson and colleagues[24] examined a combination of five risk factors (Wilson Risk Sum): weight, head and neck movement, jaw movement, receding mandible, and buck teeth. One of three levels is assigned per risk: a level of 0 represents no risk for DI and a level of 2 represents the greatest risk for DI.[24] Wilson's group suggested that a score of 2 would correspond to a test that had sensitivity of 75% and specificity of 85%, yet this test would not be applicable to children or pregnant women because of the weight classification. Oates and colleagues,[22] on the other hand, found the Wilson Risk Sum to have a sensitivity of 42%, a specificity of 92%, and a PPV of 9%. When compared with the MMP classification, the Wilson Risk Sum was found to be slightly superior. Yamamoto and colleagues[90] tested the same scoring in 3608 patients and found the sensitivity to be slightly better (55%), but the specificity and PPV were 86% and 5.5%, respectively.

Wong and Hung[62] derived the following regression equation: DL = 2.73 – 0.1 TMD – (0.01 AOE – 0.1 MMP); they concluded that the laryngoscopic grade would be higher (i.e., more difficulty intubating) if the combination of AOE and MMP yielded a more negative value. They termed the combination of AOE and MMP, both of which are independent of body build, as the Predictor of Intubation Difficulty (PID) and used a PID of 0 or less as the criterion for prediction of DI. They found a sensitivity of 71%, a specificity of 95.5%, and a PPV of 21.7%. This study of Chinese women, including pregnant women, was an attempt to neutralize the effect of body build on absolute anatomic measurements and their limitation as predictors of DI.

Bellhouse and Dore[91] identified radiographic predictors in patients with known difficult airways and suggested three closely corresponding clinical measures: MMP Class III or IV, limited AOE, and receding chin. No formal prospective evaluation of their findings has been performed, so the sensitivity and specificity of this combination of predictors are unknown.

Rocke and colleagues,[11] in their rare study involving 1500 obstetric patients, found four predictors of DI: MMP classification, receding mandible, short neck, and protruding maxillary incisors. Tse and associates[92] evaluated the combination of MMP classification, head extension, and TMD in 471 patients. They found that combinations of mediators generally seemed to improve specificity, thus decreasing the chance of false alarms, but it was at the cost of sensitivity, which means missing a large proportion of potential DIs.

El-Ganzouri and colleagues[28] prospectively studied 10,507 patients who underwent surgery under general anesthesia to determine what parameters might be associated with DI. They derived a composite airway risk index with an OR used to weigh the risk of individual parameters, including mouth opening, MMP classification, neck mobility, ability to protrude the mandible, body weight, and a history of DI. By retrospectively applying a simplified risk index (0, low; 1, medium; 2, high), they found a sensitivity of 65%, a specificity of 94%, and a

TABLE 15-2 **Evidence of Multivariate Predictors of Difficult Intubation**

Authors/Reference No.	No. of Patients	Incidence of Difficult Intubation (%)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Definition of Difficult Intubation*	Best Attempt	Population Excluded	False Negative (%)	Misclassification Rate (%)
Wong and Hung[62]	411	1.54 non-pregnant; 1.99 pregnant	71.4	95.5	21.7		1	–	Non-Chinese and Chinese men	+	
Wilson et al[24]	778	1.5	75	88	9	99	1	–	OB and ENT	0.4	12
Pottecher et al[107]	663	5.8	70	84	21	98	1	–	ENT	1.8	17
El-Ganzouri et al[28]	10570	1	65	94	10	99	2	+	OB and ENT	0.3	7
Arne et al[13] (gen surg) (simplified score)	717	2.5	94	96	37	99	4	+	ENT and OB	0.2	4
Arne et al[13] (global pop.) (simplified score)	1090	3.8	93	93	34	99	4	+	OB	0.3	7
Naguib et al[96] (discriminate eqn.) (clinical criteria)	56	42	95.4	91.2	87.5	96.9	1, 3	–			
Naguib et al[96] (discriminate eqn.) (clinical + radiologic)	56	42	95.8	96.9	95.8	96.9	1,3	–			
Oates et al[22] (Wilson Risk Sum)	675	1.8	42	92	9		1				
Yamamoto et al[90] (Wilson Risk Sum)	3608	1.3	55.4	86.1	5.9		1	+			

ENT, ear, nose, and throat; *OB,* obstetric.
*Definition of difficult intubation: (1) Cormack and Lehane grade III or IV; (2) Cormack and Lehane grade IV only; (3) no. of attempts; (4) special techniques and others.

PPV of 10%, which corresponded to a 1% incidence of DI (defined as a laryngoscopic view of Class IV alone), as assessed by an experienced anesthesiologist after the best attempt.

Caldiroli and Cortellazzi[93] proposed an algorithm based on the El-Ganzouri Risk Index (EGRI) to predict difficult laryngeal exposure with Glidescope® videolaryngoscopy. In their study of 6276 neurosurgical patients, they identified an overall 0.2% incidence of DL, defined as Cormack-Lehane grade III-IV with the best attempt used. Their decisional rule using an EGRI score of 7 as the threshold, after exclusion of patients with morbid obesity, pharyngolaryngeal or neck tumors, and large scars, resulted in a PPV of 85% and a NPV of 99%.

Arne and colleagues[13] performed a prospective analysis of 1200 ear, nose, and throat (ENT) and general surgical patients to develop and validate a clinical multifactorial risk index aimed at predicting DI. They identified seven criteria as independent predictors of DI, defined as the need to use special techniques as assessed by two senior anesthesiologists, after their best attempts in performing endotracheal intubation. A simplified risk index was formulated with the use of regression coefficients as the relative weight of individual predictors. The best predictive threshold for the sum was chosen as 11 with the use of the ROC curve. This scoring system was then prospectively evaluated in a population of 1090 consecutive patients. The sensitivity and specificity were 94% and 96% in general surgery, 90% and 93% in noncancer ENT surgery, and 92% and 66% in ENT cancer surgery cases, respectively. They claim that the index is investigator independent and has a 7% misclassification rate. The population studied included only a small number of patients with cervical spine pathology, and patients with a history of spondylosis, rheumatoid arthritis. or occipital atlanto-axial diseases were not included.

Recently, Khan and colleagues[94] prospectively studied 380 adults and identified DI in 5% of patients, defined as a grade III or IV laryngoscopy view (Cormack and Lehane). They found that ULBT has higher accuracy and specificity than SMD, TMD, and interincisor distance and also has a high NPV. Only the combination of SMD and ULBT had a better sensitivity compared with ULBT alone. Sensitivity, specificity, and accuracy of the ULBT are 79%, 92%, and 91%, respectively, similar to their earlier study. Although the ULBT has acceptable sensitivity and PPV in comparison with other tests, its high specificity and NPV make it a favorable test for identifying easy intubations. This finding is in agreement with Eberhart and colleagues.[46]

Rosenblatt and colleagues[95] studied 138 patients, and an awake intubation was planned in 44. After preoperative endoscopic airway examination (PEAE), only 16 underwent preinduction airway control. Eight of the remaining 94 patients were found to have unexpectedly difficult airway pathology and underwent awake intubation. PEAE can provide superior visual information of the airway and can be an essential component of preoperative assessment of patients with airway pathology.

Naguib and colleagues[96] evaluated 24 patients in whom unanticipated DI occurred, along with a control group of 32 patients in whom intubation was easily accomplished, using clinical and radiologic data. They identified four clinical risk factors: TMD, thyrosternal distance, NC, and MMP classification. Using both clinical and radiologic data, discriminant analysis identified five risk factors: TMD, thyrosternal distance, MMP classification, depth of the second cervical vertebrae spinous process, and the angle at the most anteroinferior point of the upper central incisor tooth. Although a PPV of 95.8% in a study population with an incidence of DI of 42% is not realistic, the possible role of advanced radiologic techniques such as three-dimensional computer imaging in the prediction of DI cannot be ignored.

Cattano and colleagues[59] demonstrated that the MMP versus Cormack-Lehane linear correlation index was 0.904. MMP Class III correlated with a Cormack-Lehane grade II (0.94), and MMP Class IV correlated with Cormack-Lehane grade III (0.85) and Cormack-Lehane grade IV (0.80).[59]

Difficult Mask Ventilation

Although failure to intubate may not necessarily lead to hypoxia and hypoxemia, failure to ventilate will cause these adverse consequences. Interestingly, the majority of the literature on prediction of the difficult airway does not include factors predicting DMV. Williamson and colleagues[97] analyzed 2000 incident reports and indicated a 15% incidence of DMV in patients who had difficult or failed intubation. El-Ganzouri and colleagues[28] found an incidence of 0.08% in their study of 10,507 patients and determined that approximately 100,000 patients would be required to apply a multivariate analysis. They defined DMV as the inability to obtain chest excursion sufficient to maintain a clinically acceptable capnogram waveform despite optimal head and neck positioning, use of muscle paralysis, use of an oral airway, and optimal application of a face mask. Langeron and colleagues[15] observed a 5% incidence of DMV, defined as the inability of an unassisted anesthesiologist to maintain oxygen saturation at greater than 92% or to prevent or reverse signs of inadequate ventilation during positive-pressure mask ventilation (MV) under general anesthesia. In their study of 1502 patients that excluded ENT, obstetric, and emergency patients, they found five criteria (i.e, age older than 55 years, BMI > 26 kg/m^2, lack of teeth, presence of a beard, history of snoring) to be independent risk factors for DMV; the presence of two of these criteria indicated a high likelihood of DMV (sensitivity, 72%; specificity, 73%). Lower rates of DMV have been reported in prospective studies by Asai and colleagues[27] (1% to 4%), Rose and Cohen[16] (0.9%), and El-Ganzouri and colleagues,[28] as mentioned earlier. Obviously, a standardized definition is lacking for DMV, which could explain the variation in the incidence.

Kheterpal and colleagues[98] found 37 cases (0.16%) of grade 4 MV (impossible to ventilate) and 313 cases (1.4%) of grade 3 MV (difficult to ventilate) of 22,660 cases. They used a grade 1 to 4 classification, in which grade 1 was easy to ventilate by mask, grade 2 was able to ventilate by mask but with an oral airway/adjuvant with or without muscle relaxant, grade 3 was difficult

ventilation (inadequate/unstable or requiring two providers) with or without muscle relaxant, and grade 4 was unable to ventilate with or without muscle relaxant. Of the 37 cases of grade 4 MV, 1 required an emergency cricothyrotomy, 10 were DIs, and 26 were easy intubations. They identified six predictors for grade 3 MV: BMI greater than 30 kg/m^2, presence of a beard, MMP Classes III and IV, age 57 years or older, reduced jaw protrusion, and snoring. Of these six predictors, the only modifiable predictor was the presence of a beard. They could identify only two predictors for grade 4 MV: snoring and TMD less than 6 cm. They also found that 84 patients with grade 3 or 4 MV were difficult to intubate (0.37%). They suggested that the mandibular protrusion test or UBLT may be an essential element of airway assessment.[98]

Between 2004 and 2008, Kheterpal and colleagues[99] reviewed 53,041 attempts at MV and found 77 cases of impossible MV, that is, 0.15% incidence. Of these 77 impossible to ventilate, 19 demonstrated DI, of which 15 were intubated successfully. Two needed surgical airways, and two were awakened and underwent successful fiberoptic intubation. Neck radiation, male sex, sleep apnea, MMP Class III or IV, and a beard were identified as independent predictors.

Killoran and colleagues[100] identified an overall incidence of DMV in 8.56% of patients in their study of 3422 anesthetic procedures. On comparison of preoperative assessment data stratified by presence of DMV, they demonstrated significant differences in patient age, weight, BMI, NC, SMD, MMP score, cervical spine abnormalities, absence of teeth, appearance of a short neck, and history of obstructive sleep apnea.

Airway Assessment and Laryngeal Mask Airway Use

McCrory and Moriarty[101] studied 100 patients by assessing their airway with MPT and then placing an LMA. Adequate ventilation was possible in 98 patients, and in 2 patients LMA insertion was abandoned and anesthetic was continued with a Guedel airway and face mask ventilation. They performed fiberoptic laryngoscopy to view the laryngeal inlet and found that seating of the LMA was suboptimal in 30 patients and that the laryngeal inlet could not be viewed in seven patients. These seven patients' airways were MPT Class III. They concluded that an increasing occlusion of the laryngeal inlet and increasing difficulty of LMA insertion occurred with MPT Classes II and III. They also found that the number of attempts needed for LMA insertion increased with MPT Classes II and III. Eighteen patients with MPT Class II needed two attempts, and for MPT Class III, five patients needed two attempts and three patients needed three attempts. In two patients with MPT Class III airways, LMA insertion was abandoned (failed insertion after three attempts). The limitation of this study was that only a small number of patients had MPT Class III airways (n = 10), seven of whom had vocal cords that could not be viewed on fiberoptic laryngoscopy and two of whom had LMA placement abandoned.

Intubatability versus Ventilatability: "Can't Intubate, Can't Oxygenate"

"Can't intubate, can't oxygenate" (CICO) is a clinical situation in which the anesthesiologist is unable to intubate or perform effective ventilation. Hypoxemia and death can occur quickly unless emergency transtracheal oxygenation is provided.[30] Nonetheless, it is evident that in a number of situations when face mask ventilation fails and intubation is difficult, the laryngeal mask can provide a satisfactory airway. Although a CICO situation is rare in elective patients, guidelines have been established (see www.das.uk.com; accessed June 11, 2012).

AREAS OF UNCERTAINTY

Preoperative evaluation is important in the detection of patients at risk of difficult airway management, and any anatomic features and clinical factors associated with the difficult airway should be noted.* However, it is still uncertain whether true prediction is possible[14,26,92,103-105] and which variables should be chosen.[10] The majority of individual predictors appear to have a strong association with the occurrence of DI, but none of the combinations previously discussed has provided satisfactory results in terms of sensitivity and specificity. The reasons could be the low incidence of the end result (e.g., DI) and the conflicting inverse relationship between sensitivity and specificity, especially because of the critical nature of the outcome (i.e., death or brain damage). Nonetheless, false-positive results are clearly less dangerous than false-negative results, and every patient undergoing anesthetic intervention is subject to the possibility of the occurrence of problems with airway management. Difficult airway management in specific patient populations, including pregnant, obese, or pediatric patients and those undergoing surgery involving the airway, may require unique considerations. Further investigation of supraglottic ventilatory devices (e.g., Laryngeal Mask Airway or Esophageal Tracheal Combitube), flexible or rigid fiberoptic laryngoscopes, predictions for difficulty in their use, and how their use can overcome DI, despite unfavorable traditional predictors for DI, is necessary. Last, the integration of practice guidelines, as outlined in the next section, into clinical practice is difficult to monitor, which also makes it difficult to directly evaluate their utility regarding patient outcome. The latest NAP4 report emphasizes the importance and usefulness of preoperative assessment, even with the lack of accuracy of the tests available.[80]

GUIDELINES

There are current guidelines published by national[7] and international[97,98,103] societies that address the issue of interventions that reduce perioperative airway complications during management of the difficult airway.

*References 4, 11, 13, 14, 16, 17, 102.

The ASA appointed a task force to develop the ASA's Practice Guidelines for Management of the Difficult Airway, which were first adopted by the ASA in 1992 and have since been revised.[10] The purpose of these guidelines is to facilitate the management of the difficult airway and to reduce the likelihood of adverse outcomes.

These guidelines include the following recommendations:

1. History

An airway history should be conducted, whenever feasible, before the initiation of anesthetic care and airway management in all patients. The intent of the airway history is to detect medical, surgical, and anesthetic factors that may indicate the presence of a difficult airway. Examination of previous anesthetic records, if available in a timely manner, may yield useful information about airway management.

2. Physical Examination

An airway physical examination should be conducted, whenever feasible, before the initiation of anesthetic care and airway management in all patients. The intent of this examination is to detect physical characteristics that may indicate the presence of a difficult airway. Multiple airway features should be assessed, as in Table 15-3.

TABLE 15-3 **Components of the Preoperative Airway Physical Examination**

Airway Examination Component	Nonreassuring Findings
Length of upper incisors	Relatively long
Relation of maxillary and mandibular incisors during normal jaw closure	Prominent "overbite" (maxillary incisors anterior to mandibular incisors)
Relation of maxillary and mandibular incisors during voluntary protrusion of the lower jaw	Patient cannot bring mandibular incisors anterior to (in front of) maxillary incisors
Interincisor distance	< 3 cm
Visibility of uvula	Not visible when tongue is protruded with patient in sitting position (e.g., Mallampati class > II)
Shape of palate	Highly arched or very narrow
Compliance of mandibular space	Stiff, indurated, occupied by mass, or nonresilient
Thyromental distance	< 3 ordinary fingerbreadths
Length of neck	Short
Thickness of neck	Thick
Range of motion of head and neck	Patient cannot touch tip of chin to chest or cannot extend neck

3. Additional Evaluation

Additional evaluation may be indicated in some patients to characterize the likelihood or nature of the anticipated airway difficulty. The findings of the airway history and physical examination may be useful in guiding the selection of specific diagnostic tests and consultation.

AUTHORS' RECOMMENDATIONS

Based on the evidence from randomized controlled trials and the vast body of literature regarding methods for airway evaluation, airway examination does not predict difficult intubation (DI). Nonetheless, although current tests are not foolproof, a careful, systematic approach to a historical and physical evaluation of the airway in each patient should be performed.

The following suggestions should serve as a guide to aid clinical judgment and help guide anesthesiologists' decisions about airway management techniques for both patients and surgeons.

- Use a list of individual predictors (Box 15-1) to select patients who need further evaluation.
- Determine whether any combinations of individual predictors are present that may suggest difficulty.
- Perform any additional testing, including radiographic or endoscopic evaluation or both, and obtain a preoperative consultation with other specialists (otolaryngologist, pulmonologist, oncologist, thoracic surgeon) for patients with a known or clinically suspicious difficult airway.
- Review recommendations 1 through 3 with an expert or team of experts to consider factors predicting difficult mask ventilation (DMV), difficult laryngoscopy (DL), DI, and difficulty in the performance of a surgical airway; together formulate a plan, as well as alternative plans, for airway management.
- Finally, the practitioner should always be prepared by having a difficult airway cart ready and available and by practicing difficult airway drills, as well as special techniques that are helpful in the management of the patient with a difficult airway.[42]

The ability to more accurately predict DMV, DL, DI, and difficulty in the performance of fiberoptic intubation or a surgical airway should, in all likelihood, reduce the number of adverse outcomes and improve the safety of airway management. At least for now, reliable prediction of a DI remains an unsolved problem and is likely to remain a decision based on clinical judgment. The preoperative assessment should be designed to facilitate judgment regarding ease or difficulty of airway management and the performance and documentation of the airway examination.

BOX 15-1 Suggested Contents of the Portable Storage Unit for Difficult Airway Management

1. Rigid laryngoscope blades of alternate design and size from those routinely used; this may include a rigid fiberoptic laryngoscope
2. Tracheal tubes of assorted sizes

Continued on following page

BOX 15-1 Suggested Contents of the Portable Storage Unit for Difficult Airway Management (Continued)

3. Tracheal tube guides. Examples include (but are not limited to) semirigid stylets, ventilating tube changer, light wands, and forceps designed to manipulate the distal portion of the tracheal tube
4. Laryngeal mask airways of assorted sizes; this may include the intubating laryngeal mask airway and the LMA-Proseal (LMA North America, Inc., San Diego, Calif.)
5. Flexible fiberoptic intubation equipment
6. Retrograde intubation equipment
7. At least one device suitable for emergency noninvasive airway ventilation. Examples include (but are not limited to) an esophageal tracheal Combitube (Kendall-Sheridan Catheter Corp., Argyle, NY), a hollow jet ventilation stylet, and a transtracheal jet ventilator
8. Equipment suitable for emergency invasive airway access (e.g., cricothyrotomy)
9. An exhaled CO_2 detector

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CHAPTER 16

Is There a Best Approach for Patients with Difficult Airways: Regional versus General Anesthesia?

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INTRODUCTION

Airway management is the essence of the practice of clinical anesthesiology. Preoperative assessment of the patient's airway is the first step in the evaluation and planning of a safe, appropriate anesthetic plan. For the majority of patients, this can be readily achieved with a brief systematic history and physical examination and does not require additional diagnostic evaluation.

It may be anticipated that some patients will be difficult to intubate, based on a history of difficult intubation or clinical predictors of difficult intubation. The American Society of Anesthesiologists (ASA) Practice Guidelines for Management of the Difficult Airway reviews some of the historical and physical examination findings possibly suggestive of a difficult intubation.[1] Some of these predictors of anticipated difficulty with conventional direct laryngoscopy (Mac/Miller) include a large overbite, large tongue, narrow mouth opening, or short chin. Various prediction models, such as correlation with Mallampati oral views I to IV to the Cormack-Lehane laryngoscopic view grades I to IV, have been proposed, but none offers 100% sensitivity for prediction of a difficult airway.[2] Despite such an evaluation, an estimated 1% to 3% of patients in the operating room have an unanticipated difficult airway to intubate with conventional direct laryngoscopy.[3]

In addition to this 1% to 3% incidence of patients, cohorts of patients have specific pathologic conditions that are known to cause difficulties with conventional laryngoscopy. These patients may require more complex or multispecialty clinician airway management that may only be readily or immediately available in specialty or tertiary care centers.

The ASA Practice Guidelines for Management of the Difficult Airway encourage all practitioners to review the airway algorithm presented in the document and provide resources for the creation of difficult airway management carts that can be readily mobilized for elective and emergency airway management.

The goal, then, of the preoperative airway evaluation is to categorize the patient into one of two categories: (1) not difficult to intubate with conventional Mac/Miller direct laryngoscopy; or (2) anticipated to be difficult to intubate with conventional Mac/Miller direct laryngoscopy. In either category, unanticipated difficulty with the chosen airway management technique is a reality.

Of the patients who have an anticipated difficult airway, a certain percentage will be scheduled for surgical procedures that are amenable to regional anesthesia as the primary anesthetic or for postoperative pain management. For example, many orthopedic limb cases, lower abdominal surgeries, and urologic procedures can be performed with a regional technique and without anticipated airway management.

In these instances, regional anesthesia can be an attractive option for some clinicians when faced with a patient with anticipated difficult intubation who is scheduled for an appropriate surgery and who does not have other contraindications to regional anesthesia. However, if, during the procedure, the regional technique needs to be converted to a general airway-controlled anesthetic and adverse outcomes may be related to the urgent nature of the airway management, many clinicians are quick to criticize the role of regional anesthesia in these patients as a primary anesthetic. They advocate that, in the case of the anticipated difficult airway, the patient's airway must be electively controlled at the beginning of the case, and regional anesthesia should only be a component of a combined regional–general technique.

This chapter reviews the evidence supporting the decision to initiate a regional or general anesthetic in patients with anticipated difficult airways who are scheduled for appropriate surgical procedures. Patients in whom difficulty with airway management is not anticipated preoperatively and patients undergoing surgical procedures not amenable to regional anesthesia alone (e.g., intrathoracic or intracranial surgery) are not addressed in this chapter.

OPTIONS/THERAPIES

The appeal of choosing a primary regional anesthesia technique is that airway management and the potential complications in these complex patients may be able to be avoided. The ability to provide safe and adequate anesthesia without using an instrument on the airway can be a relief to both the patient and the anesthesiologist. The need to address issues of extubation of the

difficult airway and postoperative care can also be avoided.

Depending on the surgical case, as well as the patient's preferences, many different regional anesthetics may be appropriate. Neuraxial techniques, such as spinal or epidural anesthesia, as well as regional blocks such as brachial plexus, lumbar plexus, and specific nerve blocks, can provide excellent anesthesia, with or without concomitant sedation. Indwelling catheter techniques, such as for epidural or some extremity blocks, also allow postoperative pain to be managed successfully in certain cases.

The potential downfall of the regional anesthesia alternative is that the regional technique may be technically difficult, may be incomplete, or may fail, necessitating the conversion to a general anesthetic with or without intubation or a protected airway. The likelihood of failure of the regional technique cannot be predicted because it depends on the skill and experience of the anesthesiologist performing the neuraxial or nerve block. In addition, patient-specific factors, such as an inability to tolerate being awake or minimally sedated (so as to avoid respiratory depression), may require conversion to general anesthesia. Finally, surgical considerations such as extension of the procedure may require a change from regional to general anesthesia.

Conversion from a regional to a general anesthetic may be required at a time when the patient's airway is relatively less accessible to the anesthesiology team, as well as at a time when the deteriorating patient condition mandates hastening the ventilation and intubation process. It is important to recognize, in the words of Benumof,[4] "Use of regional anesthesia in the patient with a recognized difficult airway does not solve the problem of the difficult airway; it is still there."[4]

On the other hand, the appeal of a planned general anesthetic is that the airway can be approached in a controlled and measured fashion. This chapter does not provide an in-depth review of airway management techniques, but basic considerations include choosing between surgical and nonsurgical approaches, asleep versus awake techniques, and spontaneously ventilating or apneic patients. Specific intubating methods could include direct laryngoscopy, rigid or flexible fiberoptic laryngoscopy, or placement of a laryngeal mask airway (LMA) as a bridge toward definitive control of the airway, among many other possible forms of intubation (Figure 16-1).

A third alternative is the combined general with regional approach to anesthesia. In such circumstances, the regional anesthetic technique is used primarily for intraoperative and potentially postoperative analgesia, while the airway is intubated in a controlled fashion in the beginning of the case. Because the combined alternative leads to airway management in the beginning of the case, it will be considered as part of the general anesthesia option for the purposes of this chapter. In the cases of combined regional with general anesthesia, it can be the contribution of the regional anesthesia that facilitates successful extubation of the patient with an anticipated difficult airway (Figure 16-2).

EVIDENCE

The endpoint of greatest importance when comparing regional versus general anesthesia for the patient with an anticipated difficult airway would be patient mortality. Given the obvious ethical problems posed by comparing two techniques that are alternatives to avoiding significant risk of patient morbidity or mortality, it is not surprising that no randomized controlled trial has been performed that addresses this issue. In the absence of any randomized controlled trials, prospective and retrospective data reviews are the next level of evidence for which to look. We are not aware of any article that directly compares regional versus general anesthesia with regard to airway outcomes. The desire to avoid publication of adverse events and the relative infrequency of lost airways combine to make literature on this topic scarce.

There are several articles that do directly compare general anesthesia with regional anesthesia, but these articles focus on cardiovascular morbidity and mortality.[5-7] Other articles that compare regional versus general anesthesia examine other variables such as return of bowel function or postoperative pain control. A good overview of the state of outcomes research with regard to regional anesthesia has been written by Wu and Fleisher.[8] Airway management is notably absent from their discussion because no evidence has been published regarding the issue of regional versus general anesthesia, particularly for the patient with an anticipated difficult airway.

CONTROVERSIES

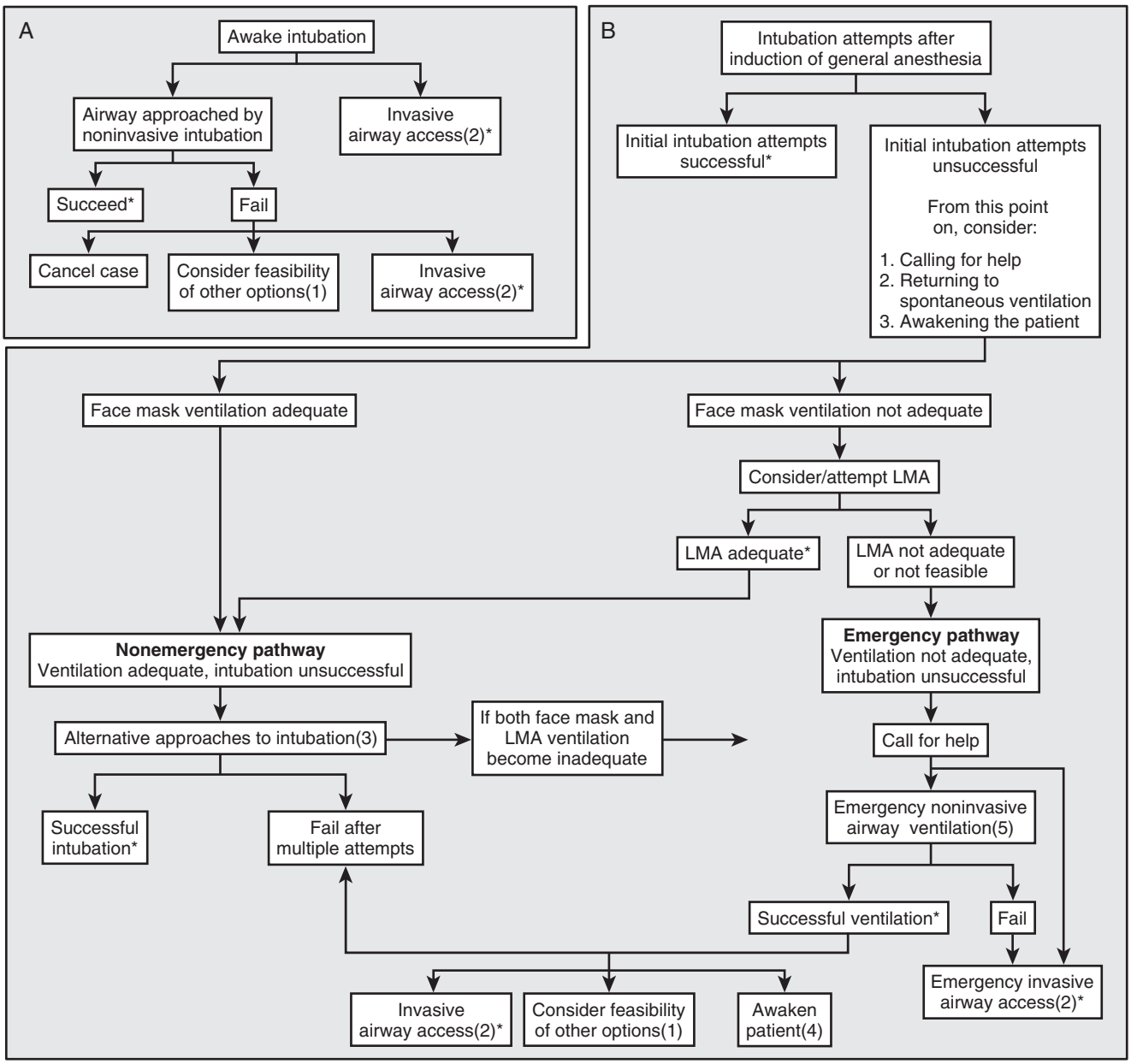
It is tempting to extrapolate some numbers from a striking article written by Hawkins and colleagues[9] that examines the relationship between anesthetic choice and maternal mortality rate for obstetric care. This study calculated the rates of death in obstetric patients receiving anesthesia in two time periods, 1979-1984 and 1985-1990. The authors found that obstetric patients receiving general anesthesia had a mortality rate of 20 per million anesthetics in the earlier period and that

FIGURE 16-1 ■ Difficult Airway Algorithm. *1,* Other options include (but are not limited to) the following: surgery using face mask or laryngeal mask airway *(LMA)* anesthesia, local anesthesia infiltration, or regional nerve blockade. Pursuit of these options usually implies that mask ventilation will not be problematic. Therefore these options may be of limited value if this step in the algorithm has been reached via the Emergency Pathway. *2,* Invasive airway access includes surgical or percutaneous tracheostomy or cricothyrotomy. *3,* Alternative noninvasive approaches to difficult intubation include (but are not limited to) the following: use of different laryngoscope blades, LMA as an intubation conduit (with or without fiberoptic guidance), fiberoptic intubation, intubating stylet or tube changes, light wand, retrograde intubation, and blind oral or nasal intubation. *4,* Consider re-preparation of the patient for awake intubation or canceling surgery. *5,* Options for emergency noninvasive airway ventilation include (but are not limited to) the following: rigid bronchoscope, esophageal–tracheal Combitube ventilation, or transtracheal jet ventilation.

1. Assess the likelihood and clinical impact of basic management problems:
   - A. Difficult ventilation
   - B. Difficult intubation
   - C. Difficulty with patient cooperation or consent
   - D. Difficult tracheostomy
2. Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management
3. Consider the relative merits and feasibility of basic management choices:

A.	Awake intubation	vs.	Intubation attempts after induction of general anesthesia
B.	Noninvasive technique for initial approach to intubation	vs.	Invasive technique for initial approach to intubation
C.	Preservation of spontaneous intubation	vs.	Ablation of spontaneous ventilation

4. Develop primary and alternative strategies:



*Confirm ventilation, tracheal intubation, or LMA placement with exhaled CO_2.

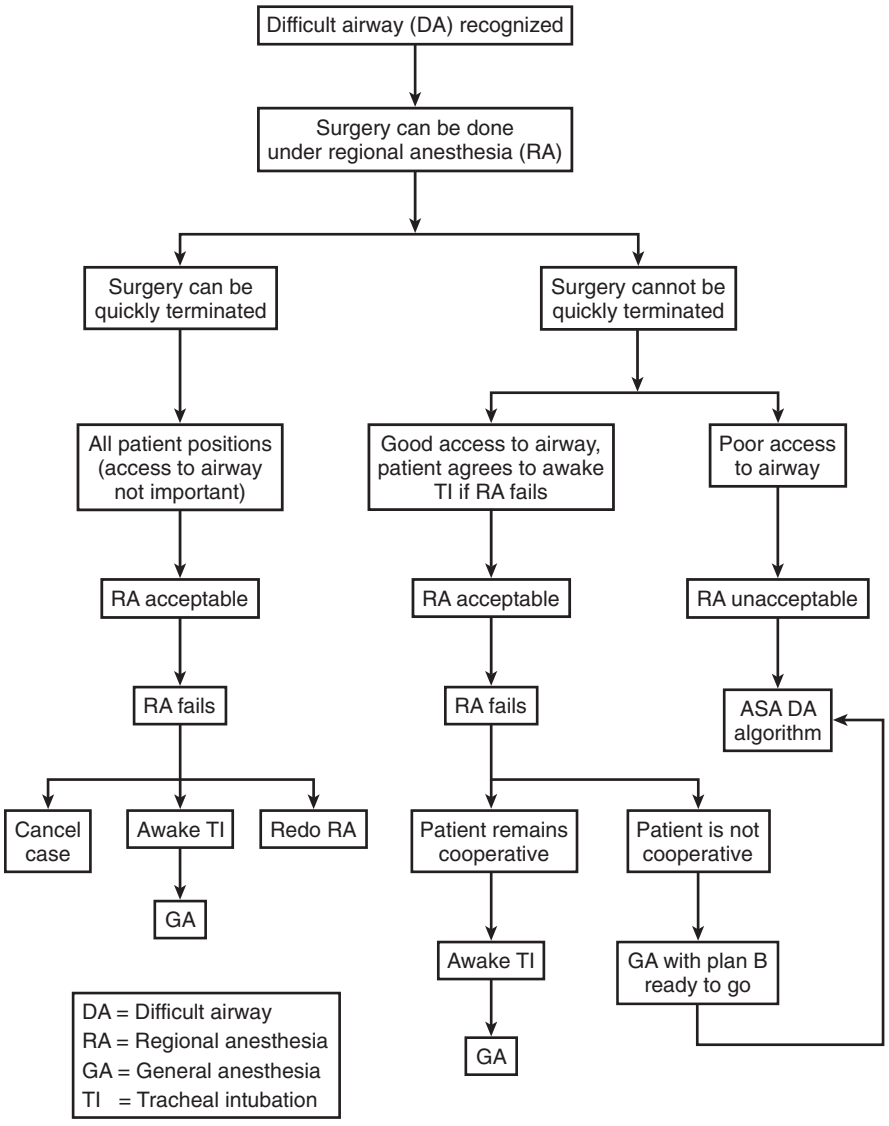


FIGURE 16-2 ■ Regional Anesthesia and the Recognized Difficult Airway Algorithm.

this rate increased to 32.3 deaths per million general anesthetics in the later period. They contrast these data to patients receiving regional obstetric anesthesia, for whom the mortality rate decreased from 8.6 deaths per million to 1.9 deaths per million. Thus both the absolute numbers and the trends seem to favor regional anesthetic techniques as being significantly safer in this population.

However, these data are difficult to interpret. The percentage of regional anesthetics requiring emergent conversion to general anesthetics is not addressed, and, of patients in whom death occurred as a result of failed intubation during an attempted conversion from regional to general anesthesia, it is not clear in which group these patients were. The apparent increased mortality rate associated with general anesthesia could be the result of failed regional blocks requiring conversion to general with uncontrolled conditions. The internal validity of the data is suspect because the accompanying editorial questions the assumptions used in calculating the mortality rates.[10] Furthermore, the external validity of this study is circumspect because the urgency of many obstetric surgical procedures and the different airway challenges that parturient patients represent (e.g., aspiration risk, edematous pharyngeal tissue, decreased functional residual capacity, and increased oxygen consumption) may not be applicable to our group of interest, which is nonpregnant patients with an anticipated difficult airway undergoing elective surgery.

AREAS OF UNCERTAINTY

As discussed earlier, the likelihood of converting from regional to general anesthesia cannot be predicted because of various anesthesiologist-, patient-, and procedure-specific factors. Therefore in the absence of reliable published data, historical institution-specific data may be the most useful for framing the question of regional versus general anesthesia for the patient with an anticipated difficult airway. The Johns Hopkins Hospital Department of Anesthesiology keeps patient data concerning adverse

events as an internal database for morbidity and mortality review. Such databases, although not predictive of each new case, can help provide institutional experience in addition to an anesthesiologist's personal experience when making this choice.

GUIDELINES

The ASA Practice Guidelines for Management of the Difficult Airway[1] should be familiar to every anesthesiologist. Although these guidelines do not specifically address the issue of regional anesthesia as an alternative to general anesthesia with a protected airway, subsequent "New Thoughts and Concepts" published by Benumof in the ASA Refresher Course book specifically address the role of regional anesthesia in patients who are anticipated to have a difficult airway.[11] He states that the use of regional anesthesia in a patient with a known difficult airway requires a high degree of judgment and concludes that it is unacceptable to do regional anesthesia with a known difficult airway when surgery cannot be terminated rapidly and there is poor access to the patient's head. In *Airway Management: Principles and Practice*,[4] Benumof provides clinicians with an algorithm for the use of regional anesthesia in the recognized difficult airway, which complements the ASA difficult airway algorithm.

AUTHORS' RECOMMENDATIONS

- Regional anesthesia may provide a reasonable alternative to general anesthesia for a patient with an anticipated difficult airway in certain circumstances. However, many surgical cases and many patients have contraindications to regional anesthesia.
- If regional anesthesia were to fail for anesthetic-, patient-, or surgical-related issues, intubation might then have to occur under suboptimal conditions. It is reasonable to assume that an airway will be more easily secured with fewer adverse outcomes when approached in a controlled fashion in the beginning of the case than in an urgent manner with possibly compromised access to the patient.[12,13]
- Therefore it is mandatory that every anesthesiologist be familiar with the ASA Practice Guidelines for Management of the Difficult Airway[1] and subsequent updates and recommendations. Review of Benumof's algorithm for the use of regional anesthesia in the patient with an anticipated difficult airway is recommended.
- Anesthesiologists must be comfortable with both the preoperative assessment of patients and appropriate consultations with colleagues who specialize in complex airway management. When appropriate, this multispecialty team must be immediately available to the patient at the time of the surgical procedure.
- Anesthesiologists must be accomplished in the use of multiple approaches and techniques to airway management and understand the limitations of various techniques.
- It is recommended that a plan for general anesthesia be prepared for every patient with an anticipated difficult airway and that appropriate equipment and supporting clinicians/staff are immediately available to the patient, even if regional anesthesia will be the primary and first choice of anesthesia for the patient. Dr. Martin Norton states, "The obligation to guarantee airway control is not obviated by epidural, spinal, or regional techniques."[14]
- Discussion of a primary regional anesthetic plan with the patient and the surgeon must include a realistic approach to the incidence of failed regional techniques or complications of regional anesthesia and a plan for airway management, if required. Regional anesthesia is an acceptable primary anesthetic only if practitioners are comfortable with their ability to secure the airway at any potential time during the surgical case. If there is any doubt about the ability to secure the patient's airway once the surgery is under way, airway management at the beginning of the case is recommended.
- Sedation as a supplement to regional anesthesia must be discussed at the time of evaluation with both the patient and the surgeon. Vigilance about ensuring airway access and state of consciousness is essential.

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CHAPTER 17

What Is the Optimal Airway Management in Patients Undergoing Gastrointestinal Endoscopy?

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INTRODUCTION

A growing number of diagnostic and therapeutic procedures are performed outside the operating room. This increase is especially noticeable in the field of gastroenterology. There is an ever increasing demand for adequate sedation or general anesthesia for successful completion of endoscopic procedures on the gastrointestinal (GI) tract, especially for the more complicated ones. These procedures can cause significant pain or discomfort in addition to preoperative anxiety. Patient comfort and cooperation are critical to the success of both therapeutic and diagnostic procedures. The endoscopy setting is challenging as a result of many factors, including patient comorbidities, type and duration of the procedure, and the need to achieve appropriate depth of sedation/anesthesia at all times, sometimes with the patient in a prone position. However, unlike most anesthesia care practiced outside of operating room settings, sharing the airway and dealing with anesthetic-associated upper airway collapse are unique to GI endoscopy.

Unfortunately, very little evidence exists as to the most appropriate method of managing the airway for these procedures, especially under propofol anesthesia. GI endoscopy anesthesia is an area of work selected by few anesthesiologists; the airway challenges and ever increasing patient comorbidities seem to be the primary reason. Most of the guidelines are based on available evidence and one author's extensive experience with these patients over many years. Particular focus will be on the airway devices and ventilation methods used to overcome respiratory compromise during these procedures.

Four stages of sedation have been described: minimal, moderate, deep, and general anesthesia.[1] At moderate sedation, patients can maintain their cardiopulmonary functions and respond purposefully to verbal or tactile stimulation. At deep sedation, patients cannot be easily aroused and airway support may be required; however, patients may still respond purposefully to repeated or painful stimulation. Finally, during general anesthesia, patients are not aroused by painful stimuli, and cardiopulmonary functions are impaired. Sedative medications commonly used alone or in combination, including midazolam, fentanyl, remifentanil, propofol, ketamine, and dexmedetomidine, have detrimental effects on ventilation.

Minimal to moderate sedation, wherein the patients maintain their airway with little or no help, is sufficient for the majority of endoscopic procedures like diagnostic esophagogastroduodenoscopy (EGD) and screening colonoscopy. However, there are always patients who might be extremely sensitive to the effects of sedative medications, which may lead to obstruction even with small doses. At the other end of the spectrum are patients who have been administered maximal allowable sedative drug doses (based on the nursing and GI departmental protocols) and are still inadequately sedated. Our emphasis will be on managing the airways of patients requiring deep sedation bordering on general anesthesia, with associated loss of consciousness and airway compromise.

EVIDENCE AND OPTIONS

The American Society of Anesthesiologists (ASA) practice guidelines emphasize that patients progress from one level of sedation to the next in a fluid manner. During sedation, respiratory compromise is commonly in the form of airway obstruction rather than apnea. Hillman and coworkers[2] investigated the upper airway during anesthesia. Upper airway obstruction is common during both anesthesia and sleep. Obstruction, either partial or complex, is caused by the loss of pharyngeal muscle tone, which is present in the awake state. The velopharynx, which connects the nasopharynx and trachea and is a particularly narrow and compliant segment, is especially predisposed to obstruction. Magnetic resonance imaging (MRI) and pharyngeal manometry evidence have elegantly demonstrated this aspect of the airway.[3,4] During sedation and anesthesia, in addition to the decrease in muscle tone associated with loss of wakefulness, drug-induced impairment of both the upper airway and neuromechanical behavior and suppression of protective arousal responses occur.

Eastwood and coworkers[5] examined the effect of increasing depth of propofol anesthesia on the upper

airway. The pressure at which the pharynx collapses is called the critical pressure, or P_{crit}. P_{crit} defines the susceptibility of the upper airway to collapse. Sedative and anesthetic medications adversely affect the collapsible pharynx by dynamic effects of negative intraluminal pressures during inspiration, resulting in its occlusion. It is obvious that such an adverse effect is especially pronounced and detrimental in patients with obstructive sleep apnea, obesity, or both.

Having established the mechanisms of airway obstruction, what are the measures available to prevent and treat such an airway collapse? It is important to recognize and treat such drug-induced airway collapse by various maneuvers and devices before they become life-threatening. If the efforts fail, one has to decide on a more definitive mode of airway control (e.g., laryngeal mask airway [LMA] or endotracheal intubation); however, it is critical to make the decision early and request that the endoscopist withdraw the scope to institute appropriate measures. Often bag-mask ventilation might be all that is necessary to tide over the crisis.

Three areas need to be addressed in relation to airway collapse: various mechanical maneuvers, the use of various devices, and newer monitoring techniques to aid early detection of airway collapse.

Optimizing head and neck position is the simplest but often neglected element of airway support. It is based on optimizing the geometry of the airway by improvement of head position. It commonly involves placing the head in the "sniffing-the-morning-breeze" position (i.e., lower cervical flexion, upper cervical extension, and full extension of the neck, when possible, to increase longitudinal tension on the upper airway and decrease its collapsibility). A chin lift with mouth closure increases the pharyngeal dimensions by increasing the anteroposterior distance between the tongue base and the posterior pharyngeal wall. Forward mandibular advancement is shown to increase the pharyngeal airway size and decrease airway collapsibility in sedated and anesthetized patients.[2,6,7] Inazawa et al[8] reported that mandibular advancement stiffens the pharyngeal airway, as indicated by a decrease in P_{crit} in healthy adults during sedation with midazolam.

Mandibular advancement can also be obtained by external jaw thrusting with the use of mechanical devices. Two such devices are the Jaw Elevation Device (JED Hypnoz Therapeutics[9]) shown in Figure 17-1 and the Jaw Support Device[10] shown in Figure 17-2. Both are applied externally and are unsuitable for prolonged use because of the risk of nerve damage.

Increasing intramural pressure is another approach for preventing airway collapse. Hillman and coworkers[2] used continuous positive airway pressure (CPAP) to splint and maintain upper airway patency when investigating upper airway collapsibility during slow induction of anesthesia with propofol. The application of CPAP in sufficient quantities can generally overcome obstruction. Although this can be easily achieved with a tight fitting face mask with or without an airway during colonoscopy, it is difficult to achieve in upper GI endoscopy. An airway adjunct that permits application of CPAP during upper endoscopy is the VBM endoscopy mask (VBM Medical);

FIGURE 17-1 ■ Jaw Elevation Device. (Courtesy of Hypnoz Therapeutic Devices [www.hypnozdevices.com] and LMA North America, Inc.)

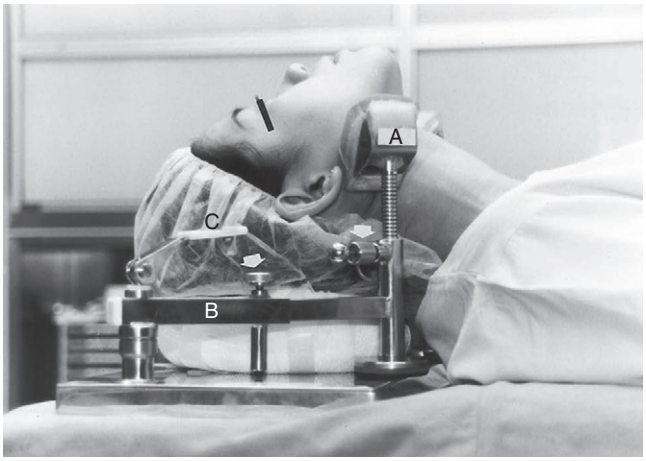

FIGURE 17-2 ■ Jaw Support Device. The device maintains jaw thrust and head extension. Bilateral heads *(A)* attached to the easy-locking poles are adjustable to the desired height and direction by simply pulling up. Bilateral universal arms *(B)* attached to a stainless board can be fixed only by pushing the levers *(C)*. The device may be additionally secured in place by using two screws *(white arrows)* on each side. The head is covered with a soft cushion that can support the angle of the jaw without discomfort, even in a conscious patient.

with sedation it allows a pain free insertion of the endoscope through the hole in the membrane (Figure 17-3).

Additionally, a VBM endoscopy mask permits the use of volatile anesthetic agents in situations in which intravenous access is problematic.[11] The mask is used during upper endoscopy in pediatric patients. CPAP may serve as a stent to keep open the upper airway, maintain alveolar recruitment, and facilitate delivery of manual pressure-support.

The definitive airway device for bypassing the collapsible segment is the endotracheal tube, which requires general anesthesia and possible use of a muscle relaxant during the endoscopic procedure. The indications for general anesthesia and intubation, which protect the

FIGURE 17-3 ■ **VBM Endoscopy Mask.** (Courtesy of VBM Medical Inc. [www.vbm-medical.com].)

patient's airway, include the presence of persistent vomiting or severe gastroesophageal reflux disease. Many other patients, in whom indications for intubation are relative, can be managed with supraglottic airway devices. Both standard LMA and ProSeal LMA are used in upper GI endoscopy procedure, including endoscopic retrograde cholangiopancreatography (ERCP).[12-14]

Providing supplemental oxygenation is universal in GI endoscopy sedation. The nasal cannula remains a popular method. Carbon dioxide monitoring is recommended by the ASA in all cases of GI endoscopy sedation. Although it is shown to be unreliable in upper GI endoscopy,[15] many newer devices that allow both oxygen delivery and capnometry are available (Figures 17-4 and 17-5).

A recently developed novel mouth guard delivers oxygen and samples carbon dioxide simultaneously from the nose and mouth, using two nasal prongs and two oral channels (Figure 17-6). It is fitted with the patient fully conscious in the semiprone position during ERCP and has been used successfully with minimal complications.[16]

The TSE mask is a technically simple and effective face tent that improves a patient's oxygenation, prevents desaturation, decreases the need for assisted ventilation, and reduces interruptions of procedures (Figures 17-7, 17-8, and 17-9).[17,18]

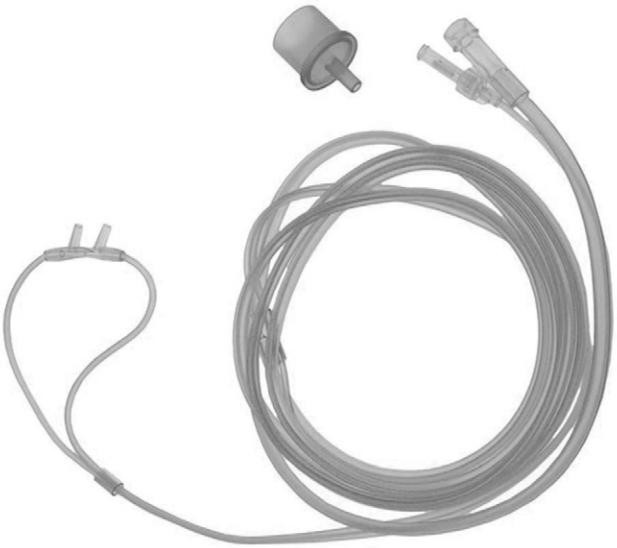

FIGURE 17-4 ■ Gas-Monitoring Nasal Cannula.

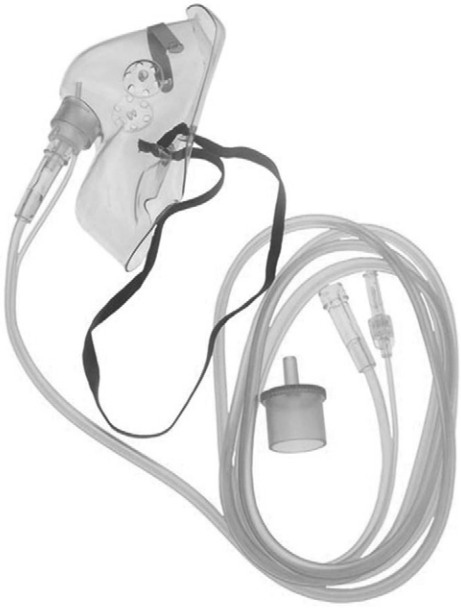

FIGURE 17-5 ■ Gas-Monitoring Face Mask.

The plastic tent acts as an oxygen reservoir, and in conjunction with a nasal cannula, it can deliver 50% to 70% oxygen with a flow rate of 4 to 5 L/min.

Ventilation Strategies

For colonoscopy and sigmoidoscopy, a mask connected to a Mapleson circuit can be strapped to the face and used for pressure support or intermittent positive pressure ventilation, if necessary. However, ERCP and upper endoscopy procedures require oral access by the proceduralist. Supplemental oxygen can be readily delivered by the nasal route. The use of a nasal trumpet attached to a Mapelson breathing system to provide supplemental oxygen and jet ventilation if necessary almost eliminated the incidence of hypoxemic episodes in patients with morbid obesity.[19]

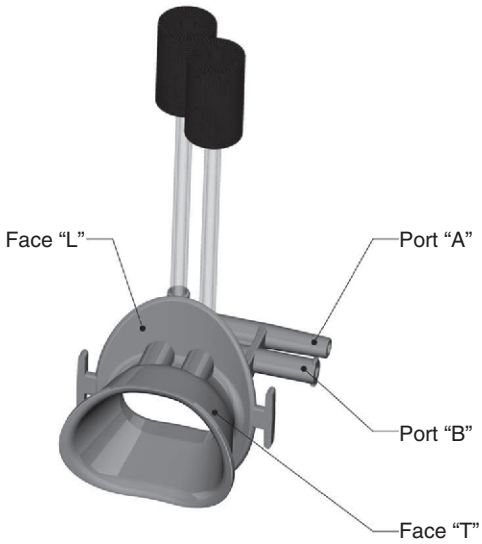

FIGURE 17-6 ■ Pennine Mouthguard. *Port "A,"* oxygen attachment; *Port "B,"* capnography attachment; *Face "L,"* position for lips; *Face "T,"* position for teeth.

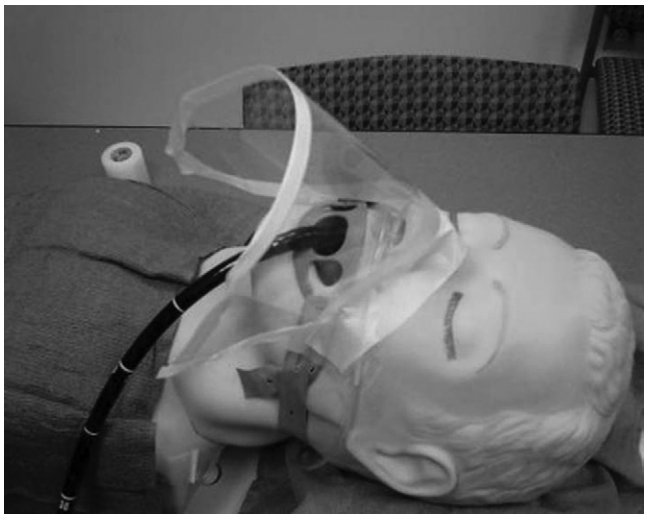

FIGURE 17-7 ■ TSE Mask in Supine Position.

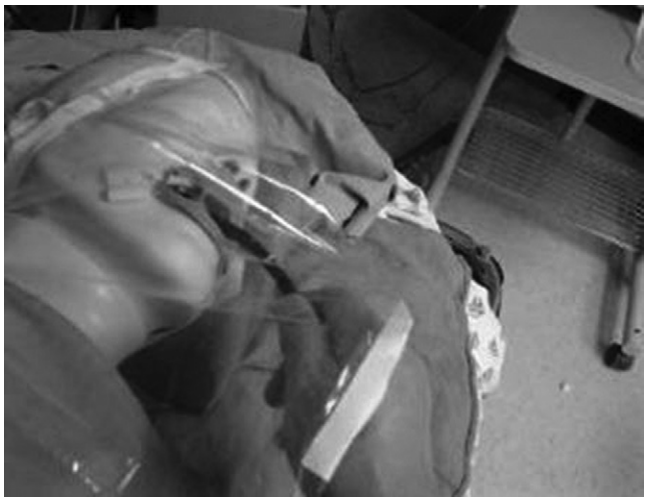

FIGURE 17-8 ■ TSE Mask in Lateral Position.

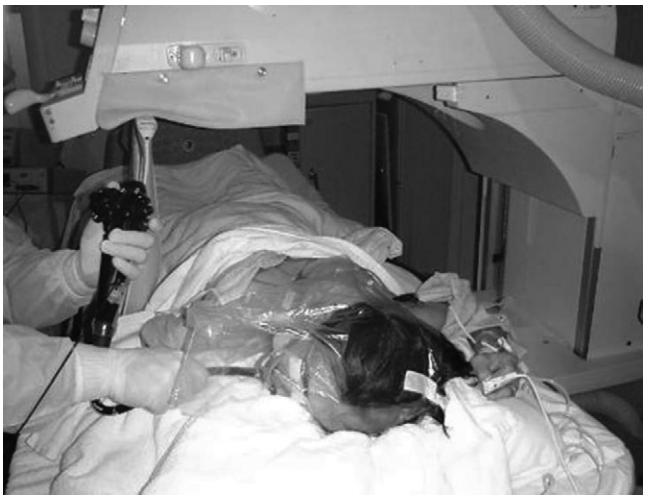

FIGURE 17-9 ■ TSE Mask in Semiprone Endoscopic Retrograde Cholangiopancreatography.

Prone Positioning

Most gastroenterologists prefer prone positioning of the patient for ERCP. Although it can pose significant airway challenges (especially in obese populations, patients with short necks, limited neck extension, or limited mouth opening), it also facilitates drainage of gastric secretions away from the airway. The head and airway are supported on a pillow and rotated toward the endoscopist and anesthesiologist. Spontaneous ventilation is desirable in this setting. In the prone position, respiratory physiology is improved. The effect is likely mediated by a combination of reduced atelectasis and improved $\dot{V}/\dot{Q}$ matching after induction of anesthesia. In a case series of spontaneously breathing patients with hypoxemia, therapeutic prone positioning resulted in significant improvement in oxygenation.[20]

CONTROVERSIES

There is little debate as to the appropriate airway management in healthy patients with normal airway anatomy and no aspiration risk factors. Most of the diagnostic EGDs and colonoscopies fall into this category. The majority of these patients can be managed with conscious sedation with a short-acting benzodiazepine (e.g., midazolam) and a short-acting opioid (e.g., fentanyl or alfentanil). These patients self-ventilate, maintain their airway, and cooperate with the endoscopist (e.g., swallow the scope). They need supplemental oxygen and occasionally a chin lift. The sedation rarely needs to be reversed with appropriate medications.

However, increasingly, endoscopic procedures are prolonged and complicated. Therapeutic interventions involve changing endoscopes during the procedure, and many complications (e.g., coughing, apnea, laryngospasm, bleeding, and perforation) are unpredictable. Decision making often involves choosing the appropriate airway for a particular patient or procedure. Many

patients who would be intubated in an operating room setting do not tend to undergo intubation in an endoscopy setting. Almost all these patients have monitored anesthesia care (MAC) but, in fact, need moderate–deep general anesthetics. Upper airway reflexes are not always protected, and the danger of aspiration is ever present. It is not uncommon to find significant residual contents in an unsuspecting patient.

Should patients with an airway classed as Mallampati IV be routinely intubated? Patients with previous surgery on the esophagus that can potentially compromise sphincter function are in another category that might be considered appropriate for rapid sequence induction–intubation in an operating room setting. Moreover, patients with moderate–severe obstructive sleep apnea pose particular challenges, as they are especially prone to airway collapse. The airway is inherently deemed insecure during anesthesia with prone positioning, yet most anesthesiologists do not intubate any of these patients, including those undergoing prolonged and complicated ERCPs.

Even though the ASA requires $ETCO_2$ monitoring in all cases of GI endoscopy, it is unreliable in upper GI endoscopy.[15] Acoustic respiratory monitoring (Masimo Rad-87 pulse oximeter) is an emerging technique that monitors the sound of transtracheal air movement. A recent modification allows the graphic display of ventilation.

GUIDELINES

There are currently no specific guidelines regarding airway management in endoscopy patients.

AUTHORS' RECOMMENDATIONS

In our practice, endotracheal intubation is used rarely, even for advanced endoscopic procedures including complicated endoscopic retrograde cholangiopancreatography (ERCP). The experience of the anesthesiologist in providing anesthesia for endoscopy procedures seems to play a major part in this decision. Anesthesiologists unfamiliar with this area of practice seem to intubate more frequently. Indeed, it is challenge trying to keep patients unresponsive and comfortable yet spontaneously breathing. It is impossible to address every situation and all patient- and procedure-related factors in guidelines for airway management; however, the following can be used as broad principles.

Anesthetizing in any location needs to be taken as seriously as in the operating room. Preoperative evaluation, especially airway and aspiration risk factors, has to be thorough. A breathing system (e.g., Mapelson C), laryngoscope, face masks, various oral and nasal airways, laryngeal mask airways, endotracheal tubes of varying sizes, and emergency drugs should be readily available. Because of the usually remote location, it is also important to have additional airway adjuncts like bougies, stylets, a video laryngoscope, and a carbon dioxide detector. It is important to check both the availability and functionality of these before the start of the day and at the start of every procedure. Often airway emergencies like laryngospasm and intractable airway obstruction occur with little warning during upper gastrointestinal (GI) endoscopy. Being ready for any airway situation (or not) could be the difference between apnea-related cardiac arrest and death and a safe discharge home.

- Most patients with normal airway anatomy and physiology seen for a short diagnostic upper endoscopy or a screening colonoscopy do not need special airway management, apart from a nasal cannula for supplemental oxygen administration.
- Most ERCPs in our hospital are performed without an endotracheal tube. Anesthesia is induced after prone positioning. A nasal trumpet is normally inserted soon after an induction dose of propofol (preceded by a short-acting opioid like fentanyl) and connected to a breathing system as in Figure 17-10. Apnea lasting 30 to 45 seconds is not uncommon; however, stimulation via gastroscope insertion helps to restart spontaneous ventilation. The nasal trumpet allows some degree of controlled ventilation, if necessary. More importantly, it allows delivery of 100% oxygen at the laryngeal inlet. Occasionally, we have used high-frequency jet ventilation to maintain oxygenation. This allows maintenance of a greater depth of anesthesia without fear of apnea. Endotracheal intubation is the airway of choice for drainage of a pancreatic pesudocyst.
- Most therapeutic upper GI endoscopies such as endoscopic mucosal resection, application of variceal banding, or resection of larger gastroduodenal polyps are performed similar to ERCPs. Because these procedures involve frequent scope changes, it is important to maintain an adequate depth of anesthesia at all times. The depth of anesthesia needs to be increased for every scope withdrawal and reinsertion to prevent coughing (e.g., with additional doses of propofol). Patients undergoing procedures that involve application of clips or glue for treatment of gastroesophageal fistulas, especially patients with a history of aspiration, should be candidates for endotracheal intubation.
- Frequently, morbidly obese patients are seen for upper GI endoscopy before weight reduction surgery. Obstructive sleep apnea is very common in this group. We use a nasal trumpet after induction that is occasionally supplemented with supraglottic jet ventilation. The use of the supraglottic jet provides ventilation and likely keeps the upper airway from collapsing. This is a technique that requires experience and maintenance of an adequate depth of anesthesia at all times. If in doubt, the anesthesiologist should use endotracheal intubation for these patients.
- Patients who have had previous esophagectomy (for cancer or achalasia) frequently are seen for esophageal dilation. In the absence of gastric motility issues, these patients can safely undergo anesthesia with supplemental nasal oxygen or a nasal trumpet connected to a breathing system. Stretching (with a balloon or a bougie) can cause stimulation, thus deepening of anesthesia in anticipation is important.
- Patients with documented pharyngeal pouches are anesthetized after awake endotracheal intubation.

AUTHORS' RECOMMENDATIONS (Continued)

Application of cricoid pressure is not useful in this scenario.

- Frequently, we see patients with limited mouth opening as a result of radiation treatment for oropharyngeal cancer. In the absence of any nasopharyngeal airway obstruction and if ventilation is not expected to be difficult, these patients can be safely managed with a nasal cannula or nasal trumpet.
- Patients who have had prior weight loss surgery are sometimes seen for gastroscopy evaluation. Evidence is insufficient to recommend endotracheal intubation in this subgroup.[21] Patients needs to be evaluated separately with regard to their potential for aspiration and managed accordingly.
- GI bleeding is common in patients with ventricular assist devices. Although it has been recommended[22] that these patients be treated as if they had full stomachs due to the position of the devices, in our practice, oxygen is delivered with a nasal cannula for an upper GI endoscope and a face mask for a colonoscopy. The potential risks of rapid sequence induction and intubation in these very sick patients outweigh any benefits.
- Many patients with possible esophageal sphincter dysfunction (e.g., previous esophagectomy or gastric bypass surgery) can be seen for a colonoscopy alone. Unlike upper endoscopy in which the patient is in a slight head-up position and the contents can be suctioned immediately, the risk of aspiration during colonoscopy is constant. If the patient's swallow study results are normal and gastric stasis is unlikely, the procedure can be performed safely under spontaneous ventilation with an unassisted airway. However, it is important to maintain a depth of anesthesia in which the upper airway protective reflexes are preserved. The use of excessive carbon dioxide to facilitate colonic examination can be uncomfortable; thus a change to a supine position is sometimes required. If any problems are expected during the procedure, intubation should be considered.

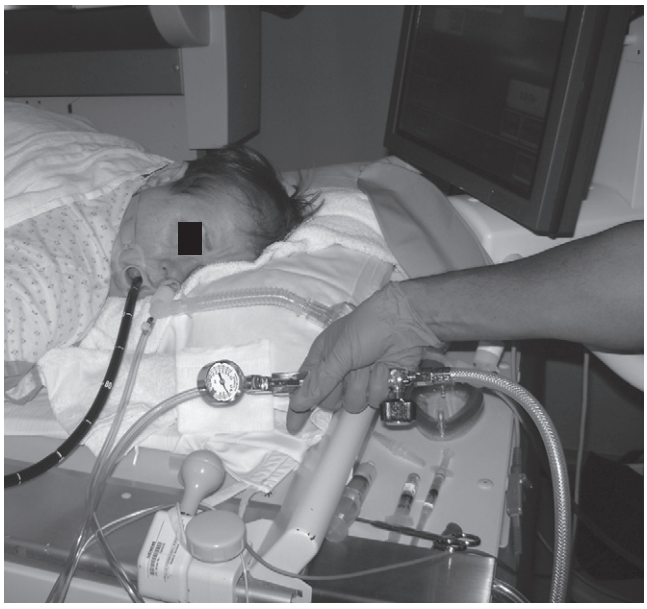

FIGURE 17-10 ■ Nasal Trumpet Attached to Mapelson Breathing System via an Endotracheal Tube Connector. Carbon dioxide sampling port is also shown connected to jet ventilation hose.

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CHAPTER 18

Is There a Best Approach to Induction of Anesthesia in Emergent Situations?

Richard P. Dutton, MD, MBA

INTRODUCTION

Most anesthesiologists take care of emergency patients in the operating room (OR) or as part of a "code team" in their hospital. Whether dealing with a surgical crisis in the OR or a trauma patient in the emergency department (ED), the anesthesiologist must have a plan for rapid and safe induction of general anesthesia. Box 18-1 is a list of potential pitfalls that can be encountered in the emergency situation. Whereas elective patients have a known medical history, optimized medications, hemodynamic stability, and an empty stomach, emergent patients may lack all of these things. Indeed, an older trauma patient brought to the ED with severe injuries might present anatomic challenges to intubation, might be hypovolemic, might have limited cardiac reserve, might be taking unknown long-term medications, have a potentially full stomach, and have a potentially unstable cervical spine. Induction of general anesthesia and successful endotracheal intubation will be critical to the long-term survival of this patient, but how are these best accomplished?

OPTIONS/THERAPIES

By definition, emergency induction is needed when the severity of the patient's presentation does not allow for the normal preoperative anesthetic assessment. Nonetheless, the anesthesiologist must take advantage of every opportunity to learn about the patient's condition while formulating a plan for his or her care. Box 18-2 is a list of suggested questions. At a minimum, the anesthesiologist should determine why the patient requires emergent induction (e.g., urgent surgery for hemorrhaging, airway protection or ventilatory support, or septic shock) and as much about the patient's history as time allows. Usually this information can be gleaned from the physicians or nurses already caring for the patient. If possible, these providers should be asked whether the patient has any allergies and what medications the patient is taking. A quick look at the medical record may be helpful. Any recent anesthetic record is especially useful, as it will provide information about the ease of intubation and the patient's tolerance of medications. A brief survey of relevant laboratory values can also help to avoid pitfalls: hematocrit (hemodynamic stability), creatinine (acute or chronic renal failure), arterial blood gas (ventilatory difficulties, acidosis), serum potassium (potential for hyperkalemia), and coagulation studies (potential for bleeding).

Physical examination of the patient must be abbreviated but is still important. It takes only seconds to assess the patient's level of consciousness by asking the patient to extend his or her neck and open the mouth, which also provides valuable insight into the airway anatomy and potential for a difficult intubation. Vital signs should be noted. New sources of pain, external hemorrhaging, or visible deformity should also be recorded.

Once this brief survey is accomplished, the anesthesiologist is ready to consider various options. Box 18-3 lists important questions that should be addressed. The first has to do with optimizing the emergency induction. If the patient is not in the OR, success can sometimes be improved by moving there, assembling more equipment, or calling for assistance but only if the benefit of doing so will outweigh the risk of delay to the patient. The second consideration is the manner of anesthetic induction and the technique for securing a definitive airway. Although a rapid-sequence approach leading to direct laryngoscopy and endotracheal intubation will most often be correct,[1] there are situations where a more gradual induction or even awake fiberoptic intubation may be more appropriate. Finally, the anesthesiologist must consider the medications to be used, and the dose of each.

EVIDENCE

There is substantial evidence to support the use of rapid-sequence intubation in most cases in which emergency induction is required. Neuromuscular blockade provides the best intubating conditions on the first approach to the airway and leads to the highest "first pass" success rate.[2] A rapid transition from awake to anesthetized reduces the patient's exposure to intermediate stages of anesthesia in which complications such as laryngospasm, pain, hemodynamic lability, combative behavior, and aspiration are most likely to occur. Several large case series have examined the use of neuromuscular blockade to facilitate rapid-sequence intubation outside of the OR, with highly favorable results.[3-5] A recent retrospective study from my institution documented the need for

BOX 18-1 Potential Difficulties during Emergency Induction of General Anesthesia

Unknown medical history
- Limited cardiac reserve
- Pre-existing neurologic conditions
- Chronic diseases with anesthetic implications (e.g., amyotrophic lateral sclerosis)

Untested airway, with limited chance for examination and inability to tolerate awake intubation
Hemodynamic instability
- Hemorrhage (e.g., trauma, gastrointestinal bleeding)
- Cardiac disease (e.g., recent myocardial infarction)
- Dehydration (e.g., small bowel obstruction)
- Uncontrolled hypertension or diabetes

Untested cervical spine stability after trauma
Presumed full stomach
Unfamiliar environment (if out of the operating room)
Inexperienced assistants
Lack of necessary equipment
Insufficient monitoring

BOX 18-2 Suggested Questions, in Approximate Order of Importance, for Assessing the Emergency Patient

Why is this situation an emergency?
Does the patient have any major medical problems?
What medications/intoxicants has the patient taken recently?
Is the patient allergic to any medications?
Has the patient had any history of problems with anesthesia?
Is there a history of neurologic deficit?
When did the patient last eat?
Are there any abnormal laboratory values?
What does the electrocardiogram show?
Are there any other positive diagnostic tests?

Answers should be sought from the most efficient and knowledgeable source among the patient, the patient's caregivers, and the medical record.

BOX 18-3 Questions to Determine the Anesthetic Plan

Is this the right location to induce anesthesia?
Do I have the necessary equipment?
Are the right people here?
Is this patient hemodynamically stable?
Is there likely to be an airway difficulty?
Are there patient factors I should take into account?
Does this patient have a full stomach?
Is the cervical spine stable?
Is the intravenous access adequate?

surgical airway salvage in only 21 of 6088 patients who underwent rapid-sequence induction within 1 hour of hospital arrival, which yielded a rate of 0.3%.[6]

The choice of neuromuscular blocking agent is determined by the clinical situation and the practice environment. Succinylcholine is the most commonly used medication for rapid-sequence intubation because it produces the most rapid onset of paralysis and thus the best intubating conditions in the shortest amount of time. Succinylcholine also has the advantage of being short acting, with return of neuromuscular function in approximately 10 minutes after usual doses. In the elective situation when a difficult airway is unexpectedly encountered, this may be beneficial in allowing the patient to wake up and resume spontaneous ventilation while other plans are considered. This will seldom be an advantage during emergency induction, however, because the conditions creating the emergency will still be present. Rapid resolution of paralysis after succinylcholine administration may enable subsequent neurologic assessment. Succinylcholine is contraindicated in patients with neuromuscular conduction abnormalities of greater than 24 hours' duration (e.g., spinal cord injury, amyotrophic lateral sclerosis, Guillain-Barré syndrome) and in patients with recent severe burns. Excessive numbers of postsynaptic choline receptors can cause a fatal hyperkalemia in these patients.[7] Although at least one article has downplayed the potential for succinylcholine to trigger malignant hyperthermia in susceptible patients,[8] the catastrophic nature of this complication makes it prudent to avoid the use of succinylcholine in patients potentially at risk. Succinylcholine will also produce transient elevation of intracranial and intraocular pressure.[9] This has the theoretic potential to put some patients at risk, although it has never been proved in the scientific literature. In reality, avoidance of succinylcholine may make intubation harder, thus contributing to hypoxia during induction and intubation that is of far more relevance to the patient's outcome.

Rapid-acting nondepolarizing neuromuscular blocking agents can produce intubating conditions almost as good as succinylcholine, almost as quickly.[10,11] The use of high-dose rocuronium or vecuronium is appropriate when contraindications to succinylcholine exist, with the understanding that the patient will remain paralyzed for a longer period of time. In most emergent situations this is not a major concern, and even if a difficult intubation is encountered, it is unlikely that waking the patient up will be a viable option.

Although complete neuromuscular blockade is the key to a rapid transition to mechanical ventilation and should be used in almost all emergency inductions, the use of sedative/hypnotic agents should be approached on a case-specific basis. Amnesia to the events of induction and intubation is desirable, as is prevention of extreme sympathetic stimulation in response to airway manipulation. Some degree of sedation is therefore appropriate in almost all emergency inductions, yet careful titration is required. Patients in shock have increased sensitivity to the central effects of sedative agents: less medication is required to achieve a similar depression in awareness.[12] Hypovolemia in patients is

especially troublesome. Reduction in compensatory sympathetic outflow, reduced cardiac filling in association with positive pressure ventilation, and the direct vasodilatory and negative inotropic effects of sedative agents may all lead to profound hemodynamic instability and cardiac arrest after normal induction doses of thiopentol, propofol, or midazolam.[1]

A number of recent reports have advocated the use of etomidate for induction of anesthesia in emergency situations because it is not a vasodilator or negative inotrope.[13] As with ketamine, however, a normal induction dose of etomidate may still lead to profound hypotension in patients in hypovolemic shock because of interruption of sympathetic outflow. Several recent reports have also described the subsequent development of adrenal insufficiency in patients receiving even single doses of etomidate for emergency induction.[14]

The choice of induction agent is thus less important than the dose selected. In general, the least amount consistent with amnesia is appropriate, unless there is reason to be concerned about a hypertensive response to intubation (e.g., a patient with an isolated traumatic brain injury has the potential for increased intracranial hemorrhage). Additional doses can always be given if the first dose is well tolerated. Familiarity with the medication chosen is also important, enabling greater precision in titration. For example, deaths attributed to the use of sodium thiopental in soldiers injured at Pearl Harbor were the result of unfamiliarity with the drug rather than with its specific function.[15]

CONTROVERSIES

There are a few situations in which securing the airway before induction of anesthesia is appropriate: significant upper airway trauma, known instability of the cervical spine, and a strong suspicion (by history or examination) of a difficult airway. In these situations the use of a fiberoptic bronchoscope, after appropriate topical anesthesia of the upper airway, can provide important diagnostic information and the safest route to a secure airway. This technique requires both time and expertise, however, and is not recommended in uncooperative or hemodynamically unstable patients. Because most trauma patients will be brought to the ED with a cervical collar and backboard in place, the incidence of unstable spinal cord injury is low, and the potential for aggravating an injury during laryngoscopy and intubation is even lower.[16] Several large series have examined the use of manual in-line stabilization of the cervical spine during emergency intubation and have demonstrated the safety of this practice.[17] Rapid-sequence intubation thus remains the preferred approach in trauma patients with "uncleared" cervical spines, unless an injury is known or strongly suspected.

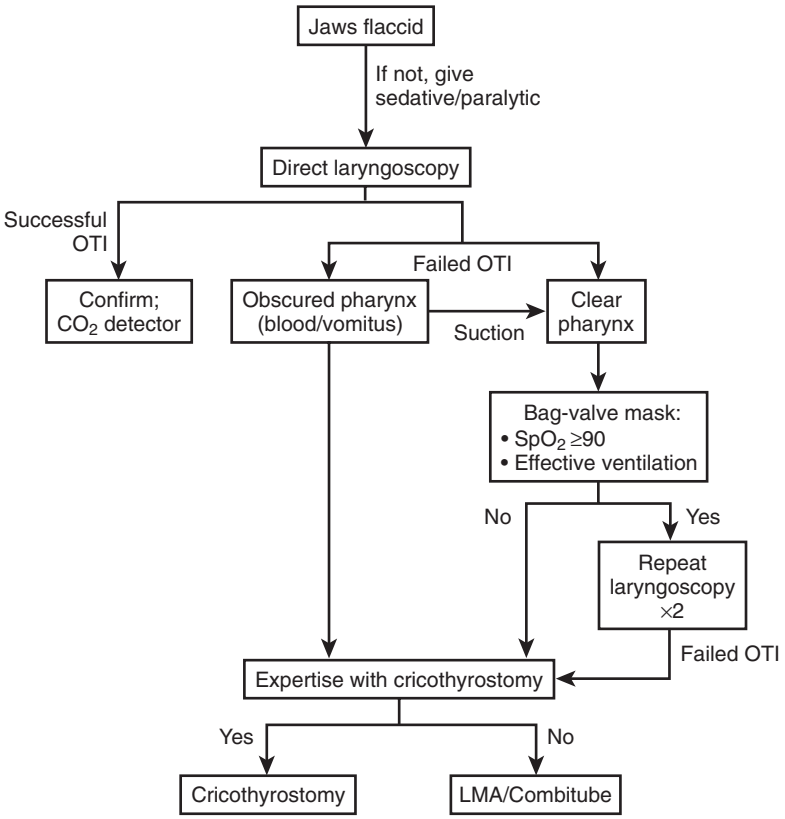
Awake fiberoptic intubation would be a diagnostic luxury in many patients with face or airway trauma, but this approach is seldom feasible. Bleeding or foreign bodies in the airway will usually make the patient agitated and will necessitate a faster and more direct approach. A rapid-sequence intubation attempt is appropriate, with immediate progression to a surgical airway as needed. Surprisingly, patients with massive facial trauma are often easy to intubate immediately after injury because fracture of the facial bones removes a barrier to direct laryngoscopy. Any delay, however, will allow for tissue swelling and distortion that will completely obscure the upper airway.[1]

The use of video laryngoscopy is becoming increasingly popular, especially in the ED. Several recent studies have examined the potential benefits of this approach compared with conventional direct laryngoscopy, but no consensus has emerged.[18,19] Advantages may include a reduced learning curve, greater ability of an expert supervisor to direct a novice intubator, the opportunity to show airway or pharyngeal pathology to other observers, and an improved success rate in certain difficult situations. The video laryngoscope is an important new tool that every anesthesia provider should be comfortable with, but it is not a panacea for all situations.

A final area of controversy surrounds the presence of a full stomach and the risk of passive reflux and aspiration during the induction of anesthesia. Paralytic ileus is common after trauma and in association with major medical diseases; thus delaying anesthesia to allow the stomach to empty is unlikely to work.[20] Instead, measures should be taken to reduce the risk of aspiration while otherwise proceeding with emergent induction. In cooperative patients not otherwise at risk, the use of a nonparticulate antacid such as bicitrate is appropriate before induction.[21] The use of cricoid pressure—the Sellick maneuver—has long been a staple during rapid-sequence induction.[22] The value of this approach in occluding the esophagus and preventing passive regurgitation has been called into question recently,[23] but the maneuver itself is free and easy to perform and the technique may confer other benefits than esophageal occlusion. Posterior displacement of the larynx can improve the view of the vocal cords and facilitate intubation, particularly in trauma patients who are being intubated in the presence of manual in-line cervical stabilization, and palpation of the larynx during intubation can help to confirm successful tube placement. If overzealous application of cricoid pressure is obscuring the laryngeal view, it can always be removed.

AREAS OF UNCERTAINTY

Most likely to change the approach to emergency induction of anesthesia in the near future is increasing experience with a wide range of supraglottic airway devices.[22] Endotracheal intubation is currently the gold standard for emergency induction, but improved laryngeal mask airways (and offshoots) already allow for more rapid opening of the upper airway, with the ability to deliver positive pressure ventilation. As the safety of these devices is established—especially their risk for potentiating aspiration—it is likely that they will assume a more prominent place in emergency airway management algorithms.



Laryngotracheal injury (severe neck injury): partial airway obstruction → OTI; severe airway obstruction → surgical airway (cricothyrostomy/tracheostomy)

FIGURE 18-1 ■ Procedural Options for Trauma Patients Needing Emergency Tracheal Intubation. *LMA,* laryngeal mask airway; *OTI,* oral tracheal intubation.

Improved markers and monitors of the patient's hemodynamic condition will allow for greater precision in dosing induction drugs in the future. Further development of neuromuscular blocking agents may eventually lead to a better replacement for succinylcholine than the agents now available, while the development of sugammadex as an instantaneous reversal agent may allow more widespread use of rocuronium and vecuronium.[23] It is unlikely, however, that the basic concept of rapid-sequence induction will change.

GUIDELINES

The most comprehensive review and guidelines for emergency airway management were published in 2003 by the Eastern Association for the Surgery of Trauma (EAST), as the result of a guidelines working group.[24] This document includes a discussion of all aspects of emergency airway management and concludes with the recommended approach seen in Figure 18-1.

AUTHOR'S RECOMMENDATIONS

A recommended "best practice" for induction of anesthesia in emergency situations consists of the following key steps:

1. Precrisis preparation, including training of personnel and availability of equipment
2. Rapid assessment and optimization of the environment, consistent with the time available
3. Preoxygenation, cricoid pressure, and manual in-line cervical stabilization, if indicated
4. Induction of anesthesia (carefully titrated dosing) and rapid deep paralysis (succinylcholine)
5. Direct laryngoscopy and intubation, facilitated by an intubating stylet, if needed
6. Confirmation of successful intubation with capnometry
7. If intubation cannot be accomplished, rescue with a laryngeal mask airway
8. Rapid progression to a surgical airway, as needed
9. Circulatory support after intubation. Gentle application of positive pressure ventilation and upward titration of sedative medications as tolerated by the patient

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CHAPTER 19

Do Inhalational Agents Have Beneficial or Harmful Effects on Ischemia–Reperfusion Injury?

Stefan G. De Hert, MD, PhD

INTRODUCTION

Experimental evidence has indicated that inhalational anesthetics have organ-protective effects against the consequences of ischemia–reperfusion injury.[1-5] Although these protective effects have been most extensively characterized in myocardial tissue, it becomes increasingly obvious that these effects are also present in other tissues.

The organ-protective effects of inhalational anesthetics have been related to not only pharmacologic preconditioning and postconditioning effects but also a protective effect during ischemia by modulation of the inflammatory response. Although a number of underlying pathways have been identified, the exact mechanisms involved in organ protection after ischemia–reperfusion injury are still under investigation. It is beyond the scope of this chapter to discuss this point, and the interested reader is referred to a number of recent review articles on the topic.[6-15]

Because cardiovascular complications still represent a significant health risk to both the cardiac and the noncardiac surgical populations, any measure that may help reduce these adverse events should be part of the perioperative treatment of patients, especially those patients that are at increased risk of perioperative myocardial ischemia.

Prevention of ischemia is traditionally focused on maintaining the balance between myocardial oxygen supply and demand.[16] It is well-known that all inhalational anesthetics decrease myocardial loading conditions and contractility. Even the newer compounds such as desflurane and sevoflurane demonstrate a similar dose-dependent depression of myocardial function.[17] These depressant effects decrease myocardial oxygen demand and may therefore have a beneficial role on the myocardial oxygen balance during myocardial ischemia. In addition to these indirect protective effects, the direct protective properties of inhalational anesthetics against ischemia–reperfusion injury, already discussed, might represent an additional tool in the treatment and the prevention of ischemic cardiac dysfunction in the perioperative period.

OPTIONS/THERAPIES

On the basis of these theoretical considerations and the experimental evidence, several study groups have hypothesized that the implementation of organ-protective properties of inhalational anesthetics in clinical practice might be associated with less organ damage and dysfunction after ischemia–reperfusion injury, ultimately resulting in a better postoperative outcome with less morbidity and mortality.

The organ that has been best explored with regard to anesthetic protection against ischemia–reperfusion injury is the heart. This is, in part, related to the fact that hemodynamic monitoring is easily accessible and that troponin assays allow for a reliable quantification of myocardial damage. Such straightforward measurements of organ function and organ damage are less available for other organ systems. The majority of clinical studies have been performed in the cardiac surgical setting. This is because cardiac surgery, unlike noncardiac surgery, is associated with a predictable and somewhat standardized period of myocardial ischemia, allowing for comparable experimental conditions.

The first clinical studies mainly focused on protective effects of an anesthetic preconditioning protocol (i.e., the protective anesthetic trigger is applied before myocardial ischemia occurs). Later on, applications during myocardial ischemia and postconditioning protocols (i.e., the protective anesthetic trigger is applied after myocardial ischemia has occurred [during early reperfusion]) were explored.

EVIDENCE

Coronary Surgery

In contrast with the large amount of data obtained in the experimental setting, only a limited number of studies have addressed the potential cardioprotective properties of volatile anesthetics in the clinical practice. This is mainly because the experimental protocol necessitates myocardial ischemia to be instituted in a standardized

and reproducible way. This situation is normally not present in clinical practice, where all efforts are directed toward the prevention of myocardial ischemia. The clinical situation that most closely resembles the sequence of standardized myocardial ischemia and reperfusion is the setting of coronary artery surgery. This type of surgery therefore allows us to transpose the experimental setting of preconditioning and postconditioning protocols into a clinical protocol sequence.

Clinical studies mainly involved either preconditioning protocols (i.e., administration of the inhalational agent before the institution of myocardial ischemia [aortic cross-clamping]) or a protocol in which the inhalational agent was administered throughout the entire operative period. It is of interest to note that the experimental anesthetic preconditioning protocols consistently showed a beneficial effect on the extent of myocardial damage and dysfunction after ischemia but that this cardioprotective effect was not as obvious in the clinical situation. A number of studies did indeed report a beneficial effect on markers of myocardial damage or hemodynamic function,[18-25] but this was not confirmed in other studies.[26-28]

Only recently, it was observed that the preconditioning protocol used might be crucial in generating an anesthetic protective effect. Both Bein et al[29] and Frässdorf et al[30] observed a cardioprotective effect only with an intermittent administration of sevoflurane and not with a continuous administration.

In the meantime, a number of research groups have evaluated the cardioprotective effects of an inhalational anesthetic regimen when administered throughout the entire surgical procedure. In contrast to the clinical preconditioning protocols, these studies observed a consistent cardioprotective effect with less evidence of myocardial damage and better preservation of myocardial function after ischemia.[31-38] Only one study failed to observe such protective effects; however, in this particular study, depth of anesthesia was deeper and concomitant opioid concentrations were higher in the control group compared with the sevoflurane group, which obscures potential different effects.[39] In addition, inhalational anesthetic agents were also shown to be cardioprotective when administered during the period of myocardial ischemia[40,41] and during the reperfusion period.[42] Taken together, it seems that a clinically significant cardioprotective effect of inhalational agents is most obvious in protocols in which the agent is given throughout the entire procedure: before (preconditioning), during, and after myocardial ischemia (postconditioning).[42]

In all these studies, cardioprotective effects of inhalational anesthetic agents were apparent from the preservation of variables of myocardial function and the decreased release of markers of myocardial damage or dysfunction. However, at this moment it is unclear whether these effects also result in a decreased incidence of outcome variables such as perioperative morbidity and mortality rates. Although some studies have observed trends such as a shorter intensive care unit and hospital length of stay,[43] a lower incidence of postoperative atrial fibrillation,[44] an improved 1-year cardiovascular outcome after coronary surgery,[45] and a decreased 1-year mortality[46] with a volatile anesthetic regimen, all these studies were severely underpowered to address any outcome issue. A Danish retrospective study on data from 10,535 cardiac surgical procedures retrieved from a national Danish registry from 1999 to 2005 compared cardiac outcome between patients anesthetized with propofol and with sevoflurane. No difference in postoperative 30-day mortality rate was observed in patients with preoperative unstable angina and/or a recent myocardial infarction. However, in the group of patients without these characteristics, the mortality rate was lower in the group anesthetized with the inhalational agent (2.28 versus 3.14; $p = 0.015$).[47] However, a number of confounding factors such as the retrospective design, the lack of randomization, the different use of anesthetic agents, and cardioplegic protection make interpretation of these results hazardous.

A few meta-analyses have also been performed on this subject (Table 19-1).[48-50] The meta-analysis by Yu and Beattie[48] included 32 trials on the subject with a total of 2841 patients. The meta-analysis by Symons and Myles[49] included 27 trials with a total of 2979 patients. In both

TABLE 19-1 **Summary of Meta-Analyses on the Effects of Inhalational Anesthetic Agents on Perioperative Mortality and Perioperative Myocardial Infarction (PMI) Rates**

Study (Year)	No. of Trials	No. of Patients	Inhalational Agents Included	Incidence of Outcome	
				INHALATIONAL MORTALITY PMI	INTRAVENOUS MORTALITY PMI
Yu and Beattie (2006)[48]	32 trials	2841 patients	Halothane Enflurane Isoflurane/sevoflurane Esflurane	18/1156 54/1402	30/1222 62/1459
Symons and Myles (2006)[49]	27 trials	2979 patients	Halothane Enflurane Isoflurane Sevoflurane Desflurane	No difference (data not reported) 51/1569	No difference (data not reported) 28/840
Landoni et al (2007)[50]	22 trials	1922 patients	Sevoflurane Desflurane	4/977 24/979	14/872 45/874

these meta-analyses, no differences were observed in perioperative mortality and myocardial infarction rates between patients anesthetized with a volatile or an intravenous anesthetic regimen. However, it should be noted that these two reports also included studies in which halothane, enflurane, and isoflurane were used as inhalational anesthetics. On the contrary, the most recent meta-analysis including only studies with the newer inhalational anesthetics desflurane and sevoflurane (22 trials with a total of 1922 patients) observed a lower incidence of postoperative mortality (odds ratio, 0.35; 95% confidence interval, 0.14 to 0.90) and postoperative myocardial infarction (odds ratio, 0.53; 95% confidence interval, 0.32 to 0.86) with the use of an inhalational anesthetic regimen.[50]

Noncoronary Cardiac Surgery

The majority of data on the perioperative cardioprotective properties of inhalational anesthetic agents has been obtained in the setting of coronary artery surgery. It is unclear whether such an effect is also present in other types of surgery. One study reported similar cardioprotective effects of an inhalational anesthetic regimen in patients undergoing aortic valve surgery.[51] In patients undergoing mitral valve surgery, the situation seems to be more complex. Data from a recent study indicated that application of a desflurane preconditioning protocol in patients undergoing isolated mitral valve surgery did not decrease postoperative troponin release. However, in patients undergoing a combined mitral valve and coronary artery surgery procedure, the application of desflurane preconditioning was associated with less myocardial damage.[52] A more recent study from the same group, however, found no difference in postoperative troponin release in patients with coronary disease undergoing mitral surgery with either a sevoflurane or a propofol-based anesthesia.[53] These observations seem to indicate that the occurrence and the extent of inhalational-induced cardioprotection may depend on specific clinical conditions.

Noncardiac Surgery

Cardioprotection

Although it can be expected from a pathophysiologic point of view that the cardioprotective properties of inhalational anesthetic agents will also have beneficial effects in patients at risk of perioperative myocardial ischemia undergoing noncardiac surgery, the unequivocal evidence for such a clinical effect may be difficult to obtain. Indeed, it seems that the extent of cardioprotection depends on specific clinical variables such as the occurrence of perioperative myocardial ischemia. Because both the occurrence of perioperative myocardial ischemia and its extent and duration may vary greatly in patients undergoing noncardiac surgery, the potential beneficial effects of an inhalational anesthetic regimen may be blunted.[54] Consequently, the available data on potential cardioprotective effects in noncardiac surgery are limited and mainly negative.[55,56] One study in 60 high-risk vascular surgery patients examining the effects of a goal-directed fluid therapy observed a lower incidence of postoperative cardiac complications in patients anesthetized with sevoflurane than in those anesthetized with propofol (0 versus 4; $p = 0.005$).[57]

Of note, although coronary angioplasty is associated with a more predictable and reproducible cardiac ischemic event, application of a sevoflurane preconditioning protocol seemed not to be associated with a measurable cardioprotective effect.[58]

Organ Protection

Another question is whether the protective effects against the consequences of ischemia observed at the level of the myocardium also extend to other organ systems. Data from a recent study in healthy volunteers indicated that the peri-ischemic administration of sevoflurane improved the postocclusive hyperemic reaction, suggesting a protective effect against the consequences of ischemia at the level of the endothelium.[59] Another study in coronary artery surgery patients observed lower postoperative levels of serum glutamic oxaloacetic transaminase, glutamate pyruvate transaminase, and lactate dehydrogenase in patients anesthetized with an inhalational anesthetic regimen.[60] However, it could not be concluded from this study whether the beneficial effect on biochemical markers of hepatic dysfunction was related to a direct protective effect on hepatic function or whether this effect was merely the consequence of better perioperative organ perfusion due to the preservation of cardiac function. However, more direct evidence has suggested that inhalational agents appear to be protective against consequences of ischemia–reperfusion injury during liver surgery[61] and one-lung ventilation.[62]

AREAS OF UNCERTAINTY

Although several studies have indicated that inhalational anesthetic agents may have a beneficial action in decreasing the harmful effects of myocardial ischemia, controversies remain with regard to these reported properties. These controversies mainly focus on two topics: (1) the reliability of the phenomenon of anesthetic preconditioning in the clinical setting and (2) the concern about the clinical relevance of the reported organ-protective properties, certainly with respect to outcome issues. For instance, although some studies suggest lower mortality rates in coronary surgery patients treated with a volatile anesthetic regimen compared with those treated with an intravenous anesthetic regimen,[46,50,63] others fail to find such relationships.[47,64] It is to be expected that any potential effect on short- and long-term outcomes is probably related to perioperative organ protection. If, for any reason, such protection is not observed, no effects on outcome are to be expected. The result is that, although sufficient clinical evidence points toward an organ-protective effect of inhalational agents, a number of clinicians still doubt the clinical relevance of the phenomenon.[65-67]

GUIDELINES

Current strategies for the prevention of adverse perioperative cardiovascular events mainly focus on the preservation of a beneficial myocardial oxygen balance and the application of therapies assumed to modulate plaque stabilization and the inflammatory response. Although these issues have been largely explored, no definitive conclusions with regard to their effectiveness in preventing perioperative morbidity have yet unequivocally been established.[65-67] Currently, the American Heart Association (American College of Cardiology/American Heart Association 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery) advocates the use of volatile anesthetic agents during noncardiac surgery for the maintenance of general anesthesia in hemodynamically stable patients at risk of myocardial ischemia.[68] Of note, the 2009 Guidelines for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology[69] did not include such a recommendation because of the lack of sufficiently powered randomized controlled trials on the topic.

AUTHOR'S RECOMMENDATIONS

Based on the available data and keeping in mind that the suggestions derived from these data do not represent clinical guidelines or a consensus statement and should not replace individual clinical judgment, a number of recommendations may serve as a guide to help anesthesiologists make a rational decision about the care of patients at risk of perioperative myocardial ischemia.

- Experimental data have clearly indicated that the use of an inhalational anesthetic regimen protects against the functional and morphologic consequences of myocardial ischemia.
- This protective effect has also been demonstrated in clinical studies in patients undergoing cardiac surgery, in that better preservation of myocardial function and less myocardial damage have been observed with the use of an inhalational anesthetic regimen.
- In the clinical setting, the cardioprotective effect of an inhalational anesthetic regimen is most consistently present when the agent is given throughout the entire operative period: before ischemia, during ischemia, and during reperfusion.
- Although no dose–response data are available, the different clinical protocols used suggest that the protective effects are already present at doses of 0.5 MAC (minimum alveolar concentration) sevoflurane or desflurane.
- Although none of the studies performed so far was sufficiently powered to address outcome issues, the majority of the available data indicate that the use of a volatile anesthetic regimen with the newer agents sevoflurane and desflurane is associated with a lower perioperative mortality rate and a lower incidence of perioperative myocardial infarction.
- Data on the potential cardioprotective properties of inhalational agents in noncardiac surgery are limited. However, the putative underlying pathophysiologic mechanisms involved in their cardioprotective action in the presence of myocardial ischemia and the clinical evidence from the cardiac surgical setting circumstantially show that these agents may provide an additional way to protect the myocardium in any patients at risk of perioperative myocardial ischemia.
- Initial data in noncardiac surgery seem to indicate that the protective actions of inhalational anesthetics may also extend to other organ systems than the heart.

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CHAPTER 20

Does Anesthetic Choice Affect Surgical and Recovery Times?

John Keogh, MD

INTRODUCTION

Many surgical procedures in the ambulatory setting are performed using general anesthesia. Recovery time after surgery and anesthesia is an important aspect that should be considered when a general anesthetic is chosen for ambulatory surgical procedures. Although mortality rates are extremely low after general anesthesia in the ambulatory setting,[1] minor morbidity in the form of postoperative pain, nausea and vomiting, fatigue, shivering, headache, and drowsiness continues to affect a large number of patients.[2] With the continuing emphasis on expansion of ambulatory surgery and the inclusion of elderly and stable American Society of Anesthesiologists (ASA) 3 and 4 patients onto operating lists, it is likely that both mortality and morbidity rates will increase in the future. Although some systematic reviews have been published in the literature comparing general with regional anesthesia for major surgery with a focus on outcome, the choice of anesthetic agents for general anesthesia in the ambulatory setting remains controversial. Specifically, the choice of anesthetic in terms of outcome after ambulatory surgery remains poorly explored.

OPTIONS

The two commonly used methods for general anesthesia for ambulatory surgery are total intravenous anesthesia (TIVA) and inhalational anesthesia. Although propofol used in conjunction with an opiate is practically the only anesthetic used for TIVA, many inhalational anesthetics are available today, and the choice of these agents has been the subject of many published studies and a great deal of controversy. Surprisingly, only two systematic reviews have been published on this interesting subject,[3,4] and the studies included both inpatients and outpatients. In this chapter, the evidence is derived from well-performed prospective studies combined with the author's experience.

ENDPOINTS OF INTEREST IN AMBULATORY SURGERY

To analyze the benefits of one type of general anesthetic over another, it is important to define the endpoints that are of interest to the patient and the hospital. One easily defined endpoint that is of great interest to both the patient and hospital is mortality risk after ambulatory surgery. However, the mortality rate is extremely low in this group of patients[1]; therefore it would be difficult to confirm that the choice of anesthetic has any significant effect on perioperative mortality risk during ambulatory surgery. Another endpoint of importance, which is less well-defined, is major morbidity. The effect of the choice of anesthetic agent on this important outcome also remains unclear.

A differentiation must be made between measuring "true outcomes" and "surrogate outcomes."[5] Examples of true outcomes include discharge times, return to work, admission, readmission, and patient satisfaction. Examples of surrogate outcomes include incidence of pain, time to first analgesic consumption, early recovery (response to commands) after anesthesia, and nausea and vomiting. Surrogate measures should be accepted only if they yield the same conclusions as their nonsurrogate endpoints.[5] Patient satisfaction is one of the outcomes that is probably one of the most important factors from the patient's perspective. Because most patients have not undergone the same operation twice with the use of different anesthetics, gathering of evidence is restricted to asking patients whether they were satisfied with the anesthetic. When patient satisfaction with anesthesia has been studied, the level of satisfaction was very high, around 97% in two different studies.[6,7] Studies in which the authors have interviewed patients about the preference of inhalational induction compared with intravenous induction (sevoflurane or desflurane versus propofol) have usually shown a preference for propofol over sevoflurane.[8] This could be because of the mood elevation after propofol anesthesia that has been suggested by many authors; however, the mood elevation effect has never been conclusively proved. The following endpoints of quality have been evaluated in this chapter to provide the evidence for the selection of the best maintenance agent during ambulatory surgery: "early" recovery ("time to open eyes" and "time to obey commands"); "intermediate" recovery ("time to transfer from phase I to phase II," "home-readiness," and "home discharge"); and minor in-hospital complications ("pain," "nausea or vomiting," "antiemetics used," "dizziness/giddiness," "drowsiness/somnolence," "headache," "shivering," and "coughing"). Patient satisfaction has been excluded because it has not been studied in relation to the choice of anesthetic for ambulatory

surgery, as discussed earlier. Pain as a postoperative complication has not been addressed because of the different ways in which it has been measured and the complexity of its interpretation. Not only do the visual analog scales (VAS) for pain vary among authors but the time to pain assessment differs, the analgesics used vary considerably between studies, and not all authors present data as VAS, preferring to present data as "time to first analgesic requirement" or "the number of patients requesting analgesics." In addition, because of the variable nature of surgery and, consequently, postoperative pain, data can be very difficult to interpret. Therefore data have not been extracted on pain intensity or analgesic requirements in this review.

EVIDENCE

Total Intravenous versus Inhalational Anesthesia

Two systematic reviews published in the literature comparing inhalational versus intravenous anesthesia have included both inpatients and outpatients,[3,4] which somewhat limits the scope of the findings. Halothane and enflurane were not taken into consideration in this review because these agents are rarely used during ambulatory surgery today.

Propofol versus Isoflurane

When a comprehensive review was performed,[9] a total of 18 studies were found that had data that could be extracted in the postoperative period. No differences were found between propofol and isoflurane in early recovery or transfer from phase I to phase II, but there was significant heterogeneity between groups in all these parameters (Table 20-1). However, home discharge was significantly earlier in the propofol group (15 minutes; confidence interval [CI], 8 to 23 minutes). There was a greater relative risk of postoperative complications, including nausea (number needed to treat [NNT], 8), vomiting (NNT, 10), and headache (NNT, 22) in the isoflurane group (see Table 20-1). The use of antiemetics (relative risk [RR], 2.7; CI, 1.7 to 4.2) was also more common in the isoflurane group. The relative risk for postoperative nausea and vomiting after 24 hours was also significantly higher in the isoflurane group versus the propofol group (see Table 20-1).

Propofol versus Sevoflurane

That same review[9] found a total of 11 studies with extractable data that compared sevoflurane with propofol in an ambulatory surgical setting. No difference was found in the time to open eyes between the sevoflurane and propofol groups, but time to obey commands was faster in

TABLE 20-1 **Postoperative Recovery Profiles and Minor Complications Associated with Propofol Compared with the Inhaled Anesthetics**

Endpoint	Propofol vs. Isoflurane	Propofol vs. Desflurane	Propofol vs. Sevoflurane
Time to open eyes (min)	0.2 (–1.6 to 1.3)*	1.3 (0.4 to 2.2)*† (D)	0.9 (–2.2 to 0.5)*
Time to obey commands (min)	0.5 (–1.0 to 1.9)*	1.3 (0.4 to 2.3)*† (D)	1.6 (0.3 to 3.0)*‡ (S)
Time to transfer from phase 1 to phase 2 (min)	4.3 (–5.4 to 14.1)*	NR	3.6 (–13.5 to 6.4)*
Time to home-readiness (min)	9.3 (–17 to 36)*	3.1 (–7.7 to 1.5)	5.6 (–3.4 to 14.5)*
Time to home discharge (min)	15 (8 to 23)† (P)	3.9 (–9.3 to 1.5)	10.3 (3.9 to 16.6)† (P)
Postoperative nausea (PON)	2.0 (1.6 to 2.5)† (P), NNH = 8	2.0 (1.4 to 2.8)† (P), NNH = 71.6	1.6 (1.2 to 2.0)† (P), NNH = 11
Postoperative vomiting (POV)	3.2 (1.3 to 7.5)† (P), NNH = 10	2.6 (1.4 to 4.8)† (P), NNH = 10	2.0 (1.3 to 3.0)† (P), NNH = 15
Postoperative drowsiness	NR	NR	0.9 (0.1 to 5.9)*
Postoperative dizziness	NR	NR	1.4 (0.8 to 2.3)
Postoperative shivering	0.8 (0.6 to 1.3)	1.5 (0.4 to 5.4)*	0.8 (0.5 to 1.3)
Postoperative headache	3.3 (1.1 to 9.6)‡ (P), NNH = 22	3.5 (0.6 to 19.8)	1.0 (0.2 to 7.1)
Antiemetics given	2.7 (1.7 to 4.2)† (P), NNH = 8.5	3.3 (1.8 to 6.0)† (P), NNH = 8	4.5 (1.5 to 14.0)† (P), NNH = 11
Postdischarge nausea (PDN)	1.8 (1.3 to 2.5)† (P), NNH = 8	1.2 (0.7 to 2.1)	1.3 (0.7 to 2.3)
Postdischarge vomiting (PDV)	2.5§(1.6 to 4.1) (P), NNH = 9	2.6 (0.1 to 62.7)	NR

All results are shown as weighted mean difference or relative risk (mean and 95% confidence intervals). Significant results are shown in favor of the following: *S,* sevoflurane; *I,* isoflurane; *D,* desflurane; *P,* propofol, when significant. *NR,* not reported (or reported in only one study); *NNH,* numbers needed to harm for significant differences.

*Significant heterogeneity.

†$p < 0.01$.

‡$p < 0.05$.

§$p < 0.001$.

From Gupta A, Zuckerman R, Stierer T, Sakima N, Parker S, Fleisher LA. Comparison of recovery profile after ambulatory anesthesia with propofol, isoflurane, sevoflurane and desflurane: a systematic review. Anesth Analg 2004;98:632–41.

the sevoflurane group (1.6 minutes; CI, 0.3 to 3.0), with significant heterogeneity between groups (see Table 20-1). No significant difference was found in the time to home-readiness between the groups, but significant heterogeneity was found between the groups. The time to home discharge was earlier in the propofol group than in the sevoflurane group (10.3 minutes; CI, 3.9 to 16.6). The relative risk for postoperative complications, including postoperative nausea (NNT, 11) and vomiting (NNT, 15), was significantly greater in the sevoflurane group than in the propofol group but with significant heterogeneity between the groups (see Table 20-1). The need for antiemetics in the postoperative period was significantly greater in the sevoflurane group (RR, 4.5; CI, 1.5 to 14.0). No other significant differences were seen between the groups.

Propofol versus Desflurane

Thirteen studies had extractable data that were included in the meta-analysis.[9] Time to open eyes was significantly faster in the desflurane group versus propofol (1.3 minutes, CI 0.4 to 2.2) ($p = 0.004$), as was the time to obey commands (1.3 minutes; CI, 0.4 to 2.3) ($p = 0.007$), with significant heterogeneity between the groups (see Table 20-1). No differences were found in home-readiness or home discharge between the groups. The relative risk for postoperative complications, including postoperative nausea (NNT, 7) and vomiting (NNT, 10), was significantly greater in the desflurane group versus the propofol group (see Table 20-1), and the need for antiemetics was also higher in the desflurane group (RR, 3.3; CI, 1.8 to 6.0) ($p = 0.0001$). No other differences were seen between the groups with respect to postoperative complications.

Summary

Although early recovery (time to open eyes and obey commands) was quicker in the sevoflurane and desflurane groups versus the propofol group, the mean differences were small (1 to 2 minutes). On the other hand, propofol (TIVA) had some important benefits in terms of home discharge and postoperative side effects, specifically less nausea and vomiting up to 24 hours. Early recovery, characterized by time to open eyes and obey commands, is faster after desflurane and sevoflurane anesthesia compared with propofol anesthesia. Intermediate recovery, characterized by home discharge (but not home-readiness), is fastest in patients anesthetized with propofol compared with sevoflurane and isoflurane but not desflurane. Postoperative complications, specifically nausea and vomiting, are lowest in the propofol group compared with desflurane, sevoflurane, or isoflurane. Another area of potential importance, based on location and type of surgery, is the decreased incidence of coughing during emergence[10] with TIVA versus inhalational anesthesia. In the end, the choice of anesthetic for maintenance of anesthesia should be guided by the training and experience of the individual physician, as well as the routines and equipment available in the hospital, because the choice of anesthetic agents appears to play a minor role in outcomes after ambulatory surgery.

Choice of Inhaled Anesthetic

Until the early 1990s the inhalational agents used were isoflurane, halothane, and enflurane. With the introduction of desflurane and subsequently sevoflurane, the popularity of enflurane and halothane has dwindled, and these agents are now rarely used. Despite the large number of articles published in the literature comparing isoflurane, desflurane, and sevoflurane, recovery after ambulatory surgery is, at best, poorly studied. A systematic review[9] was able to extract data from only 16 studies with 1219 patients in which these three agents were used in a randomized prospective manner during ambulatory surgery.

Isoflurane versus Desflurane

A total of four studies compared isoflurane with desflurane in the ambulatory setting. In all, 277 patients undergoing different ambulatory surgical procedures were included. Muscle relaxants were used during surgery in two studies, and nitrous oxide was used in all studies. A statistically significant difference was found in time to obey commands ($p < 0.01$) but in no other parameter of recovery (Table 20-2). The weighted mean differences in the recovery indices between desflurane and isoflurane were modest (4 to 5 minutes), all in favor of desflurane. No other differences were found in the incidence of postoperative complications between these groups.

Isoflurane versus Sevoflurane

Six studies could be included, and the relevant data examined a total of 634 patients undergoing a variety of ambulatory surgical procedures. Nitrous oxide was used in all studies, although four studies used muscle relaxants during surgery and the others did not. Statistically significant differences were found in the time to open eyes, time to obey commands, time to transfer from phase 1 to phase 2, home-readiness ($p < 0.00001$), and home discharge ($p = 0.05$) (see Table 20-2). The results of the latter are, however, based on two studies that could be identified with relevant data. The weighted mean differences in the recovery indices between sevoflurane and isoflurane were small, but all were in favor of sevoflurane. Drowsiness was more frequent in the isoflurane group versus sevoflurane in the postoperative period ($p = 0.03$) (see Table 20-2).

Sevoflurane versus Desflurane

The meta-analysis[9] looked at six studies comparing sevoflurane with desflurane, with a total of 246 patients. The majority of studies examined patients undergoing gynecologic laparoscopy, and nitrous oxide was used in all but one study. Muscle relaxants were used during anesthesia in four studies. Recovery parameters, including time to open eyes, were found to be statistically

TABLE 20-2 **Postoperative Recovery Profiles and Minor Complications Associated with Different Inhaled Anesthetic Regimens**

Endpoint	Isoflurane vs. Desflurane	Isoflurane vs. Sevoflurane	Sevoflurane vs. Desflurane
Time to open eyes (min)	NR	2.4 (1.8 to 2.9)* (S)	1.4 (–0.1 to 2.9)†
Time to obey commands (min)	4.6 (1.1 to 8.2)* (D)	2.4 (1.8 to 2.9)* (S)	2.7 (1.2 to 4.1)* (D)
Time to transfer from phase 1 to phase 2 (min)	1.3 (–10 to 8)	8.2 (5.7 to 10.6)* (S)	6.4 (3.7 to 9.0)* (S)
Time to home-readiness (min)	6.4 (–8.7 to 21.5)	5.1 (2.8 to 7.4)* (S)	2.0 (–16 to 12)
Time to home discharge (min)	NR	25 (0.4 to 50)‡ (S)	2.1 (–18 to 13)
Postoperative nausea (PON)	1.7 (1.0 to 3.1)	1.2 (0.8 to 1.9)†	0.7 (0.4 to 1.2)
Postoperative vomiting (POV)	0.8 (0.3 to 1.6)	0.9 (0.6 to 1.4)	0.7 (0.2 to 1.8)
Postoperative drowsiness	NR	0.6 (0.4 to 1.0)‡ (S), NNH = 9.5	1.0 (0.6 to 1.6)
Postoperative dizziness	NR	0.8 (0.4 to 1.5)	NR
Postoperative shivering	NR	NR	NR
Postoperative headache	NR	NR	NR
Antiemetics given	NR	1.0 (0.7 to 1.4)	NR
Postdischarge nausea (PDN)	NR	0.4 (0.3 to 0.7)* (S), NNH = 7.2	0.8 (0.4 to 1.7)
Postdischarge vomiting (PDV)	NR	0.8 (0.4 to 1.6)	NR

All results are shown as weighted mean difference or relative risk (mean and 95% confidence intervals). Significant differences are shown in favor of the following: *S,* sevoflurane; *I,* isoflurane; *D,* desflurane, when significant. *NR,* not reported (or reported in only one study); *NNH,* numbers needed to harm for significant differences.

*$p < 0.01$.

†Significant heterogeneity.

‡$p < 0.05$.

From Gupta A, Zuckerman R, Stierer T, Sakima N, Parker S, Fleisher LA. Comparison of recovery profile after ambulatory anesthesia with propofol, isoflurane, sevoflurane and desflurane: a systematic review. Anesth Analg 2004;98:632–41.

significant ($p < 0.005$), as well as time to obey commands ($p < 0.00001$), both in favor of desflurane (see Table 20-2). The weighted mean differences in these recovery indices between the groups were minor and in favor of desflurane. The time to transfer from phase 1 to phase 2 was, however, found to be earlier in the sevoflurane group than in the desflurane group ($p < 0.00001$) (weighted mean difference, 6 minutes). A more recent study not included in the meta-analysis[11] had similar recovery findings; however, a potentially important finding in their study was the higher incidence of coughing in the perioperative period for the desflurane group (60%) versus the sevoflurane group (32%).

Summary

Minor differences were found in the time to early recovery (in favor of desflurane and sevoflurane compared with isoflurane), but no differences were found between the inhalational agents in the intermediate recovery indices (home-readiness or home discharge). In addition, minor complications occurred with all agents, some of which favored one agent, whereas others favored another agent. With the exception of increased coughing with desflurane, only minor differences were found among the inhalational agents.

AREAS OF UNCERTAINTY

Although every effort was made to search the literature for articles meeting the inclusion criteria, some studies with relevant data may have been missed, and this remains a problem with any systematic analysis. The literature search was in English only, which could be considered a bias because many excellent studies have been published in non-English journals. Some authors did not clearly state whether the data presented applied to inpatients or outpatients. This has been a source of frustration, and limits the conclusions that can be drawn from studies that provided data for outpatients alone. One other problem was that authors used different terminology to define a similar event. Thus some authors used "time to eye-opening," whereas others used "time to awakening"; similarly, some authors used "time to response to commands," whereas others used "time to orientation"; "dizziness" and "giddiness" were probably used to mean the same thing, as were "drowsiness" and "somnolence." A distinction was made between "home-readiness" and "home discharge" because these are two different parameters. Universal agreement on many of these ill-defined parameters could be an advantage for the purpose of research in future studies. Finally, the data presented here are based on 2 to 15 studies in each group, which is a severe limitation to the conclusions; therefore more studies, with well-defined objectives, comparing a similar group of patients undergoing ambulatory surgery, are needed in the literature.

GUIDELINES

Formal guidelines regarding the choice of anesthetic agents for ambulatory surgery do not exist because of the minor differences between agents and also because

of the lack of outcome data to conclude the superiority of one agent over another. The largest trials have often concluded that the choice of anesthetic agent plays a minor role (if any) in morbidity and mortality risk after ambulatory surgery. Even the crude indicators of recovery after anesthesia, including early and intermediate recovery, as well as home-readiness and home discharge, have minimal clinical significance in efficient day surgical units. Local practices, including physician or patient preferences, availability of equipment (vaporizers and infusion pumps), and staffing patterns, would dictate the anesthetic agents that should be used for ambulatory surgery.

Although a greater number of patients can probably be "fast-tracked" using the newer inhalational agents such as desflurane and sevoflurane versus propofol, the overall advantage to the patient, or even the health care system, is probably minimal in terms of cost savings. In an excellent article published in 2002,[12] it was shown clearly that it is the efficient organization of an ambulatory surgical unit, rather than anesthetic drugs, that plays a key role in patient satisfaction.

AUTHOR'S RECOMMENDATIONS

Taking into consideration the remarks made earlier, the limited information available on many aspects of these anesthetic agents, and the evidence available in the literature on aspects of recovery, the following suggestions on the use of anesthetic agents in an ambulatory surgery practice are offered:

- *Induction of anesthesia:* Whenever intravenous access is available in adult patients, propofol offers a definite and clear advantage over thiopental during ambulatory surgery. Even when compared with an inhalational agent such as sevoflurane, propofol offers advantages in better and smoother induction of anesthesia and greater patient satisfaction with earlier recovery; therefore it should be the natural choice in all but the most exceptional circumstances.
- *Maintenance of anesthesia:* Early recovery may be delayed by 1 to 2 minutes after propofol infusion compared with sevoflurane or desflurane. However, the overall advantages of propofol in terms of reduced incidence of postoperative nausea and vomiting, as well as earlier home discharge, would favor the latter. In cases where coughing/valsalva during emergence would be undesirable, total intravenous anesthesia should be strongly considered.
- *Choice of inhalational agent:* Early recovery is faster using desflurane versus sevoflurane or isoflurane. However, the time to transfer to phase 2 is earlier in sevoflurane, and minor complications appear to be equally distributed among the three agents. Therefore factors other than recovery and minor postoperative complications should be considered when determining the inhalational agent of choice in the day surgical unit.

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CHAPTER 21

What Are the Benefits of Different Ventilatory Techniques?

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INTRODUCTION

A broad variety of techniques and modes of mechanical ventilation is now available to physicians, thanks to improvements in technology. For the most part, the design of these techniques is based on sound physiologic principles. However, there is limited evidence that ventilatory techniques and modes affect hard outcomes. Additionally, the existing randomized controlled trials (RCTs) do not indicate the superiority of any specific mode; they only support certain general strategies for mechanical ventilation, such as tidal volume (TV) limitation and the use of ventilator liberation protocols. It can be argued that clinicians should choose only those modes and techniques that are time honored and have been used in the few existing positive RCTs. Although this approach will benefit a broad population, it is common experience that many patients require a more articulated strategy. In these cases, knowledge of the benefits of the different ventilatory techniques helps the clinician to individualize respiratory care, using the available modes within a general strategy that is supported by solid evidence.

OPTIONS: DESCRIPTIONS OF VENTILATORY MODES

Assist Control Ventilation

During assist control ventilation (ACV), the ventilator delivers a mandatory breath every time the patient initiates an inspiration. A backup respiratory rate is set to guarantee that the patient always receives a minimal number of breaths, even in the absence of spontaneous inspiratory activity. Mandatory breaths can be delivered with either volume or pressure control. During ACV, the inspiratory time is preset and invariable.

Pressure Support Ventilation

Pressure support ventilation (PSV) assists each inspiratory attempt by the patient with a pressure-limited breath, thus partitioning the work of breathing between the patient and ventilator.[1,2] The patient maintains partial control of TV and respiratory rate; the operator allows the patient to perform more or less work by modifying the level of inspiratory pressure. PSV differs from ACV in the lack of a backup rate and in the fact that, during PSV, inspirations have variable durations and are terminated when inspiratory flow decreases below a predetermined threshold value.

Synchronized Intermittent Mandatory Ventilation

Synchronized intermittent mandatory ventilation (SIMV) assists with a mandatory breath only an adjustable fraction of patient's inspiratory attempts. Unlike ACV, additional inspirations are either unassisted or partially assisted with PSV. During SIMV, higher mandatory rates are used for patients who require higher levels of ventilatory assistance and are progressively decreased during the weaning process, which allows the patient to accomplish more unsupported breaths.

Proportional Assist Ventilation

Proportional assist ventilation (PAV) is characterized by the delivery of a variable airway pressure that is continuously adjusted throughout each breath to match the patient's inspiratory effort.[3] The patient's effort is estimated with the use of continuous measurement of inspired flow and volume in relation to respiratory system compliance and resistance. The clinical use of PAV is now facilitated by the incorporation of a new method to frequently measure respiratory mechanics variables at the bedside.[4]

Airway Pressure-Release Ventilation and Biphasic Positive Airway Pressure

Airway pressure-release ventilation (APRV) is a mode of ventilatory support in which the patient breathes spontaneously at a high level of continuous airway pressure, with periodic releases to a low positive end expiratory pressure (PEEP). CO_2 exchange is partly accomplished by the patient's activity and partly by exhalations during pressure releases.[5] The volume exhaled during releases depends on the patient's mechanics and on the difference between the high pressure and the PEEP. The release time is typically maintained lower than 1.5 seconds, and the PEEP is usually very low or zero. Biphasic positive airway pressure (BiPAP), also known as Bi-Level ventilation, is a variant of APRV in which a non-negligible PEEP is applied during releases, which are of longer

duration.[6] During BiPAP, a patient's inspiratory activity also occurs at PEEP.

High-Frequency Oscillatory Ventilation

High-frequency oscillatory ventilation (HFOV) is a mode of ventilatory support in which small TVs are delivered at a very high rate, in the range of 3 to 15 Hz. During HFOV, gas runs continuously through the ventilator tubing and is oscillated by a piston placed within the circuit. The oscillations are thus transmitted to the patient's lungs, producing cyclic, rapid inflations and deflations. The clinician adjusts the amplitude of the oscillations, their frequency, and the continuous gas flow rate to modulate CO_2 exchange. Arterial oxygenation is proportional to mean airway pressure, which is regulated by a valve placed on the exhaust port of the circuit. The main advantage of HFOV is that it allows the delivery of TVs, which, although not negligible,[7-9] are still lower than with any other modes of ventilation, thus minimizing alveolar overdistension.

EVIDENCE

Lung Protective Strategies

The scope of mechanical ventilation has recently shifted from pure life support to protecting patients from ventilator-induced lung injury (VILI).[9] VILI is a form of pulmonary damage that is primarily caused by excessive alveolar stress due to high TV ventilation and by elevated inspiratory pressures.[10,11] The presence of atelectasis also promotes VILI, likely through the imposition of high stress by collapsed or unstable airspaces.[12] Patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) seem to be at particularly high risk of lung damage. The clinical relevance of VILI was demonstrated by a large RCT performed by the ARDSnet investigators showing that ventilation with small TV improves outcomes of ALI compared with larger TV.[13] Additionally, low TV ventilation decreases 2-year mortality in ALI, as suggested by a recent prospective cohort study.[14] It is also likely that lung protective strategies may ameliorate other long-term outcomes, such as the pronounced disability typically affecting ALI survivors.[15] Although the use of low TV will result in impaired CO_2 clearance in many patients, lung protection should take precedence over the goal of normalizing arterial Pco_2.[16]

Lung protective strategies in ALI may also include the use of higher PEEP to prevent atelectasis-related injury.[17] In three RCTs, the survival rate was not different between groups treated with higher versus lower PEEP.[18-20] However, a recent meta-analysis suggested that high PEEP may improve the outcomes of patients who have worse oxygenation.[21] In the absence of better evidence, clinicians should continue to prioritize minimization of lung overdistention in their choice of ventilator settings. In ALI patients who seem to favorably respond to PEEP without untoward effects, maintenance of higher PEEP is probably not harmful based on the existing evidence (Table 21-1).

Use of Partial Ventilatory Support

The main goal of mechanical ventilation is to support CO_2 excretion, which can be accomplished either by having the ventilator substituting for the patient's inspiratory muscles (total ventilatory support) or by letting the patient and the ventilator share the effort of breathing (partial support). Although no RCT has suggested a superiority of either strategy, it is currently accepted that partial support is more desirable. In fact, total ventilatory support invariably requires deep sedation and often muscle relaxants. It is now recognized that minimization of sedatives is beneficial. This is based on results of RCTs in which protocols to decrease sedation improved clinical outcomes compared with standard management.[22] Additionally, complete suppression of inspiratory activity has been shown to be associated with diaphragm atrophy in animal models[23,24] and in human subjects receiving ventilatory support for longer than 18 hours.[25] Such atrophy is likely a key factor in delaying liberation from the ventilator.

PSV has been in circulation for many years and is probably one of the simplest ways to provide partial ventilatory support. However, its use is still relatively limited as shown by a large prospective cohort study[26] and is mainly relegated to the weaning process in patients who do not have severe oxygenation impairment. However, PSV can be used more broadly: in an observational

TABLE 21-1 **Highest Level of Evidence for Ventilatory Strategies in Different Groups of Patients**

Patient Group	Strategy	Level of Evidence	Comments
ALI/ARDS	TV limitation	A[13]	Avoidance of VIDD
	Use of partial support modes	D[24,25]	
	Open lung approach	A[18-20]	Possibly effective in high-severity patients
	Ventilator liberation protocols	A[35,36]	
Non-ALI/ARDS	TV limitation	B[73,74]	Possible benefit in patients at risk of ALI
	Ventilator liberation protocols	A[35,36]	
COPD/Asthma	NIV	A[69,70]	Standard of care for COPD exacerbations
	Permissive hypercapnia	B[66]	

ALI, acute lung injury; *ARDS,* acute respiratory distress syndrome; *COPD,* chronic obstructive pulmonary disease; *NIV,* noninvasive ventilation; *TV,* tidal volume; *VIDD,* ventilator-induced diaphragmatic dysfunction.

prospective study, PSV was tolerated by a majority of patients with ALI.[27]

SIMV was an early form of partial ventilatory support and is still widely used both for weaning and as a primary mode of ventilation for patients who require high-level support.[26] However, the advantages of SIMV over other modes are unclear and not demonstrated. The rationale for using[26] SIMV is to alternate spontaneous inspirations with mechanical breaths during which the patient's respiratory muscles are allowed to rest. However, it has been demonstrated that this rationale is largely flawed[28] because patient unloading is less efficient during SIMV than during PSV.[29]

APRV, BiPAP, and PAV are newer modalities of partial ventilatory support. Because of its features, PAV provides a level of support that is adjustable and always proportional to a patient's inspiratory drive and mechanical load, adapting to short-term changes in clinical conditions.[30]

Liberation from the Ventilator

It is widely recognized that early liberation from mechanical ventilation is a very desirable target because it decreases the rate of complications and the costs of medical care.[31] A large research effort has been made in evaluating strategies for ventilator weaning,[32] but studies have failed to clearly identify an ideal mode for this purpose. It is still unclear whether progressive resumption of spontaneous breathing with the use of PSV offers any advantages over daily performance of spontaneous breathing trials. Two RCTs performed in difficult-to-wean patients provided discordant answers to this question, which was likely due to methodologic differences.[33,34] However, the results of both studies suggested that SIMV was associated with delayed liberation from the ventilator compared with PSV and with spontaneous breathing trials.

Studies have demonstrated that the process of liberation from the ventilator is shortened by the use of protocols that identify and liberate patients who are able to tolerate a spontaneous breathing trial.[35,36] A more recent clinical trial evaluated a care pathway that combined daily sedation interruptions with spontaneous breathing trials in eligible patients. Compared with conventional management, the test strategy improved outcomes, including survival rates, in the absence of significant complications.[37] Although the results of these studies may not be translatable to all intensive care unit settings and patient populations, adherence to clinical pathways is probably more important than the choice of mode of ventilation used in the process.[38]

Patient–Ventilator Interaction

A considerable amount of research effort has been dedicated to improving the interaction between the patient and the ventilator, with the goal of optimizing patient comfort and decreasing sedation requirements. ACV is often suboptimal in this aspect. In fact, during volume-controlled ACV, the patient may accomplish undesired work of breathing when the ventilator does not match the patient's flow and volume demands.[39] This is due to the fact that a patient's inspiratory effort does not cease after triggering the ventilator but continues throughout the mandatory breath.[40] This problem is particularly relevant during a lung protective strategy, as suggested by the detection of high work of breathing in ALI patients undergoing ventilation with a TV of 5 to 6 mL/kg.[41] It is a common observation that these settings can lead to discomfort, although retrospective analysis of existing RCTs has not proved that TV limitation results in an increased need for sedation.[42,43] Additionally, during ACV the inspiratory time is invariable and may not match a patient's inspiratory time, which often results in patient–ventilator asynchrony, causing discomfort or hyperinflation.[44]

PSV is characterized by a high level of adaptability to patient demands. However, in certain conditions the mechanical breath may not finish exactly at the end of a patient's inspiratory time, causing asynchronies, hyperinflation, and discomfort.[44] In newer ventilators, the flow threshold that ends inspiration is adjustable, which allows the inspiratory duration to be prolonged or shortened to better match the patient's timing.[45] Another frequently encountered problem with PSV is overassistance, which occurs when inspiratory pressure is too high.[46] This may result in excessive TV and hypocapnia, thus causing central apnea episodes.[47] In fact, PSV is associated with more apneas and sleep disruptions than ACV, probably because of the fact that the latter mode has fixed TV and a backup rate.[48] Ventilator settings may be important contributors in the genesis of sleep deprivation and disruption in critically ill patients.[49] Because of its algorithm, PAV improves the matching between neural and machine inspiratory times, which should translate into improved patient comfort and better tolerance of the ventilator. In a RCT, PAV was tolerated by more patients and decreased the incidence of patient–ventilator asynchronies, in comparison with PSV.[50] In addition, PAV seems to result in less sleep fragmentation than PSV.[51]

Use of Alternative Modes

APRV and BiPAP are used in many centers for patients with severe hypoxemia because they allow maintenance of alveolar recruitment and oxygenation while avoiding alveolar overdistention, possibly decreasing VILI. In fact, APRV has been shown to achieve similar or better gas exchange at lower peak inspiratory pressures compared with other modes of ventilation.[52-55] Another advantage of APRV and BiPAP is that the presence of spontaneous breathing has been shown to improve gas exchange.[56] This effect seems to be related to improved diaphragmatic activity causing alveolar recruitment in the dorsobasal regions of the lungs.[57,58] Additional benefits of APRV that are related to spontaneous breathing are improvements in hemodynamics,[54,56] renal function,[59] and visceral perfusion.[60,61] The ability to allow unsupported breathing renders APRV and BiPAP useful in limiting sedative doses in patients who require high-level ventilatory support. APRV was associated with decreased sedation needs and earlier liberation from ventilation in two RCTs: one performed in patients recovering from cardiac surgery[61] and one in patients with ALI and

trauma.[55] However, extrapolation of the results of the latter study is hindered by the fact that the control group was receiving muscle relaxants, a rare practice in modern days. Although APRV and BiPAP have gained popularity, further research should clarify whether they have outcome advantages over modes that are routinely used. In the meantime, APRV and BiPAP should be considered only in patients who need high airway pressures to maintain gas exchange. Care should be taken to assure that TVs and peak alveolar distention are compatible with a lung protective strategy. Because of the short release time, APRV should be avoided in patients with chronic obstructive pulmonary disease (COPD) or asthma because of the risk of air trapping.

HFOV is also used in patients with severe, refractory hypoxemia, with the rationale of providing high mean airway pressures while minimizing alveolar distention and, possibly, VILI. HFOV has been extensively studied in the pediatric population, and large RCTs have been performed in newborns.[62,63] In the adult population, two small RCTs found no significant effects of HFOV on outcomes of patients with ARDS compared with conventional mechanical ventilation.[64,65] In one of these studies, a trend toward improved survival rates was detected with HFOV, although this study was underpowered to detect survival differences.[65] It is likely that HFOV may be beneficial when used in the setting of an open lung strategy. To provide support to this approach, a multinational trial on the use of HFOV versus conventional ventilation in patients with severe ALI is currently being conducted. Until such evidence becomes available, HFOV should be used as a rescue therapy in select patients who cannot achieve acceptable oxygenation while undergoing other modes of ventilation.

Management of Obstructive Lung Disease

The ventilatory management of patients with asthma and COPD is supported by a large number of physiologic studies, but few outcome trials are available. In these patients, the general goal of ventilation is to avoid hyperinflation and intrinsic PEEP. For this purpose, permissive hypercapnia is routinely practiced, but its use is only supported by an observational study on patients with status asthmaticus.[66] However, the consensus is that the adoption of this strategy has contributed to improved survival rates in these patients. Although once considered contraindicated, PEEP is commonly used to decrease the inspiratory threshold load of intrinsic PEEP.[67]

Noninvasive ventilation (NIV) is currently considered a standard treatment in COPD exacerbation.[68] This is based on strong clinical evidence from RCTs that demonstrated improved outcomes and decreased rates of intubation from its early use.[69,70] A systematic review of existing RCTs suggested that NIV might also be beneficial in other forms of hypoxemic respiratory failure, although the studies had conflicting results due to population heterogeneity.[71] Therefore NIV cannot be recommended for routine use in non-COPD patients with acute respiratory failure but should only be considered in select cases.

AREAS OF UNCERTAINTY

Although with a certain delay, the use of low TV ventilation has become common in the treatment of ALI. However, several points are unclear in the ventilator management of ALI. Studies have been unable to identify clear threshold values for TV and inspiratory pressure that may guarantee lung protection, as even moderate pressures and volumes can be associated with increased mortality rates.[14,72] Therefore significant uncertainties exist in how lung protection and stress limitation should be accomplished in patients who do not have elevated airway pressures. Additionally, low TV ventilation may require higher sedation to avoid asynchrony, and it is not clear whether lung protection should take precedence over minimization of sedation in patients with relatively mild ALI.

Recent evidence suggests that lung protective ventilation may also benefit certain patients who do not have ALI. Two observational studies documented an association between early use of high TV and later development of ALI in patients who did not have this syndrome initially.[73,74] Until RCTs are available, it is probably prudent to avoid high TV, at least in those patients who are at risk of ALI who do not have contraindications to TV limitation and who do not require high levels of sedation to tolerate such ventilator settings.

It is still unclear how PEEP should be set in ALI. PEEP is usually titrated to counteract hypoxemia, but its selection is complicated by the fact that it is still unclear what the target arterial oxygenation should be: data suggest that improved oxygenation is not necessarily associated with better outcomes.[13] It has been hypothesized that high PEEP selection may be beneficial only if titrated on each patient's individual characteristics; however, it is unclear how this task should be accomplished. Computerized tomography studies showed an increased risk of death in patients with significant amounts of atelectasis,[75] suggesting these are probably the subjects who may benefit from higher PEEP. A recent study showed physiologic improvements and suggested potential outcome benefits from setting PEEP based on transpulmonary pressure measurements obtained with the use of esophageal manometry.[76] However, this approach needs further clinical testing before being recommended.

Although there is overall agreement that muscle relaxants should be avoided, a recent RCT showed better outcomes in patients who received a 48-hour course of cisatracurium compared with the control group.[77] These controversial findings have not been clearly explained, but they could have been caused by better lung protection. Until more definitive evidence is available, neuromuscular blockers should not be routinely employed unless indicated by severe cardiopulmonary dysfunction.

GUIDELINES

Currently, no guidelines exist for the selection of ventilatory modes (Table 21-2). The lung protective strategy

TABLE 21-2 **Characteristics, Advantages, and Disadvantages of Different Ventilatory Modes**

Mode	Type of Support	Characteristics	Advantages	Disadvantages	Uncertainties
ACV	Total/partial	Assists each inspiration with volume or pressure-limited breath	Provides backup rate Guarantees safe TV (volume limited) Improves sleep	May cause patient/ventilator asynchrony Causes excessive WOB at low TV	Might increase sedation requirements at lower TV
SIMV	Partial	Assists only a fraction of inspirations with mandatory breaths	Allows unsupported breathing Provides backup rate when used with PSV	Does not unload patient WOB efficiently Delays liberation from the ventilator	Unclear role in current respiratory care
PSV	Partial	Assists each inspiration with a pressure-limited breath Ends inspiration when flow threshold is reached	Level of support is easily adjustable Improves patient–ventilator interaction Shortens weaning compared with SIMV	Lacks a backup rate May cause patient–ventilator asynchrony and overassistance May cause central apneas and sleep fragmentation	Might prolong weaning compared with spontaneous breathing trials
APRV BiPAP	Partial	Spontaneous, unassisted breaths at two levels of continuous airway pressure High levels of airway pressure are maintained for prolonged time	Improves oxygenation at lower peak inspiratory pressures Spontaneous breathing improves gas exchange Might decrease sedation needs	Risk of hyperinflation in patients with COPD	Does not guarantee safe TV delivery
PAV	Partial	Pressure assistance matches inspiratory effort	Improves patient–ventilator interaction Adjustable patient WOB Responds to changes in patient conditions Improves sleep quality	Does not guarantee TV Requires frequent measurements of respiratory mechanics	No outcome studies are available
HFOV	Total	Small TVs at very high rates	Improves oxygenation and alveolar recruitment Decreased alveolar overdistention	Requires deep sedation and/or muscle paralysis	Improves outcomes in very-low-birth-weight newborns Uncertain effects on outcome in adult population

ACV, assist control ventilation; *APRV,* airway pressure-release ventilation; *BiPAP,* biphasic positive airway pressure; *COPD,* chronic obstructive pulmonary disease; *HFOV,* high-frequency oscillatory ventilation; *PAV,* proportional assist ventilation; *PSV,* pressure support ventilation; *SIMV,* synchronized intermittent mandatory ventilation; *TV,* tidal volume; *WOB,* work of breathing.

proposed by the ARDSnet group[13] is considered the standard of care for ALI. Similar recommendations have also been adopted by the Surviving Sepsis Campaign.[78] Current guidelines emphasize the use of spontaneous breathing trials and organized protocols to facilitate the process of liberation from the ventilator.[79,80] The 2004 American Thoracic Society guidelines for the management of COPD recommended the use of NIV as initial treatment in COPD exacerbations with respiratory failure.[68] The indications and the use of NIV in acute respiratory failure were also addressed by a 2001 American–European joint consensus statement.[81]

AUTHOR'S RECOMMENDATIONS

- Consider a trial of noninvasive ventilation before intubation, particularly in patients with chronic obstructive pulmonary disease (COPD)
- Start ventilation with assist control ventilation, then reassess patients' responses based on blood gas values and respiratory mechanics
- Use low tidal volume and limit inspiratory pressures in patients with acute lung injury (ALI)/acute respiratory distress syndrome/(ARDS)
- Tolerate hypercapnia in patients with ALI/ARDS or COPD/asthma, unless contraindicated
- Select a mode of partial ventilatory support as soon as clinically feasible; avoid muscle relaxants, if possible
- Frequently assess patient–ventilator interaction and adjust settings/mode as needed to optimize comfort
- Frequently assess sedation level and follow protocols to minimize sedative doses

Continued on following page

AUTHORS' RECOMMENDATIONS (Continued)

- Consider alternative modes of ventilation (airway pressure-release ventilation/high-frequency oscillatory ventilation) if patients need high positive end expiratory pressure to maintain acceptable oxygenation
- Continuously attempt to decrease ventilator settings as patient's conditions improve
- Perform daily spontaneous breathing trials in eligible patients; promptly extubate patients who succeed
- Avoid synchronized intermittent mandatory ventilation in difficult-to-wean patients

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CHAPTER 22

Is There an Optimal Perioperative Hemoglobin Level?

Jeffrey L. Carson, MD • Manish S. Patel, MD

INTRODUCTION

Blood transfusions are common. In 2009, approximately 15 million units of red blood cells were transfused in the United States.[1] Between 60% and 70% of all red blood cell units are transfused in the perioperative setting.[2-5] Surgical patients are frequently anemic from the underlying disease, from the injury leading to the need for surgery, and from the blood loss associated with the surgical procedure.

Over the past 25 years, the trend has been to use a lower hemoglobin concentration as a transfusion trigger. The main motivation has been concern about blood safety prompted by the human immunodeficiency virus (HIV) epidemic in the 1980s. Fortunately, the risks of transmitting viral infections have become extremely low. The most recent estimates of the risk of residual units of infected blood donated by repeat donors were 1 per 1,149,000 for hepatitis C virus and 1 per 1,467,000 for HIV.[6]

New risks from infections, however, may emerge, such as West Nile virus.[7,8] Concerns about the rare transmission of variant Creutzfeldt-Jakob disease[9] have led to the increasing use of leukocyte-depleted blood and, in the United States, the elimination of donors who lived in the United Kingdom and Europe.[10,11] The result of new testing and donor policies is a blood supply that is so safe that it is difficult to measure changes in markers of disease after policy changes.[12] However, noninfectious risks such as transfusion-related acute lung injury (TRALI)[13] and transfusion-associated circulatory overload may be even more common than previously appreciated.[14]

With the improvement in safety and recently published clinical trials, it is timely to evaluate the evidence that documents when blood transfusion should be administered in the perioperative time period.

OPTIONS/THERAPIES

The indications for red blood cell transfusion are controversial. Most recommendations suggest that the decision to transfuse should be based on individual assessment of signs and symptoms of anemia. However, in practice, most clinicians transfuse at a specific hemoglobin concentration, such as 8 g/dL.[15] Opinions on the indications for transfusion of predeposit autologous blood also vary. Some clinicians argue that the indications should be the same as for allogeneic blood cells, whereas others suggest that because the risk of transfusion is less, autologous blood should be given at higher transfusion thresholds. However, predeposit autologous donation is generally not recommended because it does not reduce the overall exposure to transfusion.[16]

EVIDENCE

Several critical lines of evidence are needed to guide transfusion decisions. First, it is necessary to understand the risks associated with different levels of anemia in the perioperative period. Second, randomized clinical trials are needed to document that transfusion improves outcome. Third, as previously described, the risks of allogeneic and autologous transfusion must also be taken into account. The current data suggest that allogeneic blood transfusion is extremely safe.[1,6] To determine the efficacy of transfusion, we need to know at what point the risks of anemia increase and whether transfusions will eliminate or reduce the risks.

Risks Associated with Anemia

Studies in patients who refuse blood transfusion for religious reasons provide insights into the risks of anemia during the perioperative period. The largest study included 1958 patients undergoing surgery in the operating room.[17] Mortality rates rose as the preoperative hemoglobin levels fell. Patients with underlying cardiovascular disease, who had a hemoglobin level of 10 g/dL or less, had a higher risk of death than patients without underlying cardiovascular disease (Figure 22-1). An analysis of patients from the same cohort with postoperative hemoglobin levels lower than 8 g/dL found that mortality rates rose when the postoperative hemoglobin level was less than 7 g/dL and became extremely high with postoperative hemoglobin levels below 5 g/dL.[18] These results are consistent with an analysis of mortality and morbidity rates from case reports in Jehovah's Witness patients.[19]

Studies in volunteers who underwent isovolemic reduction of hemoglobin levels to 5 g/dL also provide insight into the risks of anemia. Two studies found that most transient and asymptomatic electrocardiogram changes occurred in 5 of 87 volunteers when their heart

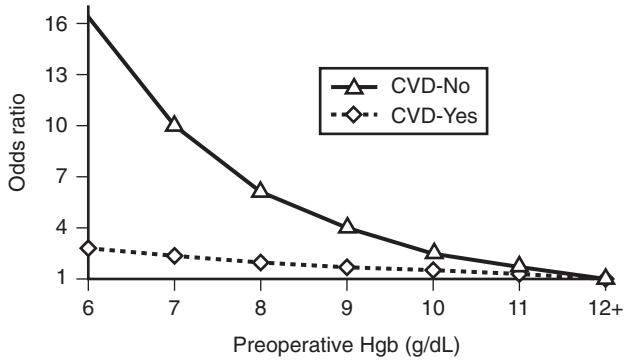

FIGURE 22-1 ■ Risk of Death in Patients with and without Cardiovascular Disease *(CVD).* (From Carson JL, Duff A, Poses RM, Berlin JA, Spence RK, Trout R, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet 1996;348(9034): 1055–66.)

rates were faster and their hemoglobin level was between 5 and 7 g/dL.[20,21] Other studies in young, healthy volunteers younger than 35 years have identified subtle and reversible cognitive changes at hemoglobin levels between 5 and 7 g/dL and increased fatigue at hemoglobin levels below 7 g/dL.[22] It is uncertain how to apply these results to older patients, although one can surmise that these changes might occur at higher hemoglobin levels.

Large cohort studies have found anemia to be associated with increased mortality and morbidity. In a study of 310,000 veterans 65 years or older undergoing major noncardiac surgery, the 30-day mortality rate rose 1.6% for each percentage point in hematocrit below 39% and above 51%.[23] Similar findings were present in a study of hospitalized patients with community-acquired pneumonia.[24]

Clinical Trials Evaluating Transfusion in Adults

A total of 6264 patients have entered trials evaluating transfusion thresholds, although only two are adequately powered to detect important differences in outcomes.[25] The first large trial is the Transfusion Requirement in Critical Care (TRICC) trial.[26,27] In this study, 838 volume-resuscitated intensive care unit (ICU) patients were randomly assigned to either a "restrictive" or "liberal" transfusion strategy. The "restrictive" group received allogeneic red blood cell transfusions at hemoglobin levels of 7 g/dL (and levels were maintained between 7 and 9 g/dL), and the "liberal" group received red blood cells at 10 g/dL (and levels were maintained between 10 and 12 g/dL).[26] The restrictive group had lower average hemoglobin levels (8.5 versus 10.7 g/dL) and fewer transfusions (2.6 versus 5.6) compared with the liberal group. The 30-day mortality rate was slightly lower in the restrictive transfusion group (18.7% versus 23.3%), although the finding was not statistically significant ($p = 0.11$). The risk of clinically recognized myocardial infarction (0.07% versus 2.9%; $p = 0.02$) and congestive heart failure (5.3% versus 10.7%; $p < 0.001$) also occurred less frequently in the restrictive transfusion group.[26] In two subanalyses, patients randomly assigned to the restrictive transfusion group who were younger than 50 years and less ill as defined by Acute Physiology and Chronic Health Evaluation (APACHE) score had a significantly lower mortality rate than patients in the liberal group.[26] In another subanalysis of patients with cardiovascular disease, there were no significant differences in mortality rate, although the confidence intervals were wide (adjusted odds ratio, 1.26; 95% confidence interval, 0.70-2.24).[28] This trial contributed 47% of the patients and 82% of the recorded deaths among all the patients entered into all the trials.

The second trial is Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS).[29] A total of 2016 patients with a history of cardiovascular disease or risk factors were randomly allocated to liberal transfusion strategy (maintain hemoglobin concentration greater than 10 g/dL) or restrictive transfusion strategy (transfuse if hemoglobin concentration was less than 8 g/dL or if symptoms of anemia developed). The restrictive group received transfusions at a hemoglobin concentration of 7.9 g/dL and the liberal group at 9.2 g/dL. The liberal group received about three times the number of transfusions as the restrictive group. There was no difference between the liberal (35.2%) and restrictive-strategy group (34.7%) for the primary outcome of walking 10 feet or across the room without human assistance at 60 days, and the results were similar at 30 days. In-hospital acute coronary syndrome or death occurred in 4.3% in the liberal and 5.2% in the restrictive groups (absolute risk difference, –0.9%; 99% CI, –3.3 to 1.6), and rates of death on 60-day follow-up were 7.6% and 6.6%, respectively (absolute risk difference, 1.0%; 99% CI, –1.9 to 4.0). The rates of other complications were similar in the two groups. This trial and the pilot study[30] were the only trials to include patient assessment for symptoms of anemia.

Twelve other randomized clinical trials have evaluated the effects of different transfusion thresholds (Table 22-1).[27,31-44] The clinical settings and outcomes were different among the studies. The transfusion thresholds varied and overlapped among the "restrictive" or "liberal" strategy.

A meta-analysis was performed by combining data from trials that compared restrictive with liberal transfusion strategies.[25] The analysis of the pooled data found that a restrictive transfusion trigger reduced the amount of red blood cells per transfused patient by 1.19 units. The restrictive group had a 1.48 g/dL lower mean hemoglobin concentration than patients who were assigned to the more liberal transfusion group. There was no difference in 30-day all-cause mortality between patients randomly assigned to a restrictive threshold compared with the liberal threshold for transfusion (relative risk for a restrictive versus liberal threshold, 0.85; 95% confidence interval, 0.70 to 1.03). There also were no differences in the risk of cardiac events or other outcomes (Figure 22-2).

TABLE 22-1 **Results of the Randomized Controlled Trials in Adults**

Study (Year)	Setting	Subjects: Eligibility and Comparability	Transfusion Strategy	Blood Usage Units/pt Mean (SD)/Median (IQR)	Proportion Transfused (%) (*n*)	Hb/Hct Levels Mean (SD)
Topley[31] (1956)	Trauma (*n* = 22)	<1 L blood loss; considered to be at no clinical risk in raising blood volume ≥100% of normal, or allowing it to reach 30% below normal	Liberal: to achieve RBC volume ≥100% of normal Restrictive: maintain RBC volume 70%-80% of normal	Total mean: 11.3 (6.9) Total mean: 4.8 (6.7)	100 (10) 67 (8)	Lowest Hb: (15.6 ± 2.0) g/dL Lowest Hb: (11.3 ± 0.7) g/dL
Blair[32] (1986)	GI bleeding (*n* = 50)	Acute severe upper gastrointestinal hemorrhage	Liberal: patients received at least 2 units of PRBCs immediately on admission to hospital Restrictive: patients were not transfused PRBCs during the first 24 hr unless Hb <8.0 g/dL or shock persisted after initial resuscitation with colloid	Total mean: 4.6 (1.5) Total mean: 2.6 (3.1)	100 (24) 19.2 (5)	Admission Hct: 28 (5.9%) Discharge Hct: 37.0 (7.8%) Admission Hct: 29 (8.2%) Discharge Hct: 37.0 (7.1%)
Fortune[33] (1987)	Trauma/acute hemorrhage (*n* = 25)	Patients who had sustained a Class III or Class IV hemorrhage and had clinical signs of shock	Liberal: Hct was brought up to 40% slowly over a period of several hours by infusion of PRBCs Restrictive: Hct was kept close to 30% by administration of PRBCs	Not available	Not available	Average Hct for 3-day period: 38.4 (2.1%) Average Hct for 3-day period: 29.7 (1.9%)
Johnson[34] (1992)	Cardiac surgery (*n* = 38)	Patients undergoing elective coronary revascularization and able to donate at least three units of packed cells preoperatively	Liberal: patients received blood transfusion to achieve Hct value of 32% as long as autologous blood was available Restrictive: patients received transfusion only if Hct value fell below 25%	Total mean: 2.05 (0.93) Total mean: 1.0 (0.86)	100 (18) 75 (15)	Hct at 4 hr postoperative: 31.3% Hct at 4 hr postoperative: 28.7%
Hebert[27] (1995)	Critical care (*n* = 69)	Critically ill patients admitted to one of five tertiary-level ICUs with normovolemia after initial treatment who had Hb concentrations < 9.0 g/dL within 72 hr	Liberal: patients were transfused PRBCs if their Hb concentration maintained at 10.0-12.0 g/dL Restrictive: patients were transfused PRBCs only if their Hb was 7.0-7.5 g/dL; Hb concentration maintained at 7.0-9.0 g/dL	Total mean: 4.8 (SD not available) Total mean: 2.5 (SD not available)	Not available	Admission Hb: 9.3 (1.3) g/dL Average daily Hb: 10.9 g/dL Admission Hb: 9.7 (1.4) g/dL Average daily Hb: 9.0 g/dL
Bush[35] (1997)	Vascular surgery (*n* = 99)	Patients undergoing elective aortic and infrainguinal arterial reconstruction surgery	Liberal: transfused with PRBCs to maintain Hb >10.0 g/dL Restrictive: transfused only if Hb level fell below 9.0 g/dL	Total mean: 3.7 (3.5) Total mean: 2.8 (3.1)	88 (43) 80 (40)	Hb during 48-hr postoperative period (g/dL): 11.0 (1.2) Hb during 48-hr postoperative period (g/dL): 9.8 (1.3)
Carson[30] (1998)	Orthopedic surgery (*n* = 84)	Hip fracture patients undergoing surgical repair who had postoperative Hb levels less than 10.0 g/dL	Liberal: patients received one unit PRBCs at the time of random assignment and then as needed to maintain Hb >10.0 g/dL Restrictive: transfusion was delayed until patient developed symptoms or consequences of anemia, or Hb value <8.0 g/dL in absence of symptoms	Total median: 2 (1-2) Total median: 0 (0-2)	98 (41) 45 (19)	Lowest Hb (g/dL): 9.4 (1.0) Last Hb (g/dL): 10.7 (0.9) Lowest Hb (g/dL): 8.8 (1.2) Last Hb (g/dL): 9.7 (0.9)

Continued on following page

TABLE 22-1 **Results of the Randomized Controlled Trials in Adults** (Continued)

Study (Year)	Setting	Subjects: Eligibility and Comparability	Transfusion Strategy	Blood Usage Units/pt Mean (SD)/Median (IQR)	Proportion Transfused (%) (*n*)	Hb/Hct Levels Mean (SD)
Hebert[26] (1999)	Critical care (*n* = 838)	Critically ill patients admitted to 1 of 22 tertiary-level and 3 community ICUs with normovolemia after initial treatment who had Hb concentrations <9.0 g/dL within 72 hr	Liberal: patients were transfused with PRBCs to maintain Hb concentration at 10.0-12.0 g/dL Restrictive: patients were transfused to maintain Hb concentration at 7.0-9.0 g/dL	Total mean: 5.6 (5.3) Total mean: 2.6 (4.1)	100 (420) 67 (280)	Mean daily Hb (g/dL): 10.7 (0.7) Mean daily Hb (g/dL): 8.5 (0.7)
Bracey[36] (1999)	Cardiac surgery (*n* = 428)	Patients undergoing first-time elective coronary revascularization	Liberal: received PRBC transfusions per individual physicians, who considered clinical assessment of patient and institutional guidelines, which propose Hb level <9.0 g/dL as postoperative threshold for PRBC transfusion Restrictive: received PRBC transfusion in postoperative period for Hb level <8.0 g/dL, unless patient experienced blood loss >750 mL since last transfusion; hypovolemia with hemodynamic instability, and excessive acute blood loss, acute respiratory failure, or inadequate cardiac output and oxygenation; or hemodynamic instability requiring vasopressors	Postoperative: 1.4 (1.8) Total: 2.5 (2.6) Postoperative: 0.9 (1.5) Total: 2.0 (2.2)	48 (104) 35 (74)	Mean net reduction in Hb (admission to discharge): 4.2 (1.9) g/dL Mean net reduction in Hb (admission to discharge): 4.2 (1.7) g/dL
Lotke[37] (1999)	Orthopedic surgery (*n* = 127)	Patients undergoing primary total knee arthroplasty who were able to donate two units autologous blood preoperatively	Liberal: received their autologous blood immediately after surgery: the first unit in recovery room and the second unit delivered on return to the ward Restrictive: received all autologous blood if Hb level had fallen below 9.0 g/dL	Not available	100 (65) 26 (16)	Mean postoperative Hb (g/dL): Day 1: 11.4 Day 3: 10.7 Mean postoperative Hb (g/dL): Day 1: 10.6 Day 3: 10.0
Grover[38] (2005)	Orthopedic surgery (*n* = 260)	Patients undergoing elective hip and knee replacement surgery	Liberal: received PRBC transfusion when Hb < 10.0 g/dL and to maintain Hb concentration at 10.0-12.0 g/dL Restrictive: received PRBC transfusion when Hb < 8.0 g/dL and to maintain Hb concentration 8.0-9.5 g/dL	Total median: 0 (0-10) Total median: 0 (0-5)	42.2 (46) 33.9 (37)	Mean postoperative Hb Day 5 (g/dL): 11.1 (0.9) Mean postoperative Hb Day 5 (g/dL): 9.8 (1.2)

Colomo[40] (2009)	GI bleeding (n = 214)	Patients with cirrhosis and acute gastrointestinal bleeding	Liberal: received PRBC when Hb < 9.0 g/dL, to maintain Hb concentration at 9.0-10.0 g/dL Restrictive: received PRBC when Hb < 7.0 g/dL, to maintain Hb concentration at 7.0-8.0 g/dL	Not available	90.5 (95) 62.4 (68)	Mean Hb (g/dL) at discharge: 10.1 (0.9) Mean Hb (g/dL) at discharge: 9.2 (1.3)
Webert[39] (2008)	Oncology (n = 60)	Patients with acute leukemia receiving induction chemotherapy or undergoing stem cell transplantation	Liberal: received two units PRBC when Hb < 12.0 g/dL Restrictive: received two units PRBC when Hb < 8.0 g/dL	Not available	93.5 (29) 89.7 (26)	Not available
Foss[41] (2009)	Orthopedic surgery (n = 120)	Patients > 65 years of age admitted for hip fracture	Liberal: received PRBC when Hb < 10.0 g/dL Restrictive: received PRBC when Hb < 8.0 g/dL	Total median: 2 (1-2) Total median: 1 (1-2)	73.3 (44) 36.7 (22)	Not available
Zygun[42] (2009)	Critical care (n = 30)	Patients admitted to critical care unit with severe traumatic brain injury	Liberal group 1: received two units PRBC when Hb < 9.0 g/dL Liberal group 2: received two units PRBC when Hb < 10.0 g/dL Restrictive: received two units PRBC when Hb < 8.0 g/dL	Not available	Not available	Not available
Hajjar[43] (2010)	Cardiac surgery (n = 502)	Patients admitted to ICU for elective cardiac surgery with cardiopulmonary bypass	Liberal: received PRBC when HCT < 30% at any time from start of surgery to discharge from ICU Restrictive: received PRBC when HCT < 24%	Total median: 2 (1-3) Total median: 0 (0-2)	78.3 (198) 47.4 (118)	Mean Hb at postoperative day 7 (g/dL): 10.8 (8.9) Mean Hb at postoperative day 7 (g/dL): 9.4 (10.5)
So-Osman[44] (2010)	Orthopedic surgery (n = 619)	Patients undergoing elective hip and knee replacement surgery	Liberal: received PRBC according to "Standard Care," which differed between hospital sites Restrictive: received PRBC using a "New Transfusion Policy," that risk-stratified patients according to age and comorbidities	Total mean: 0.86 (1.6) Total mean: 0.78 (1.4)	39.1 (119) 36.5 (109)	Mean Hb at discharge (g/dL): 11.4 (1.1) Mean Hb at discharge (g/dL): 11.4 (1.1)
Carson[29] (2011)	Orthopedic surgery (n = 2016)	Patients > 50 years of age with cardiovascular disease or cardiovascular disease risk factors who were undergoing surgery for hip fracture and have postoperative Hg < 10.0 g/dL	Liberal: received PRBC when Hb < 10.0 g/dL Restrictive: received PRBC when Hb < 8.0 g/dL or if developed symptoms of anemia	Total median: 2 (1-2) Total median: 0 (0-1)	96.7 (974) 41.1 (415)	Mean Hb (g/dL): 10.9 (0.9) Mean Hb (g/dL): 9.6 (1.1)

GI, gastrointestinal; *Hb,* hemoglobin; *Hct,* hematocrit; *ICU,* intensive care unit; *IQR,* interquartile range; *PRBC,* packed red blood cell; *pt,* patient; *SD,* standard deviation.

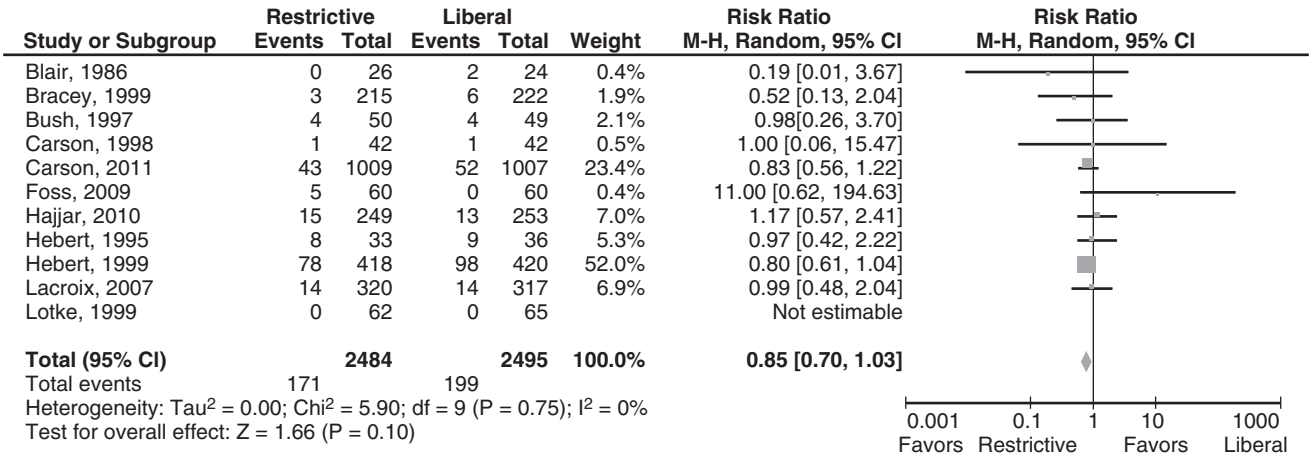

FIGURE 22-2 ■ Meta-Analysis of Transfusion Trials on All-Cause Mortality Rates. (From Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2012(4):CD002042.)

Observational Studies Evaluating Transfusion in Adults

Many observational studies have evaluated the impact of transfusion on morbidity and mortality rates. However, in general, it is not possible to obtain unbiased assessment of blood transfusion from observational studies. The decision to give a patient a transfusion is often correlated with the illness burden of the patient, and this may not be adequately adjusted for in these studies. This lack of complete adjustment for underlying disease and severity of illness might explain the variation in results of studies evaluating the impact of transfusion in patients with cardiovascular disease.[45-48]

Clinical Trials Evaluating Transfusion in Children

There have been three clinical trials evaluating transfusion triggers in children. The first trial evaluated 100 preterm infants weighing between 500 and 1300 g.[49] The patients were randomly allocated to a restrictive or liberal transfusion algorithm that considered respiratory status and hematocrit level. The restrictive group was given transfusions two fewer red blood cell units than the liberal group. None of the 15 endpoints were designated as the primary outcome. Overall, there were no differences in endpoints, with the exception that the restrictive group had more frequent apneic spells and neurologic events than the liberal group.

The second trial enrolled 451 infants with gestational ages less than 31 weeks, ages less than 2 days, and weight less than 1000 g.[50] Similar to the first study, transfusion thresholds varied by the amount of respiratory support. The composite primary endpoint was death, severe retinopathy, bronchopulmonary dysplasia, or brain injury. The primary outcome occurred with similar frequency in the two groups: restrictive group, 74%; and liberal group, 69.7%.

The most recent trial recruited 637 children admitted to a pediatric ICU and randomly allocated to 7 g/dL or 9.5 g/dL thresholds.[51] Red blood cell transfusion was administered to 46% of patients in the restrictive group and 98% in the liberal group. The primary outcome (new or progressive multiorgan dysfunction) was nearly identical in both groups. Overall, the results of the three trials in children suggest that a restrictive transfusion trigger is safe (Table 22-2).[52]

AREAS OF UNCERTAINTY

There are now three adequately powered trials that demonstrate that a restrictive transfusion is safe in the 7- to 8-g/dL range.[26,29,51] However, these trial results have not been replicated, and there are other populations of patients that would benefit from further study. Most important are patients with acute coronary syndrome because this subgroup is the most likely to benefit from liberal transfusion. Other populations of patients include (but are not limited to) those with gastrointestinal bleeding, traumatic brain injury, and elderly medical patients recovering from medical illness. Trials using lower thresholds such as 6 g/dL are also needed because the lowest threshold that has been tested is 7 g/dL.

GUIDELINES

Before the late 1980s, the standard of care was to administer a perioperative transfusion whenever the hemoglobin level fell below 10 g/dL and the hematocrit level fell below 30% (the "10/30 rule"). In 1988, a National Institutes of Health consensus conference on perioperative red blood cell transfusions concluded that there was no evidence to support a single criterion. More recent guidelines from the American Society of Anesthesiology task force guidelines,[53] the British Committee for Standards in Hematology,[54] and the Australian and New Zealand

TABLE 22-2 **Results of the Randomized Controlled Trials in Children**

Study (Year)	Setting *(N)*	Subjects: Eligibility and Comparability	Transfusion Strategy	Blood Usage Units/pt Mean (SD)	Proportion Transfused (%)(*N*)	Hb/Hct Levels Mean (SD)	Outcome
Bell[49] (2005)	100	Hospitalized preterm infants 500-1300 g	Restrictive vs. liberal transfusion based on respiratory status and hematocrit	Liberal: 5.2 (±4.5) Restrictive: 3.3 (±2.9)	Liberal: 12% (6) Restrictive 10% (5)	Not reported	No difference in 15 outcomes, including survival except restrictive group had more frequent apneic spells (0.84 vs. 0.42 per day) and intraparenchymal brain hemorrhage, or periventricular leukomalacia (6 vs. 0) vs. the liberal group
Kirpalani[50] (2006)	451	Birth weight <1000 g, gestational age <31 weeks, and <48 hr old	Restrictive vs. liberal transfusion based on hemoglobin and amount of respiratory support	Liberal: 5.7 (5.0) Restrictive: 4.9 (4.2)	Liberal: 95% Restrictive: 89%	About 1 g/dL difference	Primary outcome: death or any of the following: severe retinopathy, bronchopulmonary dysplasia, or brain injury or cranial ultrasound. Liberal: 69.7%; restrictive: 74.0% (NS). None of secondary outcomes significant.
Lacroix[51] (2007)	637	Stable critically ill children with hemoglobin <9.5 g/dL with 7 days of admission to ICU	Liberal: 9.5 g/dL Restrictive: 7 g/dL	Liberal: 1.7 (2.2) Restrictive: 0.9 (2.6)	Liberal: 98% Restrictive: 46%	2.1 g/dL difference	Primary outcome: new or progressive multiorgan dysfunction syndrome Liberal: 12% Restrictive: 12%

ICU, intensive care unit; *pt,* patient; *SD,* standard deviation.

Society of Blood Transfusion[55] generally suggest that transfusion is generally not indicated when the hemoglobin concentration is above 10 g/dL but indicated when the hemoglobin concentration is less than 6 or 7 g/dL. These societies do not recommend a specific transfusion trigger. Guidelines for adult trauma and critical care patients[56] recommended a transfusion at hemoglobin levels less than 7 g/dL, except for patients with acute myocardial ischemia. These guidelines recommended that a decision to transfuse be guided by individual factors such as bleeding, cardiopulmonary status, and intravascular volume. The latest guidelines developed by the AABB (formerly, the American Association of Blood Banks) recommends adhering to a restrictive transfusion strategy (7 to 8 g/dL) in hospitalized, stable patients including those with pre-existing cardiovascular disease.[57] The committee suggested that transfusion decisions be influenced by symptoms as well as hemoglobin concentration. No recommendations were made for or against a liberal or restrictive transfusion threshold for hospitalized, hemodynamically stable patients with acute coronary syndrome because of the lack of data.

AUTHORS' RECOMMENDATIONS

Several clinical trials have examined different transfusion thresholds in the perioperative and intensive care unit settings and found that it is safe to withhold transfusion until hemoglobin levels reach 7 g/dL to 8 g/dL or for symptoms of anemia. Important outcomes such as myocardial infarction and functional recovery have been examined and have not been adversely affected by the use of a restrictive transfusion approach. Patients with pre-existing cardiovascular disease also tolerated lower transfusion thresholds. In patients with acute coronary syndrome, the optimal threshold is unknown, and these patients with may be more vulnerable to the consequences of anemia. Thus it is necessary to rely on clinical judgment, and a more liberal transfusion approach may be reasonable in this subgroup of patients. In preoperative patients, enough blood should be transfused to anticipate operative blood loss. Patients with symptoms of anemia should be given transfusions as needed. Ultimately, careful clinical assessment with thoughtful consideration of risks and benefits should guide the transfusion decision, not a specific hemoglobin concentration. No set of guidelines will apply to every patient.

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CHAPTER 23

When Are Platelets and Plasma Transfusions Indicated?

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INTRODUCTION/BACKGROUND

The hemostatic system consisting of platelets, procoagulant and anticoagulant, and fibrinolytic and antifibrinolytic activities plays a key role in the maintenance of human viability. It achieves hemostatic balance by controlling bleeding without inducing pathologic thrombotic events.[1] Until recently, the efficacy and safety of substitution of blood products have rarely been assessed with the use of state-of-the-art methodologies such as randomized trials. In a variety of cases, surrogate endpoints hinting toward clinical benefit (e.g., laboratory test results) have been used, but, in general, clinically important outcome measures (e.g., reduction in morbidity and mortality rates) have not been studied. Although it is generally agreed that platelet transfusions provide hemostasis in thrombocytopenic patients, this agreement is also the main reason why virtually no data supporting the efficacy and safety of the currently established practices are available.

OPTIONS

Platelet Transfusions

The recommended dosing for platelet transfusion is usually 0.5×10^{11} platelets/10 kg body weight, which is the average platelet content of one single unit of whole blood (0.45 to 0.85×10^{11}). The therapeutic platelet dosage ranges from 2 to 4×10^{11} platelets, which results in a post-transfusion platelet increment of 30,000/mcL in a patient, based on an average body weight of 70 kg.[2] This therapeutic result can be achieved in the following three ways.

Platelet-Rich Plasma Preparation (United States)

In a validated process, one unit of whole blood is centrifuged. In the first step, a soft spin is used to obtain the platelet-rich plasma, followed by a hard spin to achieve sedimentation of the platelets. Sedimented platelets are then allowed to disaggregate and are resuspended in 50 to 60 mL plasma or another suspension medium (recovered platelets). The minimum content of this preparation is 0.45×10^{11}/unit (U) platelets.

Buffy Coat Pool Preparation

The buffy coat layers (i.e., platelets with leukocytes) of whole blood are prepared in a validated process by means of specific-gravity centrifugation. In the second step, 4 to 6 buffy coats are pooled, recentrifuged by soft spin to obtain platelet rich plasma, and then recentrifuged by hard spin to obtain a platelet pellet. The platelet pellet is then disaggregated and resuspended in greater than 40 mL/0.5×10^{11} platelets in plasma or nutrient solution. The minimum content of this preparation is 2.5×10^{11}/U platelets.

Single-Donor Apheresis Preparation

This blood component is obtained by platelet apheresis of a single donor with the use of automated cell separation equipment. Depending on the donor and on the machine used, the platelet yield per procedure varies from 2 to 8×10^{11}/U in a volume of greater than 40 mL/0.5×10^{11} platelets.

Platelet buffy coat pool preparations and single donor apheresis preparations are therapeutically equivalent because only patients with alloimmunization need human platelet antigen/human leukocyte antigen (HPA/HLA)–typed preparations from single donors. The significance of the exposing the recipient to a greater number of pool donors is currently under investigation.

Products for Plasma Substitution

Fresh-frozen plasma (FFP) contains a physiologic range of all the clotting factors, fibrinogen (400 to 900 mg/U), plasma proteins (particularly albumin), electrolytes, physiologic anticoagulants (i.e., protein C, protein S, antithrombin, and tissue factor pathway inhibitor), and added anticoagulants.[3,4] Because of processing and storage, FFP contains 15% to 20% less factor VIII levels compared with normal plasma. The shelf life is 1 year when stored at −18° C or lower. FFP is used as single unit quarantine plasma, pooled solvent/detergent-treated plasma, and single unit methylene blue–treated plasma. Photochemically treated FFP and solvent detergent FFP are approved methods of inactivating pathogens. However, both methods cause loss of clotting factors, particularly loss of factor VIII. Some solvent/detergent FFP preparations have reduced activity of protein S and alpha2-antiplasmin and have been associated with thromboembolic complications.[5,6]

After thawing, the activity of labile clotting factors such as factor V and factor VIII decline gradually; 5 days after thawing, the activity of factor VIII has dropped by more than 50%, and the activities of factor V and factor VII have dropped to about 20% of their initial levels.[7] Therefore it is recommended that FFP be used within 24 hours after thawing.

EVIDENCE

In perioperative and intensive care medicine, the administration of blood, blood products, and substances influencing the coagulation system is guided by individualized hemotherapy regimens. The regimens are essential therapeutic interventions and frequently have to be shared among other specialties. Issues include:

- Lack of evidence and standardized guidelines for use of blood products and some plasma derivatives and pharmacologic agents
- Lack of accurate and rapid laboratory tools for evaluating the actual status and competence of the hemostatic system
- Individual variations caused by specific pathologic conditions or anatomic disruption
- Difficulties in assessing continued bleeding and the variable impact of pretreatment with anticoagulants or antiplatelet drugs[1,8]

Bleeding is multifactorial and sometimes a dramatic event that is encountered in a multitude of clinical scenarios. However, the number of adequately designed and conducted clinical studies are limited. These limited data do not allow the generation of a broadly accepted treatment algorithm that is also applicable to therapeutic use of stable (plasmatic) and nonstable (cellular) blood products.[9] In addition, manufacturers not only are not interested but also simply do not have the necessary resources to finance and conduct the necessary clinical studies. Therefore any recommendations for the use of platelets and FFP will have to be based on limited evidence only.

Platelets are intimately involved in hemostasis and thrombosis and interact with endothelial and white blood cells. Activated platelets themselves produce both immunomodulatory and proinflammatory mediators that, in turn, affect circulating cells and the endothelium. Treatment with platelet concentrates was introduced in the late 1950s for control and prevention of thrombocytopenic hemorrhaging in an effort to reduce bleeding-associated mortality in patients with acute leukemia.[10] Since then, platelet transfusions have been predominantly used in hemato-oncologic patients in the context of bone marrow transplantation and chemotherapy.

Thrombocytopenia and severe active bleeding are widely accepted indications for therapeutic platelet transfusion (World Health Organization [WHO] grades 2 to 4) (Table 23-1). However, because of the increasing number of complex surgeries and the widespread application of platelet inhibitors today, a large percentage of platelet transfusions are used in the treatment of surgical and intensive care unit (ICU) patients, especially in the settings of cardiac and vascular surgery, postpartum hemorrhaging, and liver transplantation.

TABLE 23-1 **World Health Organization Bleeding Scale***

Bleeding Grade	Description of Bleeding
0	None
1	Petechial
2	Mild blood loss (no RBC transfusion required)
3	Gross blood loss (RBC transfusion required)
4	Debilitating blood loss

RBC, red blood cell.
*A minor hemorrhage is defined as a score of 1. A major hemorrhage is defined as a score of 2 or greater.

Nonetheless, platelet transfusions, in addition to their hemostatic function, can cause severe and potentially fatal adverse reactions such as transfusion reactions, thrombosis, inflammatory reactions, alloimmunization, refractoriness, and transfusion-related acute lung injury (TRALI).[11,12] Because of these well-known adverse side effects, the concept of prophylactic transfusion based on the patient's disease and the perceived bleeding risk should be challenged because it may put the patient at unnecessary risk and may do more harm.[13] Therefore transfusion therapy should be restricted to patients with relevant bleeding problems.

The effectiveness of platelet preparations and FFP (i.e., plasma fractionation products) should be discussed in the context of a cell–cell surface–based model of coagulation. A dynamic balance exists between a cascade of activated proenzymes and factors influencing platelets' procoagulatory and endothelial anticoagulatory functions. This balance might be challenged by underlying disease, concomitant medications, blood exposure to foreign surfaces (e.g., plastic tubing of cardiopulmonary bypass), and surgical stress. In addition, it has been demonstrated that storage significantly reduces platelets' ability to respond adequately, leading to a loss of their hemostatic potential.[14]

Monitoring

In general, immediate therapeutic interventions in hemostasis have to be performed without accurate laboratory tools. Standard laboratory tests such as platelet count, prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen level represent only a small part of the entire coagulation process and, as such, are not able to reflect the rather complex interrelationships in hemostasis in vivo. Conventional coagulation tests by themselves do not convey any information about clot stability over time, nor do these tests give any information about fibrinolysis. Therefore these tests must be regarded as poor predictors of bleeding complications and, consequently, are only of limited use in the detection and monitoring of perioperative coagulation disorders[15];

however, a combination of aggregometric and viscoelastic methods may yield a broader diagnostic spectrum. In addition, point-of-care (POC) techniques are a valuable means of testing various aspects of hemostasis rapidly and can, at least partly, compensate for the methodologic limitations and diagnostic shortfalls of conventional coagulation testing.[16] However, no single POC technique can provide adequate information about all aspects of the complex process of blood clotting (i.e., primary hemostasis, thrombin generation, clot formation/stabilization, and fibrinolysis).

Significant improvements in rotational thromboelastometric-measured variables were observed after platelet transfusion.[17,18] This supports the evidence that platelets are, indeed, functional immediately after transfusion. In addition, in other studies comparing conventional techniques of determining platelet function such as bleeding time or light transmission aggregometry with three POC devices (i.e., Multiplate, Platelet Function Analyzer-100, and VerifyNow), the treatment effects of aspirin or clopidogrel were reliably assessed; it was found that VerifyNow had the highest effect size when the effects of aspirin were studied, and Multiplate showed the highest effect size when clopidogrel was compared with placebo.[19,20] In the clinical setting, the implementation of hemostatic treatment algorithms with viscoelastic tests (thrombelastograms) reduced both the rate of transfusion of allogeneic blood products and the total cost of treatment for blood loss and coagulopathies in the majority of studies.[21-24] However, whether POC testing is beneficial as a diagnostic tool for reducing perioperative morbidity and mortality has not been able to be demonstrated as of yet.[25,26]

Platelet Transfusion

It is undisputed that patients with severe thrombocytopenia are at an increased risk of developing bleeding complications. Prevention and elimination of bleeding are therefore the main indications for platelet transfusion given either prophylactically to reduce the risk of bleeding or at the time when bleeding is actually occurring to stop the bleeding. Nevertheless, the optimal use of platelet transfusion remains unclear. Therefore severe thrombocytopenia in connection with clinically relevant bleeding is currently the only confirmed indication for transfusion of platelets; platelet counts are not a confirmed indication. All other indications should be considered relative indications that depend on the clinical circumstances of the individual patient.[2,27] Furthermore, platelet function is dependent on storage time, the preparation method, and the patient's underlying disease and comorbidities.[14,28-32]

Variability and Overuse

Platelet transfusions and the use of FFP are only one factor in the prevention and treatment of perisurgical bleedings and major blood loss.[33] Because no reliable cutoff values or guidelines are available, the variability between clinical centers in the number of platelets administered and in the percentage of patients transfused is significant.[28,34-37] This significant variability has a geographic dependency, differs by the academic status and size of the hospital, and cannot be explained solely by medical reasons.[36] It is a clinically well-accepted assumption that inadequate transfusion is associated with poor outcomes, but overtransfusion exposes the recipient to unnecessary risks such as sepsis, transfusion overloading, and infusion of variable amounts of some biologic response modifiers (BRMs). Because of the lack of demonstrated benefit and the limited availability of transfusion products due to demographic ageing and increased economic burden, the widespread overuse of platelet and plasma preparations must be stopped. In addition, the risk–benefit ratio of platelet and plasma transfusions should be re-evaluated on the basis of reliable facts so that donors and recipients are protected.

Risks of Platelet Transfusion

Platelet Transfusion Reaction

Reactions after transfusion of platelets, such as febrile nonhemolytic reactions, allergic reactions, transfusion-associated sepsis, or TRALI, are more frequently observed than transfusion reactions after transfusion with red blood cells and vary with storage time (bacteremia), leukodepletion, ABO matching, and the amount of supernatant depletion after storage.[38-42] Bacterial sepsis associated with platelet transfusion today is the most frequent infectious complication (1:2000 to 1:3000) encountered in transfusion medicine and carries a mortality risk of 1:20,000 to 1:85,000.[43,44] Storage of platelet products induces time-dependent changes in the product and the accumulation of biologically active, supernatant-soluble mediators and microparticles.[42] It is hypothesized that these mediators play a direct role in the inflammatory and prothrombotic properties of platelet transfusions. In addition to other mechanisms, platelet are also recognized as the main source of circulating soluble CD40 (sCD40) ligands, which are part of the tumor necrosis factor family of cytokines.[13,45,46] Platelet-derived sCD40 ligands not only play a significant role in the coagulation system but also are involved in the activation of neutrophils, which is one of the mechanisms of development of TRALI, the leading cause of transfusion-related fatalities (two-hit TRALI model).[11,47]

Febrile nonhemolytic reactions are most common, and prestorage leukoreduction alone does not completely prevent febrile nonhemolytic reactions. Prestorage leukodepletion reduces the risk to 14% or even to 1% when platelet transfusions are ABO identical.[48-50] Still, high concentrations of leukocyte- and platelet-derived bioactive substances can be found in stored platelet concentrates; thus a further reduction of nonfebrile nonhemolytic reactions to less than 1% can be achieved by washing with saline.[51-53] Because platelet washing significantly increases platelet activation and decreases platelet aggregability,[28,54-56] washed platelets should be reserved for patients with a history of severe allergic or anaphylactic transfusion reactions.[28]

Platelet Transfusion

Alloimmunization and Refractoriness. Platelet refractoriness is defined as a corrected count increment (CCI) of less than 7500 within 1 hour and less than 4500 within 20 hours after two transfusions of ABO-compatible fresh platelet concentrates (less than 3 days).[57,58]

$$\text{CCI} = [(\text{Post-transfusion count}) - (\text{pretransfusion count}) \times \text{body surface area in } m^2]/\text{number of platelets transfused (in } 10^{11})$$

The CCI should be greater than 7500 at 1 hour and greater than 4500 at 20 to 24 hours.

The reason for platelet refractoriness remains unclear but, in most cases, is thought to be due to nonimmunologic causes such as increased number of transfusions or septicemia or even HLA and HPA antibodies.[59] This is supported by the finding that ABO identical recipients showed significantly lower refractory rates than recipients of ABO-incompatible transfusions.[60] Therefore fresh ABO-compatible leukoreduced products are recommended in patients with WHO bleeding grade 3 to 4 when increasing the dose of platelets is found to be insufficient.[27,61,62]

Multiple randomized studies have also demonstrated that leukodepletion is beneficial by reducing alloimmunization to HLA antigens after platelet transfusion.[63] In the case of existing HLA or HPA antibodies, only compatible platelet products should be used.[64-66] In addition, transfusion of cross-matched compatible platelets may improve count increments in patients with refractoriness,[67,68] but concomitant use of steroids or intravenous IgG is not recommended.[69,70] In the event of uncontrolled hemorrhaging, a massive transfusion of platelets may be effective in select thrombocytopenic patients who are refractory to all types of available donor platelets because of severe and complex alloimmunization.[71]

Platelet Transfusion and Thrombosis

Platelet transfusions are associated with both an increased rate of venous and arterial thromboembolism and a higher risk of death during hospital stay.[72-74] This observation might be caused by higher levels of platelet-derived microparticles and increased levels of sCD40 ligands in stored platelets.[75]

Prophylactic Platelet Transfusion

In the nonsurgical setting, platelets are administered prophylactically to thrombocytopenic patients with hemato-oncologic diseases and hypoproliferative bone marrow as a consequence of bone marrow infiltration, chemotherapy, or irradiation. Chronic thrombocytopenia (≤5000/mcL) and hemorrhage grade 3 to 4 on the WHO bleeding scale[76] are still (comprehensive) recommendations for *prophylactic* platelet transfusions.[27,57,77-79] For WHO grades 1 and 2 bleeding, platelets are not indicated.[27] If additional risk factors exist, such as concomitant plasmatic coagulation defects, leukocytosis, infections, fever (>38° C), extensive tissue necrosis, concomitant platelet-inhibiting drugs, or a rapid decrease in the number of platelets, the trigger for prophylactic platelet transfusion may increase to ≤10,000/mcL when products are immediately availability or even to ≤20,000/mcL. With minimal adaptations (e.g., prophylactic platelet dose [PLADO] and strategies for the transfusion of platelets [SToP]), these recommendations have been followed because no evidence suggests a change in the current practice of using a platelet count of 10×10^9/L as the trigger value.[27,80-83] On the other hand, there is no clear evidence that either the prophylactic platelet transfusion policy or the number of platelets in the prophylactic transfusion prevents bleeding.[83-85]

In the perioperative setting, prophylactic platelet transfusions in thrombocytopenic patients are also frequently used to prevent bleeding complications in patients undergoing invasive diagnostic or surgical procedures (Table 23-2). The overall risk depends on the bleeding risk of the individual patient, the procedure planned, and, possibly, on the individual consequences if bleeding occurs.

For the perioperative setting, it is noteworthy that consensus agreements are published but no randomized studies are available.[86,87] It is generally accepted that the standard hemorrhagic risk threshold for invasive procedures (allowing for small modifications) is 50,000/mcL in patients with no platelet dysfunction and plasmatic coagulation abnormalities, regardless of the type of surgery.[87]

Perioperatively, the bleeding tendency is not increased in patients with normal platelet function and at a platelet count of more than 50,000/mcL; thus transfusion of platelets is unnecessary. Procedures with a low risk of bleeding can also be performed when platelet counts are in the range of 20,000/mcL to 50,000/mcL. Preoperative transfusion of platelets is only indicated in patients with platelet counts less than 20,000/mcL or in patients with a history of bleeding. However, the platelet count should be measured in close intervals. In procedures with high bleeding risk like neurologic and ophthalmologic surgery involving the posterior segment of the eye, the platelet count should be 70,000/mcL to 100,000/mcL or more. For epidural anesthesia and spinal anesthesia,

TABLE 23-2 **Recommended Lowest Platelet Count for Diagnostic Procedures**

	Platelet Count
Lumbar (spinal) puncture	>50,000/mcL
Transcutaneous liver biopsy	>50,000/mcL
Gastrointestinal endoscopy without biopsy	>20,000/mcL
Gastrointestinal endoscopy with biopsy	>50,000/mcL
Bronchoscopy/lavage	>20,000/mcL
Bronchoscopy/biopsy	>50,000/mcL
Biopsy of different organs	>50,000/mcL
Angiography	>20,000/mcL
Joint puncture	>20,000/mcL

From Ak K, Isbir CS, Tetik S, Atalan N, Tekeli A, Aljodi M, et al. Thromboelastography-based transfusion algorithm reduces blood product use after elective CABG: a prospective randomized study. J Card Surg 2009;24(4):404–10.

80,000/mcL or greater and 50,000/mcL or greater, respectively, are regarded as sufficient.

Therapeutic Platelet Transfusion

Severe and life-threatening hemorrhage is a clear risk when the platelet count drops below 5000/mcL. Between 5000/mcL and 10,000/mcL, the risk of spontaneous hemorrhage is increased, and at platelet counts between 10,000/mcL and 50,000/mcL, the risk of hemorrhage during hemostatic challenge is increased.[88,89] The critical threshold for hemostasis is 50,000/mcL, and higher platelet counts are recommended only for patients with multiple trauma injuries or lesions involving the central nervous system.[26] A surgical patient with active, nonsurgical bleeding rarely requires a platelet count greater than 100,000/mcL. Typical indications for platelet transfusion are as follows: microvascular bleeding with a platelet count less than 100,000/mcL (less than 150,000/mcL if undergoing cardiac bypass or extracorporeal membrane oxygenation) and no other explanation available, major surgery or trauma with a platelet count less than 80,000 to 100,000/mcL, major hemorrhage (e.g., gastrointestinal or genitourinary) with a platelet count less than 30,000 to 50,000/mcL, and bleeding into critical areas (e.g., central nervous system or diffuse alveolar hemorrhage) with a platelet count less than 100,000/mcL. In acute disseminated intravascular coagulation, if, after treatment of the underlying disease and restoration of clotting factors to normal levels, patients still have considerable hemorrhaging and thrombocytopenia, platelet transfusion may be indicated. In congenital or acquired disorders of platelet function, autoimmune thrombocytopenia, and post-transfusion purpura, therapeutic platelet transfusions are only indicated in the case of dangerous hemorrhaging.[26,80,90]

Massive transfusions carry a significant mortality rate (40%), which increases with the number of volume expanders and blood components transfused. Controversies still exist over the optimal ratio of blood components with respect to overall clinical outcomes and complications. Early trauma-induced coagulopathy is a predictor for a reduced trauma survival rate and is present in about 20% of patients on hospital admission.[91] Further studies are required to optimize the care of these patients, but pathophysiologic theories and clinical experiences justify the early use of platelets and plasma in a massive transfusion protocol using blood component ratios of erythrocytes : platelets : plasma of 1 : 1 : 1 even before the availability of the results of coagulation assays.[42,92-97] The therapeutic efficiency of platelet transfusions can be monitored by the increment or CCI, or simply by the effect on WHO bleeding signs.

Platelet Transfusion for Reversing Drug Effects

Requests for urgent reversal of anticoagulants are not uncommon, especially in the setting of critical bleeding.[98] Currently, no randomized clinical trials in platelet transfusion therapy have studied the treatment of antiplatelet bleeding caused by platelet-inhibiting medications. Only an in vitro study has shown an effect of adding normal donor platelets to drug-affected platelets.[99] With the introduction of new more powerful antiplatelet agents such as prasugrel and ticagrelor, the risk of perioperative bleeding has increased dramatically. Furthermore, an accurate and standardized method of predicting antiplatelet drug efficacy has not yet been determined, and significant interindividual variance has been shown.[100]

The challenge is to optimize the timing of surgery to minimize the risk of ischemic events before surgery and reduce both incidence rates and consequences of serious surgical bleeding. This emphasizes the importance of developing strategies for the optimization of patient management for those who are candidates for elective surgery and who have received antiplatelet therapy.[101,102] These strategies should be developed in close cooperation with the responsible specialties and include, but are not limited to, optimized coronary intervention (i.e., bare-metal stent implantation instead of drug-eluting stents, coronary artery balloon dilation preoperatively, and stent implantation after surgery), timely discontinuation of the drugs whenever possible, and bridging with shorter acting antiplatelet drugs.[103-106] Patients taking antiplatelet agents who are seen with serious bleeding or who require urgent surgical interventions may require immediate reversal of these agents' effect on platelets. However, no specific antagonists are available, and platelet transfusion therapy may be the only option to reverse the effect of antiplatelet agents; however, retrospective studies were not able to demonstrate any benefit on outcome when compared with patients who did not receive platelet transfusions.[107,108]

Desmopressin stimulates the release of stored von Willebrand factor (vWF) from the endothelium, thereby indirectly improving platelet function. As such, desmopressin might be used as an alternative to platelet transfusion and has been shown to be effective, especially in patients with uremia and in patients undergoing cardiac surgery.[109-111]

Fresh-Frozen Plasma

Despite a lack of high-quality evidence in hospital practice, there is a significant (over)use of FFP in a wide range of clinical specialties.[2,112-114] FFP is so abundantly and frequently administered as a blood component that undertransfusion may be as common as overtransfusion.[36,115,116] For example, only 37% of physicians correctly responded to basic questions about FFP, and an audit on transfusion practices suggested that approximately 50% of all FFP transfused to critical care patients is inappropriate.[117,118] On the other hand, a lack of well-conducted clinical trials determining the appropriate indications for FFP[12,83,116,119-125] has caused extensive variability in the use of FFP.[36,117,124]

The primary indication for FFP is in the treatment and prevention of bleeding in patients with prolonged coagulation tests,[36,119] and justified FFP transfusions can be lifesaving in severely bleeding patients. However, the benefit of FFP transfusions in other indications, in the ICU setting, and when used prophylactically is unclear.[120]

Risk of Fresh-Frozen Plasma

Because of extensive screening and pathogen inactivation, virus transmission rates from transfusions have been tremendously decreased: HIV transmission has decreased to 1 : 7.8 million units transfused, hepatitis C to 1 : 2.3 million units transfused, and hepatitis B virus to 1 : 153,000 units transfused.[5] To date, the clinically most significant complications are TRALI and transfusion-associated circulatory overload (TACO). TRALI is the most common cause of transfusion-related death.[126,127] HLAs and antineutrophil antibodies are commonly found in plasma from multiparous female donors, and the TRALI frequency is higher in recipients of female donor blood.[128-130] FFP from female donors carries a significantly higher risk than FFP from male donors.[131] To minimize the risk of TRALI, a male-donor only policy has been adopted in many countries and has resulted in marked reductions in TRALI.[130] Another potential mechanism involves interactions of biologically active mediators in stored plasma and lung endothelial cells.[47] TACO was the second most common cause of transfusion-related mortality reported to the Food and Drug Administration in 2010, whereby the volume of transfused plasma and the rate of transfusion were identified as transfusion-specific risk factors.[43,132] Other important transfusion-related complications include acute hemolytic reaction from anti-A and anti-B antibodies and anaphylaxis. In critically injured patients, the transfusion of FFP has been associated with increased postinjury multiple organ failure after adjusting for age, Injury Severity Score, and red cell transfusion.[133,134]

Fresh-Frozen Plasma Transfusion

In the clinical routine, FFP transfusion is most often used when a patient has abnormal tests results, either as therapy in the face of bleeding or in nonbleeding patients as prophylaxis before invasive procedures or surgery. However, FFP transfusions are very seldom indicated. Laboratory abnormalities of coagulation are considered to predict bleeding before invasive procedures, and FFP is presumed to improve the laboratory results so that this risk is reduced. However, the majority of indications according to currents guidelines for the prophylactic use of FFP are not supported by evidence from high-quality randomized clinical studies. In fact, the strongest evidence available from a randomized controlled study indicates that prophylactic plasma transfusion is not effective in a wide range of clinical settings.[85] This is supported by data from nonrandomized studies in patients with mild to moderate abnormalities in coagulation tests.[2,114,135]

The following indications for plasma transfusion are reported in the literature[2,3]:

- Correction of a congenital clotting factor defect in the absence of specific coagulation factor concentrates
- Plasma exchange therapy of thrombotic thrombocytopenic purpura, hemolytic–uremic syndrome, hemolytic anemia, elevated liver enzymes, and low platelet syndrome (syndrome of hemolysis, elevated liver enzymes, and low platelets [HELLP])
- Acquired deficiencies of multiple clotting factors under the following circumstances:

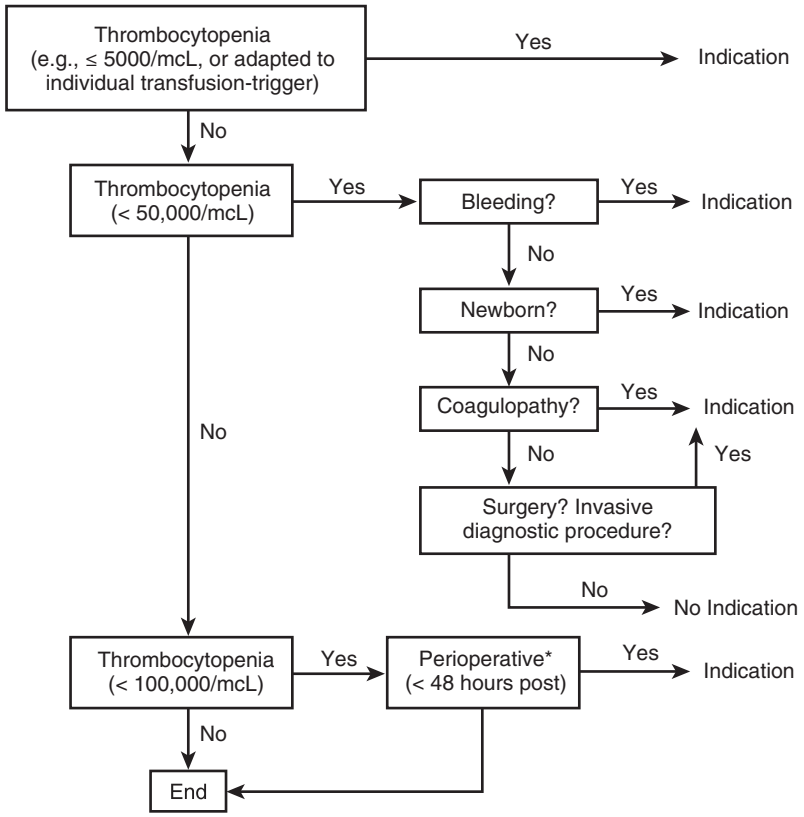

FIGURE 23-1 ■ Treatment with Platelet Transfusions. *For surgery on parenchymatous organs, inclusive eye surgery, and bleeding after surgery.

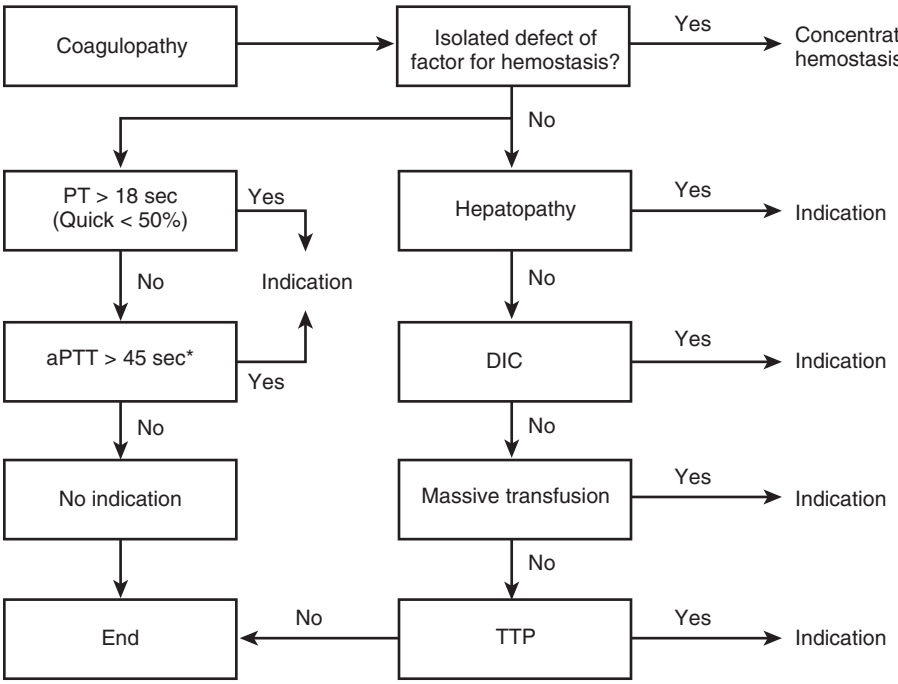

FIGURE 23-2 ■ Treatment with Fresh-Frozen Plasma. *aPTT,* activated partial thromboplastin time; *DIC,* disseminated intravascular coagulation; *PT,* prothrombin time; *TTP,* thrombotic thrombocytopenic purpura. *1.5 times the normal: diagnostic reagents dependent.

- Massive transfusion in patients with microvascular bleeding
- Bleeding greater than WHO grade 2 and invasive procedures in patients with clinically relevant liver disease
- Patients with acute disseminated intravascular coagulation *and* active bleeding in combination with the treatment of the underlying disease

The recommended therapeutic dose of FFP is 10 to 15 mL/kg body weight, but very often the clinical situation and laboratory variables would require even higher doses that cannot be administered because of the volume load.

AREAS OF UNCERTAINTY

Controversy is ongoing regarding the optimal platelet dose for transfusion, the use of platelet additive solution, and the transfusion of platelets from RhD-positive donors to RhD-negative recipients.[136]

GUIDELINES

A number of consensus statements and guidelines have been published on the use of platelets and FFP and are discussed within the evidence section. Importantly, even those publications entitled *Guidelines* are based on consensus.

AUTHORS' RECOMMENDATIONS

The authors' recommendations are incorporated into Figures 23-1 and 23-2.

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CHAPTER 24

What Drugs Decrease Perioperative Bleeding?

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INTRODUCTION

Perioperative blood loss is a common problem faced by anesthesiologists and surgeons. There is no substitute for proper surgical technique, but anesthesiologists have several ways in which they can help decrease perioperative bleeding and/or avoid transfusion of blood products. Indeed, a multidisciplinary approach to blood conservation is the most likely to succeed.[1] Not only is this beneficial for the individual patient, but allogeneic blood products are a limited and costly resource. In addition, some patients refuse blood transfusion for religious reasons (e.g., Jehovah's Witnesses) or personal preference.

The infectious risks of blood transfusion are well-documented and likely result in patients' desire to avoid transfusion. Thanks to improved donor screening, the risk of transmission of common viral illnesses, such as human immunodeficiency virus (HIV), hepatitis B, and hepatitis C, has been reduced considerably; however, it has not yet been eliminated. Donors are not routinely screened for less common or less transmissible viruses, such as hepatitis A, parvovirus B19, or Dengue fever.[2] Currently, no suitable test is available for prion-based diseases, such as Creutzfeldt-Jakob disease, although this remains quite rare: only four documented cases have been related to transfusion.[3] Bacterial contamination of platelets, which must be stored at room temperature, is always a concern. Of course, the risk will always remain for transmission of infectious agents unknown at the time. The blood supply may not be as safe in countries where screening is not as rigorous (Table 24-1).

Far more common and less frequently recognized are the noninfectious serious hazards of transfusion (NISHOTs).[4] Errors in transfusion, which include wrong product, wrong patient, or both remain the most common complication of blood transfusion. Transfusion-related acute lung injury (TRALI) was the leading cause of transfusion-related mortality in 2006. Plasma containing anti-HLA and anti-neutrophil antibodies, most frequently from multiparous female donors, are thought to be the primary cause of TRALI. As such, these donors have been excluded from the plasma donor pool in the United States, which is expected to significantly lower the incidence of TRALI. Transfusion-associated circulatory overload (TACO) manifests as hydrostatic pulmonary edema that may be difficult to differentiate from TRALI.[5]

Immunomodulation is a frequently ignored risk of transfusion, even though it may be one of the most important. It has been associated with nosocomial infections, organ failure, and even death in a dose-dependent fashion. The effect is thought to be related to transfused donor leukocytes, which suggests that leukoreduction may limit the impact.[2,6]

OPTIONS

Antifibrinolytic Drugs

Antifibrinolytic drugs have been studied extensively for use in cardiac surgery as well as in several other surgical populations that are at risk of bleeding. Epsilon aminocaproic acid (EACA) and tranexamic acid (TXA) are synthetic lysine analogs that bind competitively to plasmin and plasminogen, preventing their binding to and breakdown of fibrin (Figure 24-1). Both of these drugs undergo renal excretion and concentration, requiring dose adjustment for patients with renal insufficiency. TXA is 10 times more potent than EACA in terms of affinity for the lysine binding site.

Aprotinin is a nonspecific serine protease inhibitor derived from bovine lung. It acts at several proteases, including plasmin, kallikrein, trypsin, and factor XII (see Figure 24-1). Compared with the lysine analogs, aprotinin not only inhibits fibrinolysis but also complement activation and contact activation of both coagulation and inflammation. In addition, aprotinin also preserves platelet function after cardiopulmonary bypass.[7] There is a small risk of anaphylaxis, especially with repeated exposure. It should be noted that aprotinin artificially prolongs celite-based activated clotting time (ACT) measurements; therefore a kaolin ACT test should be used. Dosing is based on kallikrein-inhibiting units (KIU). Aprotinin was withdrawn from the U.S. market in 2008 after Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART)[8] showed an increase in the mortality rate compared with the lysine analogs (see further on).

Desmopressin

Desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) is a synthetic analog of the hormone arginine vasopressin, also known as antidiuretic hormone (ADH). It is Food and Drug Administration (FDA)-approved for

the treatment of hemophilia A (when factor VIII activity is greater than 5%), von Willebrand disease type 1, and diabetes insipidus. It has also been used off-label to treat other forms of platelet dysfunction (e.g., uremia-induced or postcardiopulmonary bypass) because of its ability to release endogenous stores of factor VIII, von Willebrand factor (vWF), and plasminogen activator, which in turn enhance platelet function. Effects are seen within 30 minutes of intravenous (IV) administration. Contraindications include moderate to severe renal insufficiency and hyponatremia. In the perioperative setting, transient hypotension due to decreased systemic vascular resistance is the most common side effect, although this is mitigated by slow infusion.

TABLE 24-1 **Commonly Cited Risks of Transfusion**

Infectious	Noninfectious
Human immunodeficiency virus	Hemolytic
Hepatitis B virus	Transfusion-related acute lung injury
Hepatitis C virus	Transfusion-associated circulatory overload
Human T-cell lymphotropic virus	Allergic reactions
West Nile virus	Febrile reactions
Cytomegalovirus	Graft-versus-host disease
Creutzfeldt-Jakob disease	Iron overload
Bacterial (platelets)	Immunomodulation

Protamine

Protamine is a strongly basic polypeptide used in the reversal of unfractionated heparin. It binds to the highly acidic heparin molecules to form a stable salt that lacks anticoagulant properties. However, protamine by itself is a weak anticoagulant, with effects on factor V, platelets, and fibrinolysis.[9-17] Inadequate or excess doses can both lead to excess bleeding. It is not effective for reversal of low-molecular-weight heparin.[18] Reactions may include histamine release and anaphylactic, anaphylactoid, and pulmonary vasoconstriction. Slow administration can help prevent some of these reactions. Treatment of a protamine reaction is supportive.

Vitamin K

Warfarin works by inhibiting the vitamin K-dependent gamma-carboxylation of factors II, VII, IX, and X, as well as proteins C and S. As such, warfarin can be reversed by the administration of vitamin K, and effects are seen in 4 to 6 hours if given intravenously. Oral administration requires up to 24 hours for full effect.[19] If more urgent reversal is necessary, fresh-frozen plasma (FFP) or prothrombin complex concentrates (PCCs) should be used (see next section), but vitamin K should still be administered because of the short half-life of exogenous factors. The American College of Chest Physicians recommends the addition of 5 to 10 mg IV vitamin K be given in addition to plasma transfusion for rapid reversal.[20] Concerns over anaphylaxis have led many to avoid IV use of vitamin K, but these reactions are quite rare,[21,22] and IV administration should not be avoided if urgent reversal is needed.

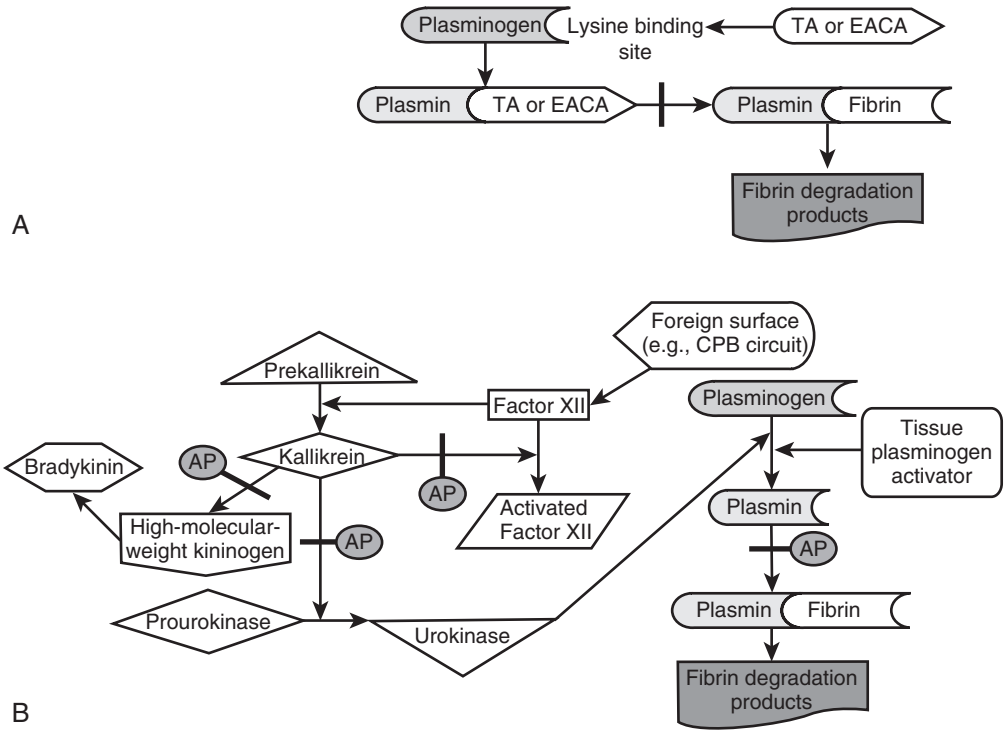

FIGURE 24-1 ■ Mechanisms of Antifibrinolytic Drugs. **A,** Fibrinolysis inhibited by binding of tranexamic acid *(TA)* or epsilon aminocaproic acid *(EACA).* **B,** Aprotinin *(AP)* inhibits fibrinolysis by inhibiting both kallikrein and plasmin. *CPB,* cardiopulmonary bypass.

Prothrombin Complex Concentrates

PCCs are isolated from pooled human plasma and contain varying amounts of the vitamin K-dependent clotting factors. They may also contain varying amounts of proteins C and S, antithrombin, and heparin. PCCs can be divided into two groups based on whether they contain significant amounts of factor VII. Those that do not are considered 3-factor PCCs, whereas those that do are 4-factor. In the United States, 3-factor PCCs are approved for the treatment of bleeding in patients with hemophilia B, and 4-factor PCCs are currently not approved at all. Recombinant factor IX products are available and are the mainstay of treatment for hemophilia B, leaving PCCs to be used off-label as an alternative to FFP. Compared with FFP, the theoretical advantages of PCCs include immediate availability without thawing, small volume of administration, rapid administration, and viral inactivation. Disadvantages include the potential for thromboembolic events, exposure to multiple donors, and cost. In addition, FFP contains more than just the specific factors found in PCCs (e.g., fibrinogen). PCCs are labeled based on their factor IX content, which can lead to confusion with purified factor IX products that do not contain any other factors.[23]

Recombinant Activated Factor VII

Recombinant activated factor VII (rFVIIa) is FDA approved for the treatment of bleeding in congenital factor VII deficiency and in hemophilia patients with inhibitors to factor VIII or IX. It has been used off-label in a variety of scenarios, including trauma, intracranial hemorrhage, surgery, and reversal of anticoagulation.[24,25] The mechanism of action is related to its ability to complex with tissue factor, allowing it to activate factors X and IX, which in turn complex with other factors to convert prothrombin to thrombin. It should be noted that rFVIIa is a relatively expensive drug, costing approximately $10,000 for a typical adult dose (Table 24-2).[25]

TABLE 24-2 **Adult Dosage Ranges in Studies**

Agent	Loading Dose	Infusion
Epsilon aminocaproic acid	80 mg to 15 g	1-2 g/hr
Tranexamic acid	2.5 mg to 100 mg/kg over 20-30 min	0.25-4 mg/kg/hr
Aprotinin (high-dose or full Hammersmith regimen)	2 million KIU (280 mg) over 20-30 min at induction with the same dose added to the CPB prime	500,000 KIU/hr (70 mg/hr)
Aprotinin (low-dose or half Hammersmith regimen)	1 million KIU (140 mg) over 20-30 min at induction with the same dose added to the CPB circuit prime	250,000 KIU/hr (35 mg/hr)
Desmopressin	0.3 μg/kg over 30 min	
Protamine	1.0-1.3 mg per 100 units circulating heparin	
Vitamin K	5-10 mg IV	
Prothrombin complex concentrate	25-50 IU/kg	
Recombinant factor VIIa	9-120 μg/kg	

CPB, cardiopulmonary bypass circuit; *KIU,* kallikrein-inhibiting units.

EVIDENCE

Approximately 50% of cardiac surgical patients require a transfusion. As a group they consume 10% to 20% of packed red blood cell units and 50% of the platelet units transfused each year in the United States. Within this group, there is a subgroup of 10% to 20% of patients that use 80% of the blood products.[26,27] It is therefore no surprise that much of the blood conservation literature has focused on this group of patients. Outcomes have mostly focused on blood loss, transfusion rates, thromboembolic complications, and mortality.

Antifibrinolytic Drugs

The landmark study BART was the first large-scale trial (n = 2331) to compare aprotinin with the lysine analogs in a head-to-head fashion.[8] It focused on patients at high-risk of bleeding, which is the population in which aprotinin was thought to be most beneficial. The trial was stopped early because of a strong trend toward a higher mortality rate in the aprotinin group—an absolute risk increase of 2.1% and a relative risk increase of 54% compared with the lysine analogs. The investigators noted a statistically significant increase in postoperative creatinine levels but only a trend toward an increased need for renal replacement therapy that did not reach statistical significance. On the basis of these data, aprotinin was withdrawn from the market in 2008. BART confirmed what had been reported in other observational studies.[28-32]

The Cochrane Collaboration recently updated their meta-analysis of antifibrinolytic drugs.[33] They evaluated 252 trials, of which 173 involved cardiac surgery. Compared with placebo, aprotinin reduced the relative rate of blood transfusion by 32%, reduced the intraoperative blood loss by 148 mL, reduced the postoperative blood loss by 370 mL, and reduced the relative risk of reoperation for bleeding by 54%. There was no statistically significant increase in mortality rates, myocardial infarction, stroke, deep venous thrombosis, or pulmonary embolus. There was a trend toward an increased risk of renal dysfunction, but this was not statistically significant.

This meta-analysis also evaluated aprotinin compared with TXA and EACA. Aprotinin was more effective at reducing postoperative blood loss, the rate of transfusion, and the need for reoperation for bleeding. There was again no statistically significant difference in myocardial infarction, stroke, and renal failure. The investigators did, however, note an increase in the mortality rate, similar to BART. Of course, the meta-analysis itself was

heavily influenced by BART itself because it was the largest in this field.

Although TXA is 10 times more potent than EACA, it was not more effective when compared head-to-head.[34-36] The previously mentioned meta-analysis also came to the conclusion that there was no significant difference in efficacy between the lysine analogs, although investigators did note that there were significantly more data available for TXA.[33] EACA is considerably less costly than TXA in the United States,[35] although this may not be the case in other countries.[37] Accordingly, a recent survey showed that EACA is used at most institutions in the United States, whereas TXA is the drug of choice in Canada.[38]

The coagulopathy of traumatic injury is complex and multifactorial, but hyperfibrinolysis appears to play a key role.[39] The highly publicized Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial compared the use of TXA with placebo in 20,211 trauma patients with (or at risk of) significant bleeding.[40] The all-cause mortality rate was reduced by 9% (from 16% to 14.5%), and deaths due to bleeding were reduced by 15% (from 5.7% to 4.9%) without any increase in thrombotic events. Interestingly, no significant reduction in transfusion rate was found, which leaves the protective mechanism of TXA unclear. Further analysis showed that the results after early administration (within 3 hours) were even more impressive, but late administration was actually harmful.[41] Although the relative risk reduction is more impressive than the absolute risk reduction, it is important to keep in mind that TXA was one of the few interventions found to be useful in a recent systematic review of the management of hemorrhage in trauma.[42]

Liver transplantation has been associated with a high risk of blood loss and transfusion, and worse outcomes are reported in patients receiving allogenic blood transfusions.[43-45] The effects of liver failure on the coagulation system are complex in that a delicate balance exists between hypercoaguability and hypocoaguability that may vary from patient to patient.[46] Hyperfibrinolysis during reperfusion of the new graft has long been recognized as a problem, prompting several trials of antifibrinolytic therapy.[47] A 2011 meta-analysis included eight trials with aprotinin, five with TXA, and one with EACA.[48] In general, the trend was toward a reduction in blood loss that did not reach statistical significance. However, only aprotinin demonstrated a statistically significant reduction in the number of products transfused to each patient. Although there are concerns that antifibrinolytics may tip the balance toward a hypercoaguable state, no differences were seen in mortality rates, graft failure, or thromboembolic events. A retrospective study specifically found a trend toward increased arterial and venous thrombosis when aprotinin was used, but it did not reach statistical significance.[49]

Limited data suggest that antifibrinolytics are useful for reducing blood loss and transfusion requirements in hepatic resection, and morbidity and mortality rates are not increased.[50]

Among orthopedic procedures, total joint replacement and spine surgery are associated with the most blood loss. Two recent meta-analyses looked at the use of TXA in total hip and knee replacement surgery, respectively.[51,52] Both showed that TXA was effective in reducing blood loss and transfusion requirements, without an increased risk of thromboembolic events. In total hip replacement, total blood loss was reduced by an average of 289 mL, and the transfusion rate was reduced by 20%.[51] The effects were even more profound in total knee replacement: the reduction in total blood loss was 591 mL, and the transfusion rate was reduced by 39%.[52] These effects seemed to be dose-dependent, but there are insufficient data to draw firm conclusions. The results are similar for aprotinin and EACA, but the data for EACA are limited; only three trials were included in a general meta-analysis of antifibrinolytic drugs.[33] Use in spine surgery has also been successful, although the data are not as robust as in total joint replacement.[33,53,54]

Postpartum hemorrhage (PPH) is a leading cause of maternal death in obstetrics. Management has generally focused on uterotonic drugs, such as oxytocin, prostaglandins, and ergometrine.[55] TXA has been used when these drugs are insufficient since at least 1996.[56] A meta-analysis of three randomized trials showed that prophylactic use of TXA reduced the incidence of PPH by 56%.[57] More recently, a randomized trial evaluated the use of TXA after PPH was diagnosed.[58] The median blood loss was reduced by 173 mL, the duration and severity of bleeding were reduced, and fewer transfusions were required. The reduction in transfusions included hemostatic products, such as FFP, platelets, and cryoprecipitate. This study was not powered to evaluate safety, but no major adverse events occurred.

The use of antifibrinolytics in pediatric surgery remains somewhat controversial because of limited data and variable dosing of the drugs. A 2009 meta-analysis[59] included 23 trials in cardiac surgery and five trials in scoliosis surgery. In cardiac surgery, TXA reduced blood loss by an average of 11 mL/kg compared with placebo, but no conclusion could be made for EACA and aprotinin because of the heterogeneous nature of the data. Aprotinin reduced the volume of red blood cell transfusion by 4 mL/kg compared with 7 mL/kg for TXA. Similar reductions were seen for FFP. In scoliosis surgery, blood loss was reduced by an average of 385 mL by aprotinin and 682 mL by TXA. TXA also reduced the volume of red blood cell transfusion by 349 mL. A systemic review from 2008[60] that focused on pediatric heart surgery noted that patient populations and dosing regimens were highly variable between studies, which made comparisons difficult. The authors concluded that the benefit was likely highest in high-risk patients, such as those with cyanosis and those undergoing complex or revision surgery. Recently, TXA has also been shown to be effective in craniosynostosis surgery.[61]

Desmopressin

Interest in the use of DDAVP in cardiac surgery increased significantly after one early trial demonstrated a reduction in blood loss by 40% in patients without platelet defects known to respond to this drug.[62] Although the study was a randomized, double-blinded

one, it included only 70 patients. Unfortunately, subsequent studies have been unable to substantiate such a large effect.

A 2008 meta-analysis[63] on desmopressin included 42 trials, 28 of which were in cardiac surgery. Most of these trials were relatively small and had limited follow-up. Overall, there was a decrease in blood loss by 80 mL per patient and a decrease in blood transfusion by 0.3 units per patient. A trend toward a reduction in platelet transfusion was not statistically significant. Results were similar in both cardiac and noncardiac surgical populations. No significant difference was found in rates of mortality, myocardial infarction, stroke, or reoperation for bleeding. Transient hypotension was the most common adverse event. An earlier meta-analysis[64] focusing on cardiac surgical patients found a small decrease in blood loss and units of blood transfused, especially when cardiopulmonary bypass times exceeded 140 minutes, but no statistically significant benefit was seen in patients taking aspirin.

Three studies have evaluated the targeted use of DDAVP in cardiac surgery based on platelet dysfunction identified by point-of-care testing. The first showed a significant reduction in blood loss and blood transfusions.[65] The second study demonstrated that DDAVP is capable of increasing platelet function, but the authors did not evaluate the clinical impact.[66] It is known that patients with severe aortic stenosis can develop type 2A von Willebrand disease.[67] When decreased platelet function was detected by a point-of-care platelet function analyzer, DDAVP was able to reduce the platelet defect and reduce blood loss during aortic valve replacement.[68]

DDAVP improved laboratory test results in patients undergoing hepatectomy in one study, but was unable to reduce blood loss or transfusion rates.[69] DDAVP showed promise in one early study of spinal fusion,[70] but this has not been confirmed in later studies.[71-74]

Protamine

Several studies have shown that excess protamine after cardiopulmonary bypass can be detrimental to clotting function. Early studies showed that a ratio in excess of 1.3 mg protamine to 100 units of circulating heparin (the lowest tested) prolonged ACT and impaired platelet function.[11] A more recent study using more sensitive tests demonstrated that ratios in excess of 1 mg protamine to 100 units circulating heparin were detrimental.[75] Precise protamine dosing based on the measured circulating heparin level has been shown to reduce blood product use in cardiac surgery.[76-78] Heparin rebound can occur 1 to 6 hours after neutralization but may be prevented with a low-dose protamine infusion (25 mg/hr for 6 hours)[79] or treated with small additional doses of protamine (5 to 15 mg).[80] Despite this evidence, many continue to administer too much protamine based on the total heparin dose.[80]

Prothrombin Complex Concentrates

The majority of the evidence related to PCCs comes from retrospective studies and case reports, most of which were focused on the rapid reversal of warfarin anticoagulation. In addition, most of these studies are from Europe, where 4-factor PCCs are readily available. Compared with FFP, 4-factor PCCs are able to more rapidly and more completely adjust the international normalized ratio (INR) in patients with intracranial hemorrhaging taking warfarin.[81,82] Similar results were seen in a study of cardiac surgical patients.[83]

One study demonstrated that a 3-factor PCC alone was not as effective as FFP alone in normalizing the INR, but a higher success rate was achieved when a small amount of FFP was combined with the PCC.[84] This was thought to be due to the lack of factor VII in the PCC, which could be provided by even a small amount of FFP. A similar study[85] showed more rapid INR reversal with a combination of FFP and 3-factor PCC and a decreased incidence of volume overload compared with FFP alone. Two recent studies showed that patients with a higher initial INR were less likely to respond to a 3-factor PCC.[86,87] Patients with a lower INR likely have higher circulating levels of factor VII and are therefore more capable of a response to a PCC lacking factor VII.

A meta-analysis[88] sought to evaluate the safety of both 3- and 4-factor PCCs in the setting of warfarin reversal, finding that there was a low incidence of thromboembolic events. The trend was toward more events with 4-factor PCCs, but this was not statistically significant. The authors noted that their analysis was limited by the lack of randomized controlled trials in this area.

For these reasons and the previously discussed theoretical benefits of PCC over FFP, the American College of Chest Physicians recommends the use of 4-factor PCCs for life-threatening bleeding in patients taking warfarin.[20]

Recombinant Activated Factor VII

rFVIIa has been used for a variety of off-label indications, and numerous case reports and small studies have supported these uses. A 2010 meta-analysis[24] focusing on the safety of rFVIIa included 4468 patients in 35 placebo controlled trials. A significant increase in arterial thromboembolic events was seen, including a 2.6 times higher rate of coronary artery events. An earlier meta-analysis[89] that focused primarily on patients with hemophilia found a low incidence (1% to 2%) of thromboembolic events, suggesting that the drug is safe when used for its approved indication.

Yet another meta-analysis[25] focusing on off-label uses analyzed the results by patient population. In cardiac surgery, there were two randomized controlled trials (RCTs) and four observational studies. There was no survival benefit but an increase in thromboembolic events. A similar effect was seen in four RCTs and one observational study of intracerebral hemorrhage. Four RCTs and three observational studies in trauma patients demonstrated reductions in transfusion requirements and acute respiratory distress syndrome but no survival benefit. Interestingly, the thromboembolic risk was not increased. In liver transplantation,

four RCTs and one observational study showed no effect on survival or thromboembolism. There was, however, a trend toward a reduction in packed red blood cell transfusion.

CONTROVERSIES

Although aprotinin has been off the market for several years, the debate continues over its use in certain clinical scenarios in which the risks may be justified.[37] Several published studies have not shown the same increase in mortality rate as BART.[90-94] A retrospective study of 15,365 cardiac surgical patients showed that aprotinin had a better risk–benefit profile than TXA in high-risk patients.[93] It should be noted that the increased risk of death in BART was in cardiac surgical patients, which may not be generalizable to other scenarios. In September 2011, Health Canada approved the reintroduction of aprotinin into the Canadian market.[95]

High-dose TXA has come under fire for an increased incidence of postoperative seizures reported in several studies.[36,94,96-102] Seizures increase the rate of other complications, including increased length of stay, prolonged intubation, and a possible increase in mortality.[101,103] This appears to occur in a dose-dependent fashion[100] and more frequently in patients with renal dysfunction.[101] The mechanism is thought to be gamma-aminobutyric acid (GABA) receptor antagonism.[104] EACA had a lower rate of seizures compared with TXA in two studies.[36,99] One of these studies also found an increased incidence of temporary renal dysfunction with EACA,[36] although this was not encountered in other comparisons of EACA and TXA.[34,35,99] No published studies have compared EACA with placebo in regard to seizures.

The timing of antifibrinolytic dosing continues to be debated and has not been consistent in all trials. Only one study[105] has evaluated timing, comparing administration preincision versus postheparin in primary coronary artery bypass graft patients; no difference was found in blood loss or transfusion requirements. This prompted the authors to recommend waiting until after administration of heparin to avoid potential thrombotic effects. Given that this small study was in a relatively low-risk population, it is hard to draw any firm conclusions.

Off-label use of rFVIIa increased 140-fold between 2000 and 2008, and 97% of all rFVIIa use in 2008 was off-label.[106] Despite the lack of effect noted in meta-analyses and the risk of thromboembolic events, some have argued that rFVIIa use is still reasonable in refractory bleeding.[107]

With regard to Jehovah's Witnesses, the definition of a blood product is now more difficult than it once was. Products that are actually derived from human blood, such as PCCs, *may* be acceptable to *some* Jehovah's Witnesses. Recombinant products, such as rFVIIa, should be acceptable under all circumstances. Synthetic drugs, including the lysine analogs and DDAVP, are, of course, also acceptable.[108,109]

AREAS OF UNCERTAINTY

Although the lysine analogs are commonly used and have been available for many years, the optimum dose remains unknown, with up to fortyfold variation between trials.[33,110] Dosing in pediatrics is even more complicated, and many questions remain.[60,111,112]

Evidence for the use of TXA in PPH is limited, especially with regard to important outcomes such as mortality and need for hysterectomy. The World Maternal Antifibrinolytic (WOMAN) trial plans to enroll 15,000 patients to further evaluate the impact of TXA on these outcomes.[113]

A novel synthetic serine protease inhibitor currently in development has been used successfully in animal models.[114-116] Ecallantide is a kallikrein-specific drug that showed promise but was found to increase mortality and bleeding rates compared with TXA in a phase II trial.[117] The manufacturer of ecallantide is no longer pursuing its use in cardiac surgery.

The utility of DDAVP remains unclear given the limited evidence and conflicting results. The authors of the aforementioned meta-analysis[63] hope to clarify this with a large multicenter RCT in patients with excessive microvascular bleeding after cardiac surgery.

Most PCC studies have been small or retrospective. A large RCT is under way to evaluate the use of 4-factor PCCs to reverse warfarin levels in patients with intracranial hemorrhage.[118] These studies have also focused on reversal of warfarin levels, which may or may not be applicable to other forms of coagulopathy seen in the perioperative setting. The focus on correction of laboratory values does not tell us about the impact on clinical outcomes such as blood loss or transfusion rates. Indeed, a recent in vitro comparison showed that both 3 and 4-factor PCCs were superior to FFP for restoration of thrombin formation in warfarin-treated blood, even though the impact on the INR was similar between the two groups.[119]

The question of 3-factor versus 4-factor PCCs also remains.[120] To date, 4-factor PCCs have proved to be efficacious, but a trend was seen toward an increase in thromboembolic events compared with 3-factor PCCs in a meta-analysis.[88] Four-factor PCCs are not currently approved for use in the United States, but trials are under way that may lead to FDA approval.

The optimal dosing of PCCs also remains unclear. The manufacturer recommendations are based on patients with hemophilia B and do not apply to off-label use. In addition, the relative and absolute factor content varies between manufacturers, and the ideal mix is still unknown.[121,122] Finally, it makes intuitive sense that dosing should be based on the degree of coagulopathy that needs to be corrected, but specific guidelines do not exist.

Several novel anticoagulants have been introduced to the market in recent years, including oral and parenteral direct thrombin inhibitors and direct factor Xa inhibitors.[123] These drugs have no known reversal agent, and it remains to be seen if any of the therapies discussed here will be beneficial in reversing their effects. Further, routine coagulation tests may not be sufficient to monitor their effects.

AUTHOR'S RECOMMENDATIONS

- Interventions to reduce bleeding are most likely to be successful when guided by laboratory testing.
- The lysine analogs tranexamic acid and epsilon aminocaproic acid appear to reduce bleeding in cardiac surgery and trauma, although the risk–benefit ratio should be weighed in each case.
- 1-deamino-8-D-arginine vasopressin use should be limited to patients with an acquired or inherited platelet defect known to respond to this drug.
- Appropriate dosing of protamine can reduce perioperative bleeding in cardiac surgery. The heparin–protamine titration method appears to be the most precise.
- Vitamin K must always be administered in addition to fresh-frozen plasma (FFP) or prothrombin complex concentrates (PCCs) when the effects of warfarin are being reversed.
- Three-factor PCCs do not appear to be as effective as 4-factor PCCs. They may still have a role in conjunction with a small amount of FFP or in patients at risk of transfusion-associated circulatory overload.
- Use of recombinant activated factor VII should be limited to bleeding that is refractory to other interventions, especially in patients at risk of thromboembolic complications.

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CHAPTER 25

Does Perioperative Hyperglycemia Increase Risk? Should We Have Aggressive Glucose Control Perioperatively?

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INTRODUCTION

The prevalence of diabetes in American society is increasing, and data for the year 2011 from the Centers for Disease Control and Prevention (CDC) show that 25.8 million people, or 8.3% of the U.S. population, have diabetes.[1] Furthermore, it is clear from observational and experimental studies that surgery elicits a stress response with the release of counter-regulatory hormones that contributes to hyperglycemia in patients with or without diabetes alike. Perioperative hyperglycemia, regardless of the cause, is associated with increased morbidity and mortality, and minimizing gross disturbances (both high and low) in plasma glucose levels should be an important part of providing perioperative care. Unfortunately, high-quality data from prospective randomized trials supporting this practice in the perioperative population are lacking, which makes it necessary for perioperative health care providers to extrapolate the results of larger trials conducted in critically ill hospitalized patients. In this chapter the evidence supporting perioperative blood glucose control is reviewed, and recommendations from relevant societies for glucose management are outlined.

OPTIONS

The goal for patients in the perioperative period is to minimize undue deviations in metabolic variables in as safe a manner as possible. With respect to perioperative blood glucose control this means avoiding profound hyperglycemia without exposing the patient to the risks of iatrogenic hypoglycemia. Perioperative hyperglycemia is strongly associated with an increased risk of morbidity and mortality. However, this association does not equate to causality. Unfortunately, the results of early studies that demonstrated a survival benefit in critically ill patients in whom euglycemia was maintained with aggressive insulin therapy were rapidly and, it appears, prematurely extrapolated to all perioperative patient populations. As a result, the literature is now teeming with studies showing excessive rates of severe hypoglycemia, even in the most heavily monitored settings, and uniformly this is associated with increased mortality. However, although strict glycemic control with aggressive insulin dosing does not appear to be well-tolerated in many patients, increasing evidence has shown that hyperglycemia of greater than 180 mg/dL is potentially deleterious in the perioperative setting.

In the perioperative setting, intravenous or subcutaneous insulin offers many advantages in the management of glycemic control, principally in terms of its favorable pharmacokinetics, which permits rapid titration in the face of changing metabolic and nutritional conditions. Although subcutaneous insulin is appropriate for ambulatory patients and stable hospitalized patients, intravenous insulin is superior in conditions in which hypoperfusion or tissue edema could compromise absorption of subcutaneous medications. The common features of any regimen should be as follows:

1. Avoidance of excessively high (>180 mg/dL) or low (<60 mg/dL) glucose levels
2. Prevention of unintended metabolic disturbances
3. Wide applicability to a variety of situations (e.g., operating room, recovery room, and general medical and surgical wards)
4. Easily understandable with clear goals of therapy

Glucose Control Regimens

Practice patterns among anesthesiologists regarding intraoperative blood glucose control have undergone substantial changes. A survey of British anesthesiologists in 1993 demonstrated that a greater proportion were likely to intervene to maintain the perioperative blood glucose levels in their diabetic patients at less than 180 mg/dL and that they were more likely to do so with separate infusions of insulin and glucose rather than glucose–insulin–potassium (GIK) solutions then they had when similarly surveyed in 1985.[2] The dramatic results of the 2001 Leuven trial of tight glycemic control in critically ill patients[3] encouraged many to extrapolate their findings to the management of perioperative and intraoperative blood glucose levels, in an attempt to aggressively target a blood glucose level of 80 to 110 mg/dL while in the operating room during anesthesia for

cardiac surgery.[4,5] Adoption of this practice has been controversial,[6] and it has become clear from investigations among critically ill patients that such tight glycemic control is associated with a substantial risk of hypoglycemia, with its attendant morbidity and mortality.[7-9] Some groups have extrapolated the Leuven results to the intraoperative period but have had difficulty achieving such tight control.[10] Additionally, achieving and maintaining tight glucose control in the intensive care unit (ICU) has proved to require a substantial outlay of resources: an average of 4.72 minutes (range, 3.13 to 8.15) *per hour* was devoted to measuring blood glucose and adjusting insulin infusions,[11] which is time that could be spent on other aspects of patient care.

Given the risk of hypoglycemia associated with tight glycemic control in the ICU as well as the increased resources needed, there is a relative paucity of clinical data to support its use in the perioperative period. Two randomized trials have attempted to address this issue for cardiac and vascular surgery,[12,13] and one meta-analysis has attempted to address the issue among a more heterogeneous population of surgical patients. In the first trial, 400 patients undergoing cardiac surgery were randomly assigned to intensive insulin control (target blood glucose level, 80 to 100 mg/dL) versus a conventional algorithm, in which patients did not receive insulin unless their blood sugar exceeded 200 mg/dL. Although the study size was small and the investigators were unable to reach their target blood glucose levels in the experimental group, they did find a statistically insignificant increase in mortality, stroke, and heart block requiring a pacemaker in the intensive insulin control group despite having equivalently low rates of hypoglycemia between the two groups.[13] In a subsequent meta-analysis, the same authors attempted to examine the effect of insulin in the perioperative period. Analysis of the pooled results in which the authors compared a heterogeneous group of patients undergoing a variety of interventions demonstrated an improvement in the 30-day mortality rate with intensive insulin therapy (relative risk [RR], 0.69; 95% confidence interval [CI], 0.51 to 0.94) but a significantly increased incidence of hypoglycemia (RR, 2.07; 95% CI, 1.29 to 3.32) in the 20 trials that included data on hypoglycemia.[14] These authors concluded that perioperative insulin use may decrease mortality rates and increase postoperative hypoglycemia but that their mortality data were too unreliable to draw definitive conclusions. In a subsequent trial, 236 patients undergoing major vascular procedures were randomly assigned to a continuous insulin infusion targeting a less aggressive blood glucose level of 100 to 150 mg/dL versus intermittent intravenous insulin boluses for blood glucose levels more than 150 mg/dL. The authors evaluated a composite primary endpoint that included death, myocardial infarction (MI), and congestive heart failure and noted a significant decrease (3.5% versus 12.3% [$p = 0.013$]) among the insulin infusion group.[12] Although the authors noted that the incidence of hypoglycemia (8.8% versus 4.1% [$p = 0.18$]) was similar in both groups, there did appear to be a trend toward more frequent hypoglycemia in the insulin infusion arm. In light of these studies, as well as the abundant literature on glycemic control among the critically ill, the American Diabetes Association/American Association of Clinical Endocrinologists revised their recommendations for critically ill patients to include maintenance of blood glucose between 140 and 180 mg/dL.[15] Similarly, the Society for Thoracic Surgeons recommends a target blood glucose range of less than 180 mg/dL for patients undergoing cardiac surgery.[16]

Intravenous Infusion of Insulin and Blood Glucose Measurement

Intravenous administration of insulin is generally preferred to subcutaneous injection during the perioperative period for hospitalized patients undergoing surgery and anesthesia because of ease of administration, quick dose adjustment, and more reliable pharmacokinetics.[17] However, subcutaneous injection of insulin is still recommended by the Society for Ambulatory Anesthesia and the UK National Health Service for the perioperative management of hyperglycemia in patients undergoing ambulatory surgery.[18,19] The perioperative state may be characterized by rapidly changing insulin requirements, and the slower absorption and onset of action of subcutaneous insulin may be inadequate for effective and timely control of hyperglycemia in this setting.[20] In addition, choice of administration site, edema, and impaired perfusion to skin and subcutaneous tissues leads to marked variation in the pharmacokinetics of insulin, particularly in patients with hemodynamic instability, shock, or a critical illness.[20-24] This variability may lead to repeated administration of subcutaneous insulin and protracted hypoglycemia with deleterious consequences for the patient.[25]

Although point-of-care capillary blood glucose monitors are ubiquitous in the perioperative setting and they correlate well with reference laboratory values in hemodynamically stable patients, they can be inaccurate in the perioperative setting, particularly in patients with hypothermia, hypoperfusion, or anemia.[23,26,27] Blood sugar measurements using capillary blood glucose values have been shown to have a greater than 20% variability when compared with values obtained in whole blood in surgical patients.[27] This discrepancy was particularly notable in patients who had evidence of hypoperfusion. Additionally, because glucose dissolves into the aqueous components of blood to a greater degree than erythrocytes, the glucose concentration recorded in whole blood (as with a capillary blood glucose meter) is generally 11% lower than that recorded from plasma (as is generally done with a central laboratory or a blood gas analyzer).[28] The majority of such devices correct for this by multiplying the values obtained by a correction factor of 1.11. It is important for anesthesiologists to be aware of the many limitations of point-of-care devices for blood glucose measurement as well as conditions in which they may not be accurate.[29]

Glucose–Insulin–Potassium Infusion

Interest in GIK solutions (typically, 30% dextrose, 50 Units/L insulin, and 80 mEq/L KCl) is principally related to its putative role in myocardial preservation during periods of myocardial ischemia and reperfusion rather

than as a means of controlling blood glucose. However, because they have also been used to control blood glucose levels, they will be discussed here. Initial reports of the clinical utility of GIK focused on the importance of increasing intracellular potassium concentrations in cardiac myocytes to maintain membrane polarization during periods of ischemic stress.[30] Although the preferred substrate for cardiac myocytes is free fatty acids, glucose is an alternate energy source for myocardial metabolism during periods of ischemia because it can be metabolized anaerobically via glycolysis. Additionally, glucose can serve as a precursor to substrates depleted via the citric acid cycle in order to re-energize the myocardium during periods of reperfusion.[31] The reason for addition of insulin in this case would be to promote glucose and potassium uptake by cardiac myocytes rather than to control blood glucose levels. Additionally, GIK solutions have been shown to have beneficial effects in myocardial free fatty acid[32] and phosphate[33] metabolism, as well as in the prevention of arrhythmias thought to be due to these metabolic derangements.[32]

The theoretical effects of GIK solutions have primarily been evaluated in the setting of myocardial ischemia due to myocardial infarct and revascularization. Animal experiments[34] and early reports of smaller trials using GIK,[35,36] as well as a meta-analysis of these early trials,[37] had demonstrated a potential survival benefit during MI and revascularization. The results of two randomized trials, the DIGAMI trial, which investigated the early infusion of insulin–glucose (but not potassium),[38] and the ECLA pilot trial of early infusion of GIK, both demonstrated a survival benefit with the use of this intervention; however, the follow-up DIGAMI 2[39] and CREATE-ECLA[40] trials were unable to duplicate these findings and did not demonstrate a survival advantage. Testing the hypothesis that the timing of administration in these latter trials was too late (after the ischemic insult), the IMMEDIATE investigators evaluated GIK administration in patients with suspected acute coronary syndromes in the prehospital period but were unable to demonstrate a survival advantage.[41] When GIK solutions were evaluated in CABG surgery for control of hyperglycemia, investigators demonstrated positive effects with respect to atrial fibrillation, length of stay, and the mortality rate at 2 years.[31] Studies in which GIK solutions were infused in similar populations, but without control of hyperglycemia, showed that the GIK infusion resulted in hyperglycemia with no demonstrable beneficial effects.[42,43] Currently, although the available evidence does not favor using GIK solutions in all patients with myocardial ischemia, some data do suggest that diabetic patients undergoing cardiac surgery sustain a benefit from such therapy.[44]

EVIDENCE

Perioperative Hyperglycemia and the Outcome of Critically Ill Patients

Hyperglycemia associated with insulin resistance is common in critically ill patients regardless of whether they have previously been given a diagnosis of diabetes[45-47] and is associated with adverse outcomes in this group.[48-51] The management of hyperglycemia in critically ill patients has undergone revision with the publication of conflicting results from large-scale randomized controlled trials.[3,8,9,52] Initial enthusiasm for intensive insulin therapy, targeting a blood glucose level of 110 mg/dL, was based on the results of a study of surgical ICU patients at a single center in Leuven, Belgium.[3] At the time of this study the standard of care in most centers was to tolerate hyperglycemia that did not reach the threshold for glycosuria (serum glucose level of 215 mg/dL). Thus the investigators used this threshold as the control arm in their trial.[53] In patients randomly assigned to intensive insulin therapy (maintenance of blood sugar at or below 110 mg/dL), the authors demonstrated a 34% reduction in the in-hospital mortality rate, a 46% reduction in bloodstream infections, and a 41% reduction in acute renal failure requiring hemodialysis or hemofiltration when compared with patients receiving conventional therapy (insulin infusion if the blood glucose level exceeded 215 mg/dL with maintenance between 180 and 200 mg/dL).[3] The results of this trial were so compelling that they were rapidly incorporated into guidelines issued by professional organizations,[54,55] as well as practice patterns in ICUs internationally.[56,57]

However, the authors of the Leuven trial were unable to reproduce the survival benefit of intensive insulin control in a follow-up study of medical ICU patients comparing the same blood glucose control strategies as in their earlier work.[52] Although they were able to demonstrate a survival advantage for the subset of patients who required a prolonged (greater than 3 day) ICU stay, they also found a disturbing association between intensive insulin therapy and increased mortality rate in the subset of patients that stayed for shorter periods in the ICU.[52] A large meta-analysis carried out at the same time was similarly unable to demonstrate a survival benefit,[58] but did find a significant association between intensive insulin therapy and the development of hypoglycemia. This association between intensive insulin therapy and hypoglycemia was again demonstrated in two subsequent randomized controlled trials involving tight glycemic control, both of which were terminated because of unacceptably high rates of hypoglycemia,[7,8] which has led many to question the safety of intensive glucose control regimens.

Coincidently, the Normoglycemia in Intensive Care Evaluation—Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) investigators were completing a large multicenter randomized controlled trial comparing intensive insulin therapy versus standard therapy.[9] This trial was not designed to address the safety concerns raised by the interceding trials but rather was powered to detect an absolute difference in mortality favoring intensive insulin therapy as compared with standard glucose control at the time (140 to 180 mg/dL). In stark contrast to the Leuven group's findings, the NICE-SUGAR investigators found that the intensive insulin group had a significantly higher mortality rate (27.9% versus 24.9%; $p = 0.02$) than did control subjects and was also associated with much higher rates of severe hypoglycemia.[9]

While tight glycemic control with intensive insulin therapy was widely and rapidly embraced after the publication of the Leuven trial, the results of more recent studies demonstrating a significant association with hypoglycemia and particularly increased mortality rates with intensive insulin therapy have largely led to its abandonment. Currently, the American Diabetes Association recommends targeting a blood glucose range of 140 to 180 mg/dL for the majority of critically ill patients, reserving a more stringent target of 110 to 140 mg/dL for select patients as long as this can be achieved without significant hypoglycemia.[59]

Effect of Stress-Related Hormonal Changes on Metabolic Changes in Diabetic and Nondiabetic Patients

The effects of surgery and the stress response on the development of hyperglycemia have been recently reviewed.[20,60] Activation of the sympathetic pituitary and adrenal systems in response to acute stress (e.g., injury in the perioperative period) leads to the secretion of counterregulatory hormones such as epinephrine, norepinephrine, glucagon, cortisol, and growth hormone, which stimulate increased hepatic glucose production and peripheral insulin resistance. Increased hepatic glucose synthesis through gluconeogenesis is responsible for the majority of stress-induced hyperglycemia and is primarily a response to the increased glucagon secreted by the pancreas in response to high levels of circulating catecholamines, particularly epinephrine.[61,62] Insulin secretion from the pancreas is inhibited by circulating catecholamines, particularly norepinephrine through alpha-2 dependent pathways.[20] The mechanism of peripheral insulin resistance is poorly understood but is mediated, in part, by cortisol and epinephrine and involves reduced insulin-mediated glucose uptake (IMGU) through the insulin-inducible facilitated glucose transporter GLUT-4 found in skeletal muscle and adipose tissue, as well as reduced skeletal muscle glycogen synthesis.[63,64] Insulin resistance also promotes lipolysis with the formation of excessive free circulating fatty acids.[20] The net effect of these pathways is elevated levels of glucose and free fatty acids. Hyperglycemia and hyperlipidemia induce oxidative stress through increased free radical generation and reduce the bioavailability of nitric oxide, which leads to vasoconstriction and platelet aggregation.[65] Hyperglycemia also stimulates inflammation through increased cytokine production and causes increased release of tissue factor, which activates the coagulation cascade.[66,67]

The degree of stress-induced hyperglycemia has been shown to be proportional to surgical stress in postoperative patients,[68] to the degree of myocardial stress in patients with acute MI[69] and with the severity of neurologic injury in patients with trauma.[70] Although it has been well-documented that stress-induced hyperglycemia is associated with morbidity and mortality, several lines of evidence indicate that the mortality effect of stress-induced hyperglycemia is different for patients with diabetes and without diabetes. It appears that patients without diabetes incur a higher degree of morbidity and mortality for a given elevation of blood glucose level. Among ICU patients it has been demonstrated that ICU mortality is greater for patients without diabetes than for patients with diabetes at any blood glucose level.[71] In patients who have sustained a MI the mortality effect of short-term blood glucose elevation was greater for patients without diabetes in a large observational study and a meta-analysis.[72,73] Similar results have been demonstrated in patients with ischemic stroke and intracranial hemorrhage.[74-76]

Effect of Perioperative Hyperglycemia on Wound Healing and Postoperative Infections

Observational studies have established that diabetic patients are at greater risk of developing a variety of infections, including pneumonia, cystitis, and surgical site infections.[77] Acute hyperglycemia frequently accompanies severe physiologic stress (e.g., surgery) and has also been shown to be associated with an increased risk of infectious complications.[78-82] Hyperglycemia is a potent immunomodulator, leading to significant and sustained decreases in the function of neutrophils, which decreases chemotaxis, adherence, phagocytosis, and bacteriocidal activity, all of which culminate in an increased susceptibility to bacterial infections at blood glucose levels greater than 200 mg/dL.[83-89] In experimental models, many of these effects could be reversed with improved glycemic control.[90] The beneficial effects of insulin and glycemic control on wound healing have been demonstrated in animal studies.[91-93]

Although it is clear that hyperglycemia is associated with an increased risk of infection in the perioperative period, data to support a causal relationship between the two are inconclusive. The Leuven trial, which is still one of the largest randomized clinical trials that used infection as a primary endpoint, demonstrated a 46% reduction in bloodstream infections with tight glycemic control (blood glucose target, <110 mg/dL) in a predominantly postsurgical population.[3] However, subsequent data have called into question the safety of such a target in critically ill patients.[9] Five randomized trials have been conducted in perioperative patients in order to determine the effect of perioperative insulin infusion and blood glucose control on infectious complications, and their results have been summarized in a recent Cochrane review.[13,31,94-97] Ghandi et al[13] investigated the effect of intensive intraoperative insulin therapy in a randomized trial of 400 cardiac surgery patients targeting a blood glucose level of 80 to 100 mg/dL and was unable to demonstrate an association with surgical site infections. Bilotta et al[95] examined strict glycemic control (blood glucose level, 80 to 120 mg/dL) versus conventional control (blood glucose level, 80 to 200 mg/dL) in 180 patients undergoing emergency cerebral aneurysm clipping and found a statistically insignificant trend toward lower infection rates in the tight glycemic control group, although there was also a trend toward hypoglycemia in this group. Grey and Perdrizet[96] randomly

assigned 61 hyperglycemic surgical ICU patients to strict glycemic control (blood glucose level, 80 to 120 mg/dL) versus standard control (blood glucose level, 180 to 220 mg/dL) and found more nosocomial infections in the conventional control group; however, they did not report rates of hypoglycemia. The authors of the Cochrane review stated that there was no evidence to support the use of tight glycemic control, below the standard blood glucose target of less than 200 mg/dL for prevention of infections in postoperative patients.[94]

Perioperative Hyperglycemia and Outcome after Cardiovascular Surgery

Cardiac surgery, particularly hypothermic cardiopulmonary bypass, presents several unique challenges to the management of perioperative blood glucose levels. The etiology of hyperglycemia during cardiopulmonary bypass is multifactorial. Hypothermia during bypass suppresses insulin secretion in the face of hyperglycemia. Furthermore, insulin resistance may be profound as a result of increased levels of counter-regulatory hormones such as epinephrine, cortisol, glucagon, and growth hormone, which, in conjunction with increased glucose reabsorption by the kidneys, may lead to profound hyperglycemia.[98-101] Multiple lines of evidence have indicated that the resulting hyperglycemia is an independent factor associated with increased short- and long-term morbidity and mortality after cardiac surgery; however, many conflicting results exist in the literature, and the magnitude of this risk and the ideal blood glucose level for risk reduction remain unclear.

Many of the earliest reports suggesting an association between hyperglycemia and morbidity or mortality after cardiac surgery were retrospective studies using historical control subjects, used a variety of definitions for hyperglycemia, and were subject to the confounding influence of the many other improvements in the care these patients were exposed to during the study period. However, these trials demonstrated significant associations between elevated perioperative blood glucose levels and mortality,[102] particularly among higher risk individuals,[103] and morbidity, including sternal wound infection, hospital length of stay, and new onset atrial fibrillation.[104] The results of observational studies comparing hyperglycemia and the incidence of morbidity and mortality among cohorts of cardiac surgery patients have been less consistent: there have been positive trials demonstrating such an association[105-108] and negative trials that were unable to demonstrate associations between perioperative hyperglycemia and morbidity or mortality.[78,109,110] These trials used a heterogeneous definition of hyperglycemia from 150 mg/dL to greater than 360 mg/dL, making their aggregate results somewhat difficult to interpret. Gandhi et al[111] used logistic regression to demonstrate that a 20-mg/dL increase in intraoperative blood glucose level was associated with a 30% increase in negative perioperative outcomes.

The results of the few randomized trials of intraoperative blood glucose control in cardiac surgery have examined a diverse group of endpoints but have been generally negative. An early pilot study attempting to achieve normoglycemia during cardiopulmonary bypass demonstrated a significant association with postoperative hypoglycemia, even though the investigators were unable to achieve adequate blood glucose control intraoperatively.[10] A larger study examining the effect of an insulin infusion to maintain a target blood glucose level of 100 mg/dL versus placebo was unable to demonstrate an association between decreased intraoperative blood glucose levels and neurocognitive events after cardiopulmonary bypass.[112] One small randomized trial of 40 cardiac surgery patients compared a GIK solution to maintain a target blood glucose level of 100 to 180 mg/dL versus intravenous insulin boluses when blood glucose levels exceeded 180 mg/dL and demonstrated decreased blood glucose levels, improvement in lactate clearance, and a decreased requirement for postoperative inotropic support, although they provided no data on intraoperative blood glucose control.[113] The largest randomized trial specifically designed to examine the effects of intraoperative blood glucose control on morbidity and mortality in cardiac surgery involved 400 patients randomly assigned to receive intensive insulin therapy with a target blood glucose level of 80 to 100 mg/dL intraoperatively (similar to the Leuven trial) versus intermittent intravenous insulin for blood glucose levels greater than 200 mg/dL.[13] Although the investigators were unable to reach their blood glucose targets in their treatment group, and the study was unable to demonstrate an association between intraoperative hyperglycemia and a composite outcome of death and major morbidity, the investigators did note a trend toward higher rates of death ($p = 0.061$) and stroke ($p = 0.02$) in the intensive treatment group, findings which, although statistically insignificant and not part of their a priori hypothesis, do agree with those of the NICE-SUGAR investigators and support the conclusion that intensive blood glucose control as defined in the Leuven trial is associated with an unacceptable risk of major adverse outcomes in a variety of settings—in this case, intraoperative blood glucose control during cardiac surgery. Using these results and extrapolating from the conclusions of trials in critically ill patients, the Society for Thoracic Surgeons Practice Guidelines for Blood Glucose Management during Adult Cardiac Surgery currently recommend maintenance of blood glucose levels at less than 180 mg/dL intraoperatively and postoperatively, reserving a tighter postoperative threshold of less than 150 mg/dL for patients who are expected to be in the ICU for longer than 3 days.[16]

Glycemic Control in the Setting of Acute Myocardial Infarction

Hyperglycemia is a common feature of MI, present in up to 50% of patients with an ST segment elevation MI.[114] Cardiovascular stress from MI is a potent stimulus for release of the counter-regulatory hormones that act to increase circulating levels of glucose and free fatty acids.[69] Hyperglycemia and hyperlipidemia are associated with increased generation of free radicals and oxidative damage and have been shown to be associated with an increase in inflammation and arrhythmias as well as decreased rates

of successful thrombolysis in acute MI.[65] Hyperglycemia leads to poorer 12-month survival rates in MI regardless of diabetic status,[114] and there appears to be a dose-response relationship between increases in blood glucose level and mortality, at least among patients without diabetes.[115] This relationship between increasing blood glucose levels and mortality has also been demonstrated prospectively in the CREATE-ECLA trial.[40] However, determining whether hyperglycemia is simply a marker of more severe injury (i.e., an epiphenomenon) or is causally related to negative outcomes after MI requires further prospective evaluation.

The results of prospective trials of blood glucose control in MI have been mixed. One early trial demonstrated a significant reduction in 1-year mortality among patients randomly assigned to receive an insulin infusion with a modest target blood glucose level of approximately 120 to 180 mg/dL followed by subcutaneous insulin therapy.[116] Early reports of GIK infusions in patients with MI, infused for cardiomyocyte metabolic substrate therapy without the intention of controlling blood glucose levels, indicated that insulin may have salutatory effects in MI other than blood glucose regulation.[117,118] A randomized trial of insulin infusion to maintain blood glucose levels at less than 180 mg/dL for 24 hours after MI found no association between this therapy and the primary endpoint (heart failure or reinfarction); however, subgroup analysis showed that the mortality rate was lower among patients with mean blood glucose levels less than 144 mg/dL during the first 24 hours.[119] A trial of intensive insulin therapy (blood glucose target, 72 to 108 mg/dL) compared with standard therapy (blood glucose target, 108 to 144 mg/dL) in survivors of out-of-hospital cardiac arrest was unable to demonstrate a difference in 30-day mortality rates, although, similar to many other studies, an increased incidence of moderate hypoglycemia in the intensive insulin arm was noted.[120] The largest trial evaluating blood glucose control in MI was to be the 3000-patient DIGAMI 2 trial comparing three arms.[39] The target blood glucose range of 126 to 180 mg/dL was initiated for the first 24 hours in the first two experimental groups. After 24 hours the first group continued at this target, while the second reverted to standard therapy administered by "local routines" (not defined). The third group had standard therapy throughout. The trial was stopped early after recruiting only 1253 patients because of slow enrollment and was unable to demonstrate a significant difference in its primary endpoint, mortality. The low recruitment, differences in baseline variables, lack of definition of standard therapy, and crossover between treatment groups make the results of this trial difficult to interpret. It is important to note, however, that among this study population hyperglycemia was still one of the most important prognostic predictors.[39]

Perioperative Hyperglycemia and Neurologic Outcome after Brain Injury

Hyperglycemia is independently associated with the development of secondary brain injury and portends a poor clinical prognosis in stroke, subarachnoid hemorrhage, and traumatic brain injury.[121-125] Neurologic injury is a potent stimulator of the stress response with activation of the sympathetic nervous system and release of counter-regulatory hormones that stimulate hyperglycemia. However, it is now evident that this hyperglycemia contributes to and propagates secondary brain injury through a variety of mechanisms, including synthesis of reactive oxygen species, promotion of intracellular acidosis, inflammation, and changes in endothelial cell function and nitric oxide metabolism, all of which favor a milieu of vasoconstriction and thrombosis.[126-132] While hyperglycemia potentiates secondary brain injury, the brain relies almost exclusively on glucose for metabolism. Thus the injured brain, with a compensatory increase in glucose demand, is particularly sensitive to the effects of hypoglycemia. This has been demonstrated in patients who have sustained a stroke in which there is a J-shaped association between blood glucose levels and mortality. Similarly, in patients with subarachnoid hemorrhage, moderate hypoglycemia is associated with vasospasm and cerebral infarction, and in traumatic brain injury, evidence demonstrates a significant imbalance in energy substrate and requirements when intensive insulin therapy is used.[133-135]

Although it is clear that both hyperglycemia and hypoglycemia can potentiate acute brain injury by a variety of mechanisms, clinicians have only sparse data from prospective trials to help guide them in the management of blood glucose levels in the brain-injured patient. The majority of prospective trials have been conducted in stroke patients and includes one large trial and several pilot studies, all evaluating the effects of intensive insulin therapy on outcomes in this population. The largest of the trials, the Glucose in Stroke Trial (GIST) randomly assigned 933 patients with stroke and hyperglycemia on admission to receive intensive blood glucose control (target, 72 to 126 mg/dL) with the use of a GIK infusion compared with normal saline infusion in control subjects.[136] The trial was stopped well short of its calculated 2355 patient sample size at 933 patients because of slow enrollment and was unable to demonstrate an effect on either morbidity or mortality. Importantly, however, the investigators did demonstrate in post-hoc subgroup analysis that there was a significant increase in mortality rates among patients in the GIK group that had a greater than 36-mg/dL decrease in blood glucose levels.[136] Several small pilot studies have evaluated the feasibility of tight glycemic control using intensive insulin therapy in stroke patients[137-139] and, although each individually was underpowered to detect a mortality difference, a recent Cochrane review has attempted to consolidate their findings with those of the GIST trial.[140] The Cochrane review concluded that maintenance of tight glycemic control did not provide any benefit in terms of morbidity or mortality and exposed patients to a greater risk of hypoglycemia.[140] Much less data exist from prospective randomized trials regarding blood sugar control in other types of neurologic injury. In a small, randomized trial after aneurysm clipping in patients with subarachnoid hemorrhage, it was shown that intensive insulin therapy (target blood glucose level, 80 to 120 mg/dL) was associated with decreased rates of postoperative

infection, but no difference was seen in the rates of vasospasm, mortality, or neurologic recovery.[95] Importantly, the investigators did not report rates of hypoglycemia in the two groups other than to note that 10.5% of the intensive insulin therapy group had blood glucose values below 80 mg/dL versus 3.5% in the control group.

Although there is sufficient evidence to state that hyperglycemia worsens secondary neurologic injury in stroke, subarachnoid hemorrhage, and traumatic brain injury, analysis of available evidence does not provide any clear guidance as to appropriate blood glucose targets in this patient population. Additionally, the significant risks of further neurologic injury from hypoglycemia and the lack of evidence of efficacy from tight glycemic control would argue against adopting intensive forms of insulin therapy in this group.

AREAS OF UNCERTAINTY

A few areas in clinical hyperglycemia and its intervention are in dire need of further research. Although it is clear from observational studies that hyperglycemia is associated with morbidity and mortality in perioperative patients, the results of prospective studies testing interventions to lower blood glucose levels have been mixed. This leaves two questions unanswered. The first relates to causality: is hyperglycemia involved in the etiology of this excess mortality or is stress hyperglycemia merely a sign of more severe injury with a greater likelihood of death and disability? Second, what is the appropriate target for blood glucose management in the perioperative period, and is it different among subgroups of patients? More prospective clinical trials are needed to inform decisions regarding blood glucose management in perioperative patients. For example, the Leuven trial demonstrated that tight glycemic control with a target blood glucose of 110 mg/dL was superior to a blood glucose levels greater than 215 mg/dL in critically ill patients. Similarly, NICE-SUGAR demonstrated in a similar population that 110 mg/dL was associated with excess mortality when compared with more moderate blood glucose elevations of 140 to 180 mg/dL.[3,9] The question that remains unanswered is whether moderate blood glucose control, with a limit of 140 to 180 mg/dL, is superior to hyperglycemia in critically ill patients or, for that matter, if there is a more ideal target. Additionally, there is very little evidence to guide decisions about intraoperative blood glucose control.

GUIDELINES

Current clinical guidelines issued by the American College of Endocrinology and the American Diabetes Association for critically ill patients are to maintain blood glucose levels within a target range of 140 to 180 mg/dL with the use of intravenous insulin in critically ill patients.[15] Furthermore, they recommend that premeal blood glucose values for noncritically ill hospitalized patients be less than 140 mg/dL and that random blood glucose values should be less than 180 mg/dL. Separately, the Society for Thoracic Surgeons recommend maintenance of blood glucose values at less than 180 mg/dL while in the ICU, unless the patient may potentially be dependent on a ventilator for longer than 3 days, in which case they suggest a potential benefit from tighter glycemic control with a threshold of less than 150 mg/dL as long as hypoglycemia may be avoided.[16] In the absence of clearer data from prospective randomized trials, most clinicians have adapted these guidelines for intraoperative blood glucose management and would recommend intravenous insulin for the maintenance of blood glucose levels less than 180 mg/dL in intraoperative patients while exercising great care to avoid intraoperative hypoglycemia.

AUTHORS' RECOMMENDATIONS

- Although the ideal targets for perioperative blood glucose control are yet to be defined, excessively high (>180 mg/dL) and low (<60 mg/dL) blood glucose values should be avoided.
- Use of regular insulin, because of its favorable pharmacokinetics, allows for easy titration in response to the dynamic metabolic requirements common in the perioperative period.
- Although subcutaneous administration of insulin is efficacious in hemodynamically stable patients without significant fluid shifts, absorption from subcutaneous tissues may become unpredictable in situations characterized by diminished tissue perfusion or significant edema (e.g., hemodynamic instability, critical illness, or shock states). In these situations, intravenous administration of insulin is recommended.
- Capillary blood glucose monitors can be inaccurate in the perioperative setting, particularly in patients with significant tissue edema, hypothermia, hypoperfusion, or anemia. In these settings, direct whole blood glucose measurement, as with a blood gas analyzer, is preferred.

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CHAPTER 26

When and Why Should Perioperative Glucocorticoid Replacement Be Administered?

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INTRODUCTION

Glucocorticoids were introduced into clinical practice in 1949 with the release of a purified preparation known as cortisone. The treatment was revolutionary for patients with primary adrenal insufficiency (AI) and for the management of other acute and chronic diseases such as rheumatoid arthritis and systemic lupus erythematous. Shortly after the introduction of cortisone, two case reports were published describing surgical patients receiving long-term glucocorticoid treatment whose treatment was held in the perioperative period. The first involved a 34-year-old man who had cortisone therapy (25 mg twice daily) discontinued 48 hours before surgery.[1] His subsequent death was attributed to acute AI caused by abrupt withdrawal of glucocorticoids. However, extenuating circumstances may have contributed to his death. The second case involved a 20-year-old woman who had been taking 62.5 to 100 mg of cortisone daily for approximately 4 months.[2] She died less than 6 hours after surgery; autopsy findings confirmed bilateral adrenal hemorrhages and cortical atrophy indicative of AI. From these case reports came the conventional wisdom to supplement patients receiving exogenous steroids with large "stress doses" throughout the perioperative period. This practice came under scrutiny because of questions about efficacy and concern about side effects from excessive doses.

Endogenous glucocorticoids are cholesterol derivatives produced in the zona fasciculata of the adrenal cortex. Their release is controlled by a feedback mechanism known as the hypothalamic–pituitary–adrenal (HPA) axis (Figure 26-1). Corticotropin-releasing hormone (CRH), released by the hypothalamus, acts on the anterior pituitary gland to initiate the production of adrenocorticotropic hormone (ACTH or corticotropin). ACTH then stimulates the adrenal glands to produce cortisol, which acts as negative feedback for CRH in the hypothalamus. Intracellular glucocorticoid receptors known as NR3C1 are ubiquitous, and glucocorticoids are integral factors in modulating normal cellular homeostasis and metabolism. Cortisol potentiates production of catecholamines and regulates the synthesis, responsiveness, coupling, and regulation of beta-adrenergic receptors. Glucocorticoids also regulate the normal metabolism of carbohydrates, proteins, and lipids. Glucocorticoid hormones modulate cardiovascular function and wound healing and have numerous other important metabolic functions.[3-5]

Daily endogenous glucocorticoid secretion is estimated to be between 5 and 10 mg/m^2. This corresponds to 5 to 7 mg/day of oral prednisone or 20 to 30 mg/day of hydrocortisone. Cortisol synthesis can increase under conditions of stress to 100 mg/m^2/day.[6-15]

Deficiencies of glucocorticoid production result in AI, which can be classified as a primary, secondary, or tertiary process with acute and chronic forms (Table 26-1). Primary AI occurs in patients who have destruction of more than 90% of the adrenal glands by hemorrhage, tumor, infection, or an inflammatory process. This results in deficient production of both mineralocorticoids and glucocorticoids. Primary AI is relatively rare, most often resulting from autoimmune destruction of the adrenal glands. In developing regions of the world, it is most commonly due to tuberculous destruction of the adrenals. Patients with primary AI always require steroid replacement/supplementation with a medication(s) that include glucocorticoid and mineralocorticoid effects. Secondary AI is also relatively uncommon and results from insufficient production of ACTH resulting from destruction or dysfunction of the hypothalamus or pituitary gland.[6,16] Patients with secondary AI typically require only glucocorticoid replacement and not mineralocorticoid replacement because mineralocorticoid activity is regulated primarily through the renin–angiotensin system and remains intact.

Tertiary, or iatrogenic, AI is the most commonly encountered type. Tertiary AI results from the suppression of the HPA axis over time, as a result of the administration of exogenous glucocorticoids. Long-term ACTH suppression from steroid treatment leads to adrenal atrophy. This can result in a potentially harmful situation if exogenous glucocorticoids are discontinued because the adrenals can no longer produce adequate cortisol.[17]

NORMAL RESPONSE TO SURGICAL STRESS

Salem and colleagues[7] reviewed seven prospective analyses performed between 1957 and 1975 examining cortisol

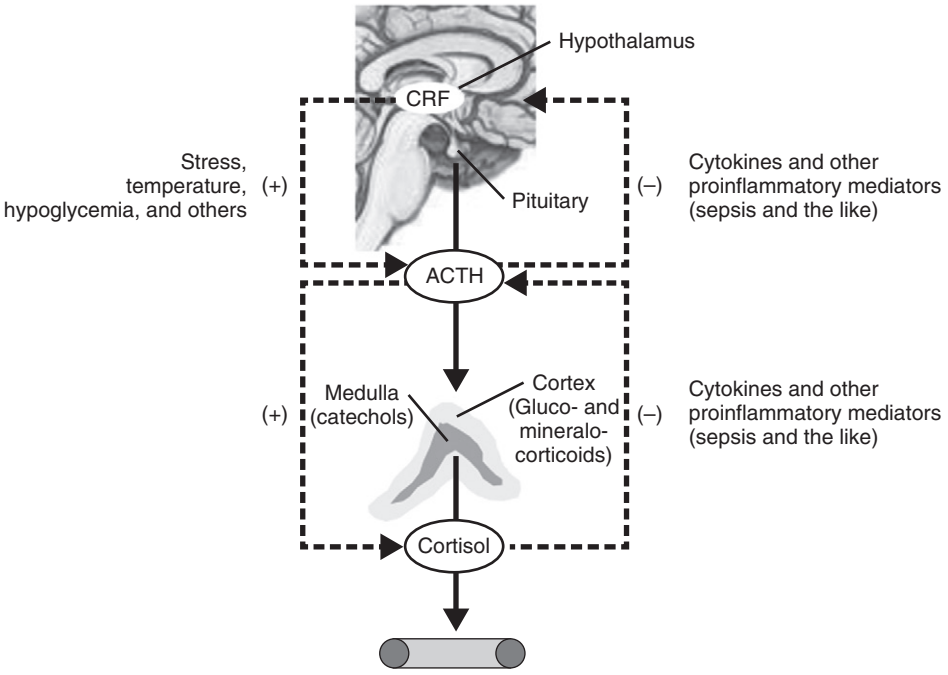

FIGURE 26-1 ■ The Hypothalamic–Pituitary–Adrenal Axis. Plus signs indicate stimulation, and minus signs indicate inhibition. *ACTH,* adrenocorticotropic hormone (corticotrophin); *CRF,* corticotropin-releasing factor.

TABLE 26-1 **Characteristics of Adrenal Insufficiency (AI)**

Type	Features	Incidence	Etiologies
Primary	ACTH independent Adrenal gland dysfunction, destruction, or replacement; requires >90% loss of adrenal tissue Loss of mineralocorticoid and glucocorticoid production Increased ACTH production Requires lifetime therapy	Prevalence: 40-110 cases/million Incidence: 6 cases/million per year	Autoimmune (70%-90% of U.S. cases) frequently associated with a polyglandular deficiency syndrome Infectious: HIV is most common infectious cause in the United States Tuberculosis is most common infectious cause worldwide Inflammation Cancer Acute Addisonian crisis Infection Shock Stress Hemorrhage
Secondary	ACTH dependent Signs and symptoms usually caused by loss of glucocorticoid function Usually have intact mineralocorticoid function Rarely hypovolemic, more commonly hypoglycemic	Uncommon	Decreased or absent ACTH (may be panhypopituitary or anterior pituitary dysfunction) Pituitary depression, dysfunction/damage Tumor, postpartum, hypothalamic failure or dysfunction
Tertiary	Caused by hypothalamic/pituitary depression or absence	Most common form	Usually from iatrogenic corticosteroid therapy and suppression of the HPA axis

ACTH, adrenocorticotropic hormone (corticotrophin); *HIV*, human immunodeficiency virus; *HPA axis*, hypothalamic–pituitary–adrenal axis.
From Coursin DB, Wood KE. Corticosteroid supplementation for adrenal insufficiency. JAMA 2002;287:236–40.

secretion after major surgery. Combined, the total number of subjects in these investigations was only 40. None of the patients examined were known to be adrenally insufficient or taking glucocorticoids. The reported range of 24-hour cortisol secretion was wide, varying from 60 mg/24 hr to 310 mg/24 hr. In 1972 Wise and colleagues[10] reported 24-hour postoperative cortisol secretion to be 60 mg. The following year, Kehlet and Binder[11] reported an immediate postoperative cortisol secretion rate of 10 mg/hr, which decreased to 5 mg/hr 24 hours after surgery. It is generally accepted, however, that most healthy, non–steroid-dependent patients will secrete somewhere between 75 and 150 mg of cortisol in the first 24 hours after major surgery or up to 100 mg/m^2.[1,6]

INTEGRITY OF THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS IN PATIENTS TAKING LONG-TERM STEROIDS

Several studies have confirmed that patients taking small doses of steroids (≤5 mg of prednisone or its equivalent per day) retain normal HPA function. In 1973 Kehlet and Binder[15] performed a prospective case-control study to determine whether patients receiving long-term glucocorticoid therapy could mount a physiologic response to major surgery if steroids were discontinued perioperatively. With 14 non–steroid-dependent surgical patients serving as control subjects, they prospectively followed up 74 patients on long-term glucocorticoid therapy undergoing major surgery (prednisone dose, 5 to 80 mg/day) and 30 steroid-dependent patients undergoing minor surgery (prednisone dose, 5 to 30 mg/day). Glucocorticoids were stopped 36 hours preoperatively and restarted 24 hours postoperatively. Plasma cortisol levels were measured for the first 24 hours postoperatively. Approximately 30% of the glucocorticoid-treated patients exhibited a blunted adrenocortical response to surgery, but only one patient showed any clinical signs or symptoms of AI. Interestingly, the majority of the control subjects in the minor surgery category showed little or no cortisol response to surgery. The authors concluded that subnormal adrenal stress responses were more prevalent in patients maintained on steroids at either higher doses or longer durations. Patients who received more than 12.5 mg of prednisone for more than 6 months, more than 10 mg of prednisone for more than 2 years, or more than 7.5 mg of prednisone for more than 5 years all showed an impaired adrenocortical response. The one patient who was symptomatic had no detectable plasma cortisol but was treated without resultant morbidity. Based on this report it has been hypothesized that the dose and the duration of steroid therapy influence cortisol response to stress.

In 50 patients receiving long-term low-dose prednisone (<10 mg/day for a mean duration of 41 months), La Rochelle and colleagues[18] observed that all the patients receiving 5 mg/day or less had a normal response to a standard-dose rapid cosyntropin stimulation test. Those receiving 5.5 to 6.8 mg/day displayed an intermediate response, and those with mean doses greater than 6.8 mg/day displayed a suppressed response to ACTH stimulation.

Subsequently, Friedman and colleagues[19] prospectively evaluated 28 patients receiving long-term glucocorticoid therapy undergoing major orthopedic surgeries. The mean duration and dose of prednisone therapy before surgery in this group was 7 years and 10 mg/day, respectively. Although patients were administered their baseline therapy up to the time of surgery, perioperative stress doses of steroids were not given. Despite this omission, no hemodynamic or biochemical changes consistent with perioperative glucocorticoid deficiency were observed.

Kenyon and Albertson[20] performed a prospective study on 40 patients taking prednisone (doses from 5 to 10 mg/day) who were admitted to the hospital for illness, metabolic abnormalities, or surgery. No stress-dose steroids were given at any time during hospitalization. Over the first 36 hours, the authors measured serum cortisol, 24-hour urine cortisol, and ACTH levels. Once the patients' clinical condition improved, a cosyntropin stimulation test (250 μg) was repeated. Although the response to the cosyntropin stimulation test was blunted in 63% of the subjects, 97% had normal or increased urinary cortisol concentrations. This implies that despite long-term steroid treatment, adrenal function and endogenous glucocorticoid production were sufficient to meet the stress of illness or surgery.

EVIDENCE THAT SURGERY-INDUCED ACUTE ADRENAL INSUFFICIENCY IS HARMFUL

The case reports from Fraser et al[1] and Lewis et al[2] were sufficient to convince the medical community that acute AI from perioperative glucocorticoid withdrawal had the potential to cause serious morbidity and mortality risks. In 1976 Kehlet[21] produced an extensive review of 57 case reports from 1952 to 1973 documenting perioperative shock or death in patients taking glucocorticoids. In all cases, adverse outcomes were suspected to be secondary to stress-induced AI. The interval between surgery and shock or death ranged from preoperatively to 48 hours postoperatively. Interestingly, only 3 cases of the 57 displayed hypotension and low plasma cortisol levels, suggesting acute AI. The remainder of the cases were inconclusive or had no evidence to link the outcomes to AI.

In contrast, two large studies support the rarity of acute AI secondary to inadequate perioperative glucocorticoid coverage. Mohler and colleagues[22] performed a retrospective review of 6947 urologic procedures in glucocorticoid-treated patients. Only one case of perioperative AI was identified (0.01% of patients). Alford and colleagues[23] performed a similar review of 4346 cardiothoracic surgeries and confirmed only five cases of AI (0.1% of patients). These reviews support the fact that surgically induced AI can occur, although it is a relatively rare occurrence.

One group of patients that may deserve special consideration is elderly surgical patients. To determine the incidence and outcome of AI in elderly patients having high-risk surgery, Rivers and colleagues[24] performed a prospective, observational case study. A total of 104 consecutive adult patients (excluding patients with a history of steroid use, known adrenal dysfunction, and those administered etomidate) who required vasopressor therapy postoperatively despite adequate volume resuscitation received a cosyntropin (synthetic ACTH) stimulation test with plasma cortisol measurements at 30 and 60 minutes. Empiric hydrocortisone (100 mg intravenously [IV] for three doses) was given at the discretion of the primary team. Adrenal dysfunction (defined as a serum cortisol concentration less than 20 mg/dL with a change in cortisol concentration of less than 9 mg/dL after ACTH) or functional hypoadrenalism (serum cortisol

concentration less than 30 mg/dL with a change in cortisol concentration of less than 9 mg/dL after ACTH) was found in 32.7% of patients. The mortality rate was significantly lower in the hydrocortisone-treated patients with AI (21% versus 45%, $p < 0.01$). This incidence of relative AI is higher than would be expected for both the general surgical population and for those receiving long-term steroid treatment.

EVIDENCE FOR PERIOPERATIVE STEROID REPLACEMENT

Most of the clinical data on adrenal replacement therapy in the perioperative period are based on case series or drawn from clinical experience. There are few well-designed, prospective, randomized, blinded clinical trials investigating optimal perioperative steroid supplementation. Nonetheless, because of the potential for morbidity and mortality related to acute AI, it is generally agreed that certain patient populations should receive empiric perioperative steroid supplementation. The difficulty lies in determining the dose and duration of treatment.

For many years, all surgical patients taking glucocorticoids were given a standardized dose of supplementary steroid throughout the perioperative period. This method eventually came under question because of the deleterious effects of large doses of steroids, including poor wound healing, inadequate glucose control, fluid retention, hypertension, electrolyte imbalances, immunosuppression, gastrointestinal bleeding, and untoward psychological effects.[25]

In 1975, Kehlet[26] suggested that procedures be divided into "major" and "minor" categories. For major surgeries (e.g., intrathoracic, major vascular, or major abdominal operations), the recommendation was for 25 mg IV hydrocortisone at induction, followed by 100 mg IV hydrocortisone every 24 hours until the patient was able to resume oral steroid therapy. The goal of this approach was to adequately replace the increased cortisol requirements of 75 to 150 mg in the first 24 hours. For minor surgeries (surgeries taking less than 1 hour and those performed under local anesthetic), Kehlet suggested 25 mg IV hydrocortisone at the start of surgery and the resumption of oral therapy postoperatively. This recommendation was based on a study showing that healthy subjects often do not mount a stress response to minor surgery and, at most, secrete 50 mg/day of cortisol.[15]

In 1978, Gran and Pahle[27] recommended depot-betamethasone acetate/phosphate as a single intramuscular (IM) injection in perioperative patients receiving glucocorticoids. In a prospective cohort study on 1461 surgical patients receiving long-term steroid therapy, patients were given depot-betamethasone before surgery: 2 mg for major procedures and 1 mg for minor procedures. There were no reports of AI, delayed healing, or gastrointestinal bleeding. The authors contend that ease of administration is a major benefit of this regimen.

Salem and colleagues[7] advised that perioperative supplementation should be individualized and based on prior steroid dose, duration, and degree of anticipated surgical stress. For minor surgeries, 25 mg hydrocortisone or an equivalent dose (oral prednisone or a parenteral equivalent) was suggested, and the long-term dose should be resumed the day after surgery. For procedures of perceived moderate stress, such as an open cholecystectomy or segmental colon resection, 50 to 75 mg/day of hydrocortisone or an equivalent dose (oral or parenteral) with a rapid taper over 1 to 2 days was recommended. For major surgery, such as cardiac surgery involving bypass, a target of 100 to 150 mg of hydrocortisone (or equivalent) per day with a rapid taper over 2 to 3 days was advised (see Table 26-3 later in this chapter).

Most recently, Zaghiyan et al[28] reported no significant benefit to perioperative glucocorticoid administration (100 mg hydrocortisone IV at the time of surgery, then 100 mg hydrocortisone every 8 hours for 24 hours, then 20 mg oral prednisone tapered over 3 days) compared with no perioperative steroids among patients with inflammatory bowel disease who had received corticosteroids any time during the year preceding colon surgery. None of the patients was receiving steroids at the time of surgery. Thirty-eight patients underwent 49 surgical procedures. Perioperative glucocorticoids were administered and not administered for 11 and 38 procedures, respectively. No differences in postoperative surgical morbidity or mortality were identified between groups, although the group receiving steroid treatment had more tachycardia.

AREAS OF EVOLVING INTEREST AND ONGOING CONTROVERSY

There are several areas of specific interest in the therapeutic administration of glucocorticoids in critically ill patients. These include treatment of patients with severe sepsis and septic shock, acute respiratory distress syndrome (ARDS), community-acquired pneumonia (CAP), meningitis, traumatic brain injury (TBI), and acute spinal cord injury (SCI). The use of etomidate in critically ill patients, a topic of renewed interest, is also reviewed.

Severe Sepsis and Septic Shock

A myriad of host regulatory responses are elicited in response to severe infection, manifesting anywhere along the spectrum of sepsis to septic shock. The result may be proinflammatory. Under normal conditions glucocorticoid production is increased to prevent the inflammatory state from overwhelming the host. However, during severe infection, the body's ability to regulate the inflammatory state by increasing glucocorticoid production can be overwhelmed—a condition termed critical illness–related corticosteroid insufficiency (CIRCI).[29,30] The recognition of this phenomenon formed the basis for several seminal studies performed in the 1970s and 1980s, in which supraphysiologic doses of corticosteroids (e.g., 30 mg/kg methylprednisolone) up to several times per day were administered to patients with septic shock. However, no survival benefit was realized, and in some instances morbidity was increased as a result of an increased incidence of secondary infectious complications.[31-36] More recently, Annane and colleagues[37] showed a survival

benefit in septic patients receiving low- to moderate-dose ("physiologic") glucocorticoids. In a prospective, randomized, placebo-controlled trial (RCT) of low-dose corticosteroids, 300 patients with septic shock refractory to fluid resuscitation and vasopressors were randomly assigned to receive 50 mg IV hydrocortisone every 6 hours plus 50 μg oral fludrocortisone daily for 7 days versus placebo. All underwent cosyntropin stimulation testing. In the 229 patients who were nonresponders to ACTH testing (76%), there was a significant reduction in the risk of death in the steroid versus placebo group (53% versus 63%, $p = 0.02$). In addition, the duration of vasopressor therapy was significantly shorter in patients treated with steroids. There were no significant differences in adverse events between groups. This influential study led to renewed interest and widespread clinical use of physiologic supplementation (200-300 mg/day of hydrocortisone or its equivalent) of glucocorticoids in the treatment of septic shock and sepsis-induced hypotension.

In contrast, the 499-patient Corticosteroid Therapy of Septic Shock (CORTICUS) trial reported no benefit of corticosteroid supplementation on overall survival or reversal of shock.[38] The largest multicenter RCT to date, this study randomly assigned patients with septic shock unresponsive to fluids and vasopressors to receive steroids (50 μg hydrocortisone every 6 hours for 5 days, followed by a 6-day taper) or placebo. All underwent cosyntropin stimulation testing before treatment. In a departure from the study by Annane, there was no difference in mortality rate between the hydrocortisone and placebo groups in those unresponsive to cosyntropin stimulation. In patients whose shock was reversible, reversal occurred more quickly in the hydrocortisone group, although there were more superinfections in the treatment arm. Other side effects noted were hyperglycemia and hypernatremia.

Evidence on the administration of steroids in the treatment of sepsis is continually evolving. The 2008 Surviving Sepsis Campaign international guidelines for the management of severe sepsis and septic shock recommend that stress-dose steroid therapy only be given after conventional treatment with fluids and vasopressors has failed to restore adequate perfusion. The guidelines also suggest that cosyntropin stimulation testing not be used to identify those with septic shock who will receive hydrocortisone treatment.[39]

Acute Respiratory Distress Syndrome and Community-Acquired Pneumonia

Corticosteroids, in doses of 1 mg/kg/day methylprednisolone or equivalent, have been reported to lead to improvement in clearing lung inflammation and lung physiologic parameters.[40] A single-center randomized trial involving 24 patients in the fibroproliferative phase of ARDS (at 7 days after onset) reported improved lung function and survival with moderate-dose, prolonged corticosteroid administration.[41]

However, the ARDSnet Clinical Trial Group study, a 180-patient multicenter RCT of steroids in persistent ARDS, did not report a survival benefit with steroid treatment.[42] In this study, methylprednisolone (2 mg/kg for one dose, then 0.5 mg/kg every 6 hours for 14 days with an extended taper) was associated with reductions in shock symptoms and ventilator days, improved respiratory system compliance, and reduction in the need for vasopressor therapy but not with an improved survival rate. In addition, significantly increased 60- and 180-day mortality rates were identified in steroid-treated patients enrolled greater than 14 days after disease onset. Infectious complications were not increased, but the incidence of neuromuscular weakness was higher in the methylprednisolone-treated patients.

Conversely, another prospective RCT that administered methylprednisolone by continuous infusion in 91 patients with early ARDS (onset less than 72 hours) reported improvements in lung function and extrapulmonary organ function and reductions in both duration of mechanical ventilation and intensive care unit (ICU) length of stay.[43] It should be noted that strict infection surveillance, tight glucose control, and avoidance of neuromuscular blocking drugs were integral parts of the protocol.

Glucocorticoid supplementation has also been recently advocated as an adjunct to antibiotics in the treatment of CAP. Despite an initial negative trial of hydrocortisone versus placebo in treatment of CAP, subsequent trials reported more promising results, which have included improved gas exchange (as evidenced by PaO_2 to FiO_2 ratio), a decreased length of ICU stay, and a lower occurrence of progression to septic shock.[44-46] The largest of these trials enrolled 304 patients with severe CAP and prospectively randomized them to receive either 5 mg daily dexamethasone or placebo for 4 days.[47] No survival benefit was seen, but the median hospital length of stay was 1 day shorter in those receiving steroids.

Given the inconsistencies in clinical evidence, the precise role of corticosteroids in ARDS and pneumonia remains elusive and requires further study before definitive recommendations can be made.

Meningitis, Traumatic Brain Injury, and Acute Spinal Cord Injury

One RCT indicates that dexamethasone, administered in conjunction with the first antibiotic dose, significantly reduces mortality rate, severe hearing loss, and neurologic sequelae in adults with community-acquired bacterial meningitis.[48] A 2010 meta-analysis supports the reduction in hearing loss and neurologic sequelae but failed to find a survival benefit.[49]

Despite a significant incidence of hypoadrenalism (25%) soon after TBI, there is strong evidence against routine corticosteroid treatment in head-injured patients.[50] In a large multicenter study the risk of death from all causes within 14 days was higher in those patients with TBI who received a 48-hour infusion of corticosteroids when compared with those administered placebo. Furthermore, at 6 months, the relative risk of death or severe disability favored the placebo group.[51,52]

The treatment of acute SCI with steroids is controversial. Evidence from the National Acute Spinal Cord Injury Studies (NASCIS) in the early 1990s supported high-dose methylprednisolone (30 mg/kg with infusion

of 5.4 mg/kg/hr for 24 hours) after acute SCI, ideally administered within 8 hours of injury.[53] Based on these initial studies, the treatment was widely adopted and became a standard of care. However, there has been much criticism of the study design and statistical analysis, and other conflicting clinical evidence has emerged, causing some clinicians to abandon use because of an unacceptable risk–benefit ratio.[54-56] However, a 2012 Cochrane review also supports methylprednisolone use in SCI to improve both motor and sensory outcomes.[57] The review recommends the same dosing as the NASCIS study but also recommends that therapy duration be extended to 48 hours if treatment is initiated between 3 and 8 hours after injury. In an investigation by Leypold and colleagues[58] comparing acute SCI lesions by magnetic resonance imaging characteristics, patients who received methylprednisolone had significantly less intramedullary spinal cord hemorrhage than those who were not treated.

Indicative of the situation is a survey of 305 spine surgeons that found 90% would initiate methylprednisolone, especially if within the 8-hour window. Interestingly, many cited institutional protocols and medicolegal reasons as justification for use; only 24% used steroid treatment because of a belief in improved outcomes.[59] An area of ongoing debate, high-dose methylprednisolone use may be effective in promoting some degree of neurologic improvement if given early after injury, although more well-designed RCTs are necessary.

Etomidate

Interest has been increasing recently in the use of the induction agent etomidate in critically ill patients, in particular for facilitation of intubation. An imidazole derivative, etomidate is often a first-line agent for endotracheal intubation or procedural sedation in the critically ill because of its minimal hemodynamic side effects. However, it is known to inhibit the 11beta-hydroxylase enzyme responsible for converting 11beta-deoxycortisol into cortisol within the adrenal gland. The potent suppression of adrenal steroidogenesis by etomidate was first described in 1984 by Wagner and White and has been shown to occur after even a single dose of etomidate.[60-62] A systematic review of etomidate use in the critically ill found not only a significant increase in AI but also more ventilator-dependent days, longer hospital and ICU lengths of stay, and an increased mortality rate (relative risk for mortality versus patients not receiving etomidate, 1.19; confidence interval, 1.10 to 1.30).[63] The risk of harm was greatest in the subset of patients with a diagnosis of sepsis. Conversely, in a retrospective review of septic patients who received either etomidate or an alternate agent to facilitate intubation, no significant outcome differences between groups were found.[64] In an RCT in which patients without sepsis who received etomidate were randomly assigned to either receive daily hydrocortisone (200 mg IV continuous infusion) or placebo, the patients receiving steroid supplementation required vasopressor therapy for a shorter duration.[65] However, there was no difference in length of stay, duration of ventilator use, or 28-day mortality. The results of these studies highlight the need for further investigation, as the clinical relevance of the effect of etomidate on adrenal function remains open for debate. Until further evidence is available, some authors recommend that etomidate be used judiciously in the critically ill, whereas others recommend discontinuing its use altogether, particularly in patients with severe sepsis or septic shock. In response to these concerns, an etomidate derivative, carboetomidate, has been developed. It is reported to be a less potent inhibitor of in vitro cortisol synthesis by three orders of magnitude and, in rats, caused minimal hemodynamic changes without suppressing adrenocortical function.[66] However, human testing has yet to be performed.

GUIDELINES

Currently, accepted guidelines on the perioperative use of glucocorticoid replacement are limited. A 2009 Cochrane analysis on perioperative steroid management for patients with adrenal insufficiency was inconclusive because of small patient numbers included in the analysis.[67] A systematic review of the literature published in 2008 included the two small RCTs analyzed in the Cochrane review as well as seven additional cohort studies for an analysis of 315 total patients.[68] The authors of the review recommend against routine steroid supplementation in the perioperative period for patients taking disease-modifying doses of glucocorticoids as long as the regular daily dose of steroid continues to be administered. In contrast, patients receiving steroid therapy for primary disease of the HPA axis do require supplemental "stress dose" steroid supplementation in the perioperative period. Routine cosyntropin stimulation testing of the HPA axis is not recommended in the review.

AUTHORS' RECOMMENDATIONS

- Patients receiving long-term glucocorticoid therapy of more than 5 mg/day of prednisone or its equivalent (Table 26-2) should receive their daily therapeutic dose either orally or parenterally (especially if there is a question about enteral absorption) before a procedure or during an illness. A graduated supplementation schedule of the patient's basic glucocorticoid dose (as outlined in Table 26-3) is advocated for patients sustaining increasingly stressful procedures or illnesses. Supplemental doses should be tapered to baseline relatively quickly (within a day or so), depending on the stress of surgery or illness and on patient response. Oral medications should be administered when the patient is able to ingest and absorb them. Patients with primary adrenal insufficiency (AI) usually require both mineralocorticoid and glucocorticoid replacement unless the total hydrocortisone dose is in excess of 50 mg within 24 hours. Most patients with secondary or tertiary AI have intact aldosterone synthesis and usually only require glucocorticoid

replacement. Rarely, if ever, do patients require greater than 200 mg/day of hydrocortisone or its equivalent for glucocorticoid replacement or mineralocorticoid supplementation therapy. Although perioperative adrenal crisis is rare, a physiologically based glucocorticoid replacement schedule appears to be efficacious in limiting untoward side effects and avoiding potential compromise secondary to acute AI. The relatively high rate of functional hypoadrenalism in septic patients and the elderly should be appreciated. These patients should receive physiologic perioperative steroid replacement as needed, based on the clinical situation.

- Routine use of corticosteroids in patients with septic shock or acute respiratory distress syndrome (ARDS) is not recommended but should be used on a case-by-case basis, whereby the absolute cortisol level is evaluated in patients with septic shock and the risk–benefit ratio is evaluated for patients with sepsis or ARDS. Cosyntropin stimulation is not recommended routinely in the evaluation of patients with septic shock. If used in ARDS, corticosteroids should not be initiated more than 14 days from the onset of ARDS and likely should be started within the first 7 to 10 days.
- A short course of steroids is routinely recommended in the early treatment of common causes of bacterial meningitis, particularly *Streptococcus pneumoniae*.
- Corticosteroid treatment for acute spinal cord injury is controversial, although it may be used if initiated within 8 hours of the injury. Methylprednisolone bolus within 8 hours of injury followed by a 24- to 48-hour infusion is advised when used.
- Corticosteroids are not recommended as a measure to lower elevated intracranial pressure or reduce edema in the early treatment of traumatic brain injury.
- Etomidate is associated with transient inhibition of adrenal steroidogenesis and should be used judiciously in the critically ill patient. Routine corticosteroid supplementation in patients who have received etomidate does not appear to be warranted; rather, close attention should be given to clinical and laboratory indications of AI in these patients, and treatment with corticosteroids should be individualized.

TABLE 26-2 **Comparative Steroid Potency (mg Basis)***

Steroid Preparation	Glucocorticoid Effect	Mineralocorticoid Effect	Biologic Half-Life (hr)	Formulation
Hydrocortisone	1	1	6-8	PO, IV, IM
Prednisone	4	0.1-0.2	18-36	PO
Methylprednisolone	5	0.1-0.2	18-36	IV
Dexamethasone	30	<0.1	36-54	PO, IV
Fludrocortisone	0	20	18-36	PO

IM, intramuscular; *IV,* intravenous; *NPO,* nil per os (nothing by mouth); *PO,* per os (by mouth).
*Intravenous supplementation is the preferred route for patients who are NPO, have unpredictable or poor absorption of medications, or have major stresses or critical illness. Prednisone is not recommended in patients who are unable to methylate it into an active form.

TABLE 26-3 **Guidelines for Adrenal Supplementation Therapy**

Medical or Surgical Stress	Corticosteroid Dosage
Minor	
Inguinal hernia repair Colonoscopy Mild febrile illness Mild-moderate nausea/vomiting Gastroenteritis	25 mg of hydrocortisone or 5 mg of methylprednisolone IV day of procedure only
Moderate	
Open cholecystectomy Hemicolectomy Significant febrile illness Pneumonia Severe gastroenteritis	50-75 mg of hydrocortisone or 10-15 mg of methylprednisolone IV day of procedure Taper quickly over 1-2 days to usual dose
Severe	
Major cardiothoracic surgery Whipple procedure Liver resection Pancreatitis	100-150 mg of hydrocortisone or 25-30 mg of methylprednisolone IV day of procedure Rapid taper to usual dose over next 1-2 days

From Coursin DB, Wood KE. Corticosteroid supplementation for adrenal insufficiency. JAMA 2002;287:236–40.

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CHAPTER 27

Does the Choice of Fluid Matter in Major Surgery?

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INTRODUCTION

Numerous preparations of intravenous (IV) fluid are available for the replacement of perioperative fluid losses in patients undergoing major surgery. The selection of a specific fluid may be influenced by multiple factors, such as availability, cost, and tradition. Of late, attention has focused on the possible systemic effects of the various fluid preparations. Additionally, there is awareness that particular fluids may not only influence clinical variables during the intraoperative period but may also affect postoperative outcome. Clinicians' choice of fluid replacement therapy for patients undergoing major surgical procedures is increasingly influenced by the beneficial or detrimental effects of IV fluids, independent of their efficacy as blood volume expanders.

Many clinical and experimental studies have been carried out to determine the potential clinical effects of IV fluids. Unfortunately, there is a paucity of large, prospective, randomized, blinded clinical studies of the effects of the intraoperative administration of IV fluids on clinical outcomes, despite the fact that approximately 3 million major surgical procedures are performed annually in the United States alone. However, multiple outcomes have been examined in small investigations in numerous and diverse patient populations and in studies of healthy volunteers.

In addition to the fluids themselves, a separate body of literature has looked at the way in which these fluids are administered. Fluid studies are often labeled *restrictive*, *liberal*, or *goal directed*. *Goal-directed fluid therapy* is a term that relates to the use of an algorithm to guide administration of fluids to optimize hemodynamic status.

To address the question "Does the choice of fluid matter in major surgery?" we will consider the available data from clinical studies of intravascular volume replacement in patients undergoing major surgery. The interpretation of studies of IV fluids is somewhat confounded by their size and design. In many cases, only small numbers of patients have been studied. These trials may not have sufficient power to detect differences in clinically relevant outcomes, and their results are therefore interpreted with this caveat in mind.

OPTIONS/THERAPIES

Traditionally, IV fluids have been classified according to whether they are crystalloid or colloid in nature. Crystalloid fluids comprise electrolyte solutions with or without bicarbonate or one of its precursors, such as acetate or lactate. The colloids contain a complex sugar or protein suspended in an electrolyte solution. A further distinction between IV fluid types may be based on the nature of the solution. Preparations based on 0.9% normal saline (NS) (crystalloid or colloid) contain no electrolytes other than sodium and chloride. In contrast, balanced salt (BS)-based fluids such as lactated Ringer (LR) solution are those that contain other electrolytes with or without bicarbonate or a bicarbonate precursor.

Several types of colloid are available, but three are most commonly used: hydroxyethyl starch (HES), gelatin, and albumin. The HES preparations differ from one another according to their concentration, molecular weight, and extent of hydroxyethylation or substitution, with resultant varying physiochemical properties. HES solutions may be described according to concentration (3%, 6%, 10%), weight-averaged mean molecular weight in kilodaltons (kDa) (high-molecular weight [450-670 kDa], middle-molecular weight [200-270 kDa], low-molecular weight [70-130 kDa]), and the molar substitution (0.4-0.7). HES 670/0.75 and 130/0.4 are available in an NS solution (e.g., HES 130/NS) and in a BS solution (e.g., HES 130/BS). Two forms of gelatin are available: modified (succinylated) and the polygelines. Although all of these colloids are used in Europe, gelatins are not available in the United States, and the only HES preparations approved by the Food and Drug Administration (FDA) are the 670 kDa BS (Hextend, Hospira, Lake Forest, Ill), 670kDa NS (Hespan, B Braun, Irvine, Calif), and 130/NS (Voluven, Fresenius Kabi, Germany) formulations.

EVIDENCE

Does the Choice of Crystalloid Matter in Major Surgery?

Crystalloid therapy is an essential part of all fluid therapy regimens. Electrolyte-containing crystalloid solutions are distributed throughout the extracellular compartment

and are used to replace insensible and evaporative losses and urine output during major surgery.

The most commonly used crystalloid in the world is 0.9% NS. However, evidence is emerging that it may cause significant harm. NS is not *normal* in the physiologic meaning of the word because it contains 154 mmol/L of chloride, which is significantly more than the plasma concentration of 105 mmol/L. Administration of NS and NS-based fluids therefore causes a predictable hyperchloremic metabolic acidosis.[1-6] This phenomenon has been known for many years, but the question remains, does this acidosis cause any harm?

Shaw and colleagues[7] investigated this risk of harm in a recently published large retrospective database analysis comparing the administration of either NS alone or a balanced crystalloid solution (Plasma-Lyte, Baxter, Ill) alone on the day of surgery. They found that in the NS group the use of special investigations (measurement of arterial blood gases and lactate levels) and treatments (buffers, blood products) was increased, presumably because saline-induced acid–base abnormalities needed to be investigated and managed. When compared with administration of a balanced electrolyte solution, the administration of NS was also found to cause a significantly greater risk of postoperative infection and renal failure requiring dialysis. It is known that hyperchloremia may cause renal vasoconstriction and a decrease in the glomerular filtration rate,[8] which may explain, in part, the mechanism for NS-induced changes in renal performance. Alternatively, the metabolic acidosis itself may induce vasoconstriction and redistribution of intrarenal blood flow with subsequent effects on function.

Several prospective, randomized studies have compared the effects of NS-based and BS-based fluids and have observed a worse urinary output in patients treated with the NS-based fluid preparations.[2,3,9] Other investigators have not noted superior renal function after the administration of BS fluids. Intraoperative urine output was greater in patients who received NS than in patients who were given LR during abdominal aortic aneurysm repair.[5] However, NS-treated patients received a larger volume of fluid than patients in the LR group, as well as significant quantities of sodium bicarbonate intraoperatively for treatment of hyperchloremic metabolic acidosis, which suggests that the prevention or treatment of hyperchloremic metabolic acidosis may have negated the negative impact of NS on renal function in some way.

Two studies have looked at the impact of crystalloid choice in patients undergoing kidney transplantation.[10,11] In both studies patients were randomly assigned to receive either NS or LR for intraoperative fluid resuscitation, and investigators found that hyperkalemia and acidosis were more common in the NS group. In the study by O'Malley and colleagues,[11] eight patients (31%) in the saline group versus zero patients (0%) in the LR group were treated for metabolic acidosis. In addition, five patients (19%) in the saline group had potassium concentrations greater than 6 mEq/L and were treated for hyperkalemia versus zero in the LR group. These results suggest that acidosis-induced extracellular shift of potassium causes a greater risk of hyperkalemia than the small amount of potassium in LR and challenges the dogma that NS should be administered to patients with renal failure.

Other studies suggest NS-based fluids may be associated with more bleeding than BS solutions.[12,13] Waters and colleagues[5] reported that patients undergoing abdominal aortic aneurysm repair who received LR solution were given smaller volumes of platelets and had less blood product exposure than those treated with NS. HES 670/NS may also be associated with more bleeding than HES 670/BS solution. In a study of 120 major surgical patients, blood loss was greater among patients who received HES 670/NS than in patients who received HES 670/BS.[9]

When differences between fluid types are seen, they may be mediated through impaired platelet function, possibly as a consequence of diminished circulating von Willebrand factor (vWF) antigen and vWF:ristocetin cofactor in patients treated with NS-based rather than BS-based fluids. A second possible explanation is the lack of calcium in NS and related fluids. Calcium is a necessary cofactor at several points in the coagulation process. It is necessary for activation of clotting factors, as well as for normal platelet function. In particular, calcium binding is a prerequisite for the stability and function of the platelet GPIIb/IIIa receptor. This receptor binds fibrinogen and vWF with resultant platelet activation and aggregation. With blood loss and IV fluid administration, ionized calcium levels may fluctuate, and this variation may affect coagulation. Ionized calcium levels may be lower after administration of NS and related fluids rather than after administration of BS fluids.[2,9] The presence of calcium in IV fluids may maintain more constant plasma calcium levels, avoiding the potential detrimental effect of low or fluctuating ionized calcium levels on coagulation. Thirdly, the role of hyperchloremic acidosis must also be considered because acidosis has been implicated in coagulation derangements.[5]

Wilkes and colleague[2] have also implicated NS-based fluids in splanchnic ischemia and postoperative nausea and vomiting. Elderly surgical patients were randomly assigned to receive either a combination of HES 670/BS and LR or a combination of HES 670/NS and NS for intraoperative fluid replacement. In the BS-based-fluid–treated group there was a smaller intraoperative increase in the CO_2 gap, indicating that BS-based fluids are associated with superior splanchnic perfusion as compared with NS-based fluids. It was postulated that impaired gut perfusion or hyperchloremia associated with NS-based preparations might have caused an impairment of splanchnic perfusion in the patients who were administered NS and HES 670/NS. Of note, the poor splanchnic perfusion in patients treated with the NS-based regimen may have been mediated by generalized vasoconstriction (perhaps secondary to metabolic acidosis), given that these patients also exhibited other evidence of vasoconstriction such as lower urine flow rates and lower peripheral-to-core temperature gradients (reflecting peripheral vasoconstriction).

It is also interesting to note that in a randomized crossover study of healthy volunteers, subjective deterioration in mental status (i.e., lassitude and difficulty in abstract thinking) was reported only by individuals who received NS and not by those who received LR.[14] The

possible effect of different IV fluid preparations on central nervous system function has not yet been explored in prospective, randomized clinical studies of patients undergoing major surgical procedures.

The one area of practice in which the use of NS may be prudent is in traumatic brain injury. A post hoc subset analysis of the SAFE study for patients with traumatic brain injury ($n = 460$) revealed a lower mortality rate in patients treated with NS compared with albumin (33.2% versus 20.4%).[15] Otherwise, the use of balanced crystalloid solutions seems to cause no harm and could possibly be beneficial. Unfortunately, no significant studies have compared different balanced regimens. In particular, there are no data comparing the different anions (i.e., lactate, acetate, and gluconate) used as alternatives to chloride.

Does the Choice of Colloid Matter in Major Surgery?

Colloids have a smaller volume of distribution than crystalloids, and the majority of the solution remains in the intravascular space. Colloid therapy is therefore frequently used to restore intravascular volume depletion from blood loss or protein-rich shifts to the interstitial space during major surgery.

Impact of Colloids on Coagulation

Albumin has not been associated with significant clotting abnormalities or perioperative bleeding. The gelatins have been associated with minor abnormalities in coagulation, possibly because of derangements in fibrinogen polymerization.[16] However, this has not been associated, other than on an anecdotal basis, with clinically significant perioperative bleeding.

There have been consistent reports of coagulation impairment with the older HES preparations since they were introduced into clinical practice. HES macromolecules interact with platelets and the coagulation cascade, causing a decrease in factors such as factor VIII and vWF.[17,18] In a study of patients undergoing off-pump cardiac surgery, HES 670/BS increased bleeding and transfusion requirements compared with 4% albumin.[19] Two large observational studies found HES 670/0.7 was an independent risk factor for postoperative hemorrhaging.[20,21]

The effect of third-generation starches on coagulation is controversial. Voluven130/NS (Fresenius Kabi, Bad Homburg, Germany) was designed with a better coagulation profile in mind and has a molar substitution of 0.4 and a C_2/C_6 ratio of approximately 9 : 1. Third-generation starches formulated in BS solutions are available around the world but are not commercially available in the United States at the current time.

Several in vitro studies have demonstrated that third-generation HES products have a lesser effect on coagulation.[22-24] However, in vitro studies can be misleading because they cannot mimic the in vivo environment that will occur during progressive hemodilution. The administration of a large volume of any type of IV fluid will cause dilution of platelets and coagulation factors and may lead to coagulopathy. Because of the multifactorial etiology of bleeding during surgery, it is impossible to know, in any given patient, whether the type of fluid administered is a cause of bleeding independent of the impact of hemodilution. Only properly designed, randomized, clinical trials can determine fluid-specific effects on bleeding and other clinical outcomes. Although many studies report some clinical outcomes related to bleeding, a large number focus on measurements or markers of coagulation and have not been designed to explore outcomes of more clinical relevance such as blood product usage and surgical re-exploration for bleeding.

With this in mind, several studies demonstrated that Voluven has fewer adverse effects on coagulation compared with the higher molecular weight starches[25-27] or has an impact on coagulation similar to gelatin.[28,29] A recent meta-analysis showed a small reduction in bleeding and blood product transfusion with HES 130/0.4 compared with HES 200/0.5.[30] However, other studies have showed similar effects on coagulation with different HES solutions (Table 27-1).[31,32]

In pediatric cardiac patients, Hanart and colleagues[33] compared pump priming with HES 130 or 4% albumin and showed no difference in bleeding; however, a greater need for allogeneic blood was seen in the albumin group. In another randomized controlled trial (RCT) of pediatric noncardiac surgery patients assigned to HES 130/0.4 or albumin, no differences in blood loss or coagulation variables were seen.[34] Conversely, other studies in cardiac[35,36] and noncardiac surgery[37] have shown impaired thromboelastographic variables with HES 130/0.4 compared with albumin. Among patients with severe head injuries, high doses of HES 130/0.4 showed no difference in coagulation variables or bleeding compared with a combination of HES 200/0.5 and 5% albumin.[38]

It is therefore difficult to draw firm conclusions on the effect of the third-generation starches on coagulation. HES 130/0.4 may have a lesser effect on coagulation than older starches; however, whether this is comparable with albumin needs to be confirmed in larger studies.

Impact of Colloids on Renal Function and Urine Output

The biggest concern about the administration of colloids, with the exception of albumin, is the effect on renal function. There are no reports of renal dysfunction after administration of albumin, even in severe sepsis.[39] In contrast, some data suggest that gelatins may have some effect on renal function in patients with severe sepsis,[40] although this is far from conclusive. By far the biggest concern, however, is with the HES solutions. The administration of older HES solutions to critically ill patients in the intensive care unit (ICU) is associated with the development of renal dysfunction.[41-43] The Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study showed higher rates of acute renal failure and the need for renal replacement therapy with HES compared with LR.[44] However, the investigators used large doses of a hyperoncotic 10% pentastarch, frequently in excess of the daily dosing limit. Because the adverse effects of hyperoncotic starches on renal function is well-known,[45] the general applicability of these results is open to interpretation.

Currently, the main controversy is regarding the effect of third-generation starches on renal function. Very few RCTs have studied the impact of HES 130 on renal function in the perioperative period. Two small studies compared HES 130/0.4 with gelatin in cardiac[28] and major vascular surgery[46] and showed no differences in renal function. Godet and colleagues[47] suggested that HES 130/0.4 was comparable with gelatin in patients with preexisting renal impairment undergoing abdominal aortic surgery (Table 27-2).

Therefore most of our information on effects of HES 130/0.4 on renal function comes from observational studies in the ICU. In a retrospective analysis of data from 3147 critically ill patients in the Sepsis Occurrence in Acutely Ill Patients (SOAP) study, HES 130/0.4 was not an independent risk factor for adverse effects on renal function, even in the 822 patients with severe sepsis or septic shock.[48] However, in another large observational study of 2911 surgical ICU patients, HES 130/0.4 at doses greater than 33mL/kg was an independent risk factor for acute renal failure.[49]

As this book goes to press, the 6S (Scandinavian Starch for Severe Sepsis/Septic Shock) Trial has just been published.[49a] This large RCT compared fluid resuscitation on the ICU in patients with severe sepsis. Patients were assigned to either HES 130/0.4 or Ringer acetate at a dose of up to 33 mL/kg of ideal body weight per day. Patients given HES 130/0.4 had an increased risk of death at day 90 and were more likely to require renal replacement therapy compared with those receiving Ringer acetate. Therefore the use of any hydroxyethyl starch in severe sepsis cannot be recommended. Crystalloid versus Hydroxyethyl Starch Trial (CHEST), a multicenter trial comparing 90-day all-cause mortality rates after infusion of HES 130/NS or NS alone in 7000 ICU patients, has also just been completed.[50] Results were expected in late 2012.

TABLE 27-1 **Impact of HES 130/0.4 on Perioperative Coagulation: Prospective, Randomized Clinical Trials of the Intraoperative Administration of ≥1 L of IV Fluid**

Author, Year	Control Fluid(s)	*N*	Type of Surgery	Outcome
Gallandat Huet,[25] 2000	HES 200/0.5	59	Cardiac	Less effect on vWF with HES 130/0.4 Less blood loss and use of blood products with HES 130/0.4
Hanart,[33] 2009	4% albumin	119	Pediatric cardiac	No difference in blood loss Higher use of blood products in the albumin group
Langeron,[27] 2001	HES 200/0.5	100	Orthopedic	Less effect on FVIII levels and APTT with HES 130/0.4 No difference in use of blood products
Kasper,[31] 2003	HES 200/0.5	120	Cardiac	No difference in blood loss or use of blood products
Sander,[32] 2003	HES 200/0.5	60	Major gynecologic	No difference in coagulation tests or blood loss
Van der Linden,[29] 2005	3% gelatin	132	Cardiac	No difference in blood loss or use of blood products
Gandhi,[26] 2007	HES 670/0.75	100	Orthopedic	Less effect on FVIII and vWF levels with HES 130/0.4
Mittermayr,[37] 2007	LR	66	Orthopedic	Less clot firmness measured by TEG in the HES group
Mukhtar,[82] 2009	5% albumin	40	Liver transplant	No difference in coagulation tests or use of blood products
Ooi,[28] 2009	4% gelatin	90	Cardiac	No difference in blood loss or use of blood products
Schramko,[35] 2009	HES 200/0.5 4% albumin	45	Cardiac	Less clot firmness measured by TEG in both HES groups No difference in blood loss
Schramko,[36] 2010	4% gelatin Ringer acetate	45	Cardiac	Less clot firmness measured by TEG in the HES group No difference in blood loss

APTT, activated partial thromboplastin time; *FVIII,* factor VIII; *HES,* hydroxyethyl starch; *IV,* intravenous; *LR,* lactated Ringer; *TEG,* thromboelastography; *vWF,* von Willebrand factor.

TABLE 27-2 **Impact of HES 130/0.4 on Perioperative Renal Function and Urine Output: Prospective, Randomized Clinical Trials of the Intraoperative Administration of ≥1 L of IV Fluid**

Author, Year	Control Fluid(s)	*N*	Type of Surgery	Outcome
Gallandat Huet,[25] 2000	HES 200/NS	59	Cardiac	No difference in urine output or serum creatinine
Langeron,[27] 2001	HES 200/NS	100	Orthopedic	No difference in urine output
Mahmood,[46] 2007	HES 200/NS Gelatin/NS	62	Abdominal aortic aneurysm	No difference in urine output. Less derangement in markers of glomerular and tubular function with HES 200/NS and HES 130/NS
Ooi,[28] 2007	4% gelatin	63	Cardiac	No difference in estimated glomerular filtration rate
Godet,[47] 2008	3% gelatin	65	Abdominal aortic aneurysm	No difference in urine output, creatinine clearance, or adverse renal events
Mukhtar,[82] 2009	5% albumin	40	Liver transplant	No difference in serum creatinine, creatinine clearance, or cystatin C levels

HES, hydroxyethyl starch; *IV,* intravenous; *NS,* 0.9% NaCl or normal saline–like solution.

Other Effects of Colloid Solutions

In a randomized study of 40 patients receiving either HES 200/NS or a gelatin solution during elective infrarenal aortic aneurysm repair, lower levels of inflammatory markers (i.e., C-reactive protein, microalbuminuria, and plasma vWF) were observed in the HES-treated group than in the gelatin-treated group after cross-clamp removal.[51] These data suggest that HES may mediate the inflammatory response after major surgery.

Hyperamylasemia is associated with the administration of HES but not with other fluid types.[52,53] Amylasemia is caused by HES through the formation of an HES–amylase complex with consequent reduction in elimination of amylase by the kidneys. This effect is greater with HES 200/NS than with HES 130/NS, which is consistent with the pharmacokinetics of different HES preparations.[25,27] Intraneural deposition of HES has been purported to cause pruritus after HES administration.[54] Small retrospective studies, in a number of patient populations, have reported a high incidence of HES-induced pruritus.[55-57] However, no large epidemiologic studies examining this phenomenon have been performed in patients undergoing major surgery who have received large volumes of fluid. Interestingly, the incidence of postoperative pruritus in a prospective study of 750 surgical patients was similar (10%) in patients who received 500 mL of HES 200/NS and in patients who received 1000 mL of LR.[58] The most important potential adverse effect of IV fluids is the occurrence of possibly life-threatening anaphylactic or anaphylactoid reactions. The incidence of severe anaphylactic reactions is 0.038% to 0.345% with gelatins, 0.0004% to 0.058% with HES administration, and 0.099% in patients who receive albumin.[59]

Finally, significant cost reduction (32% to 35%) has been shown when HES was used for intraoperative fluid replacement rather than 5% albumin.[4,60]

Perioperative Fluid Management

It is common for patients to receive IV fluid amounts that greatly exceed perioperative losses. Perioperative IV fluid regimens in abdominal surgery can lead to patients receiving 3.5 to 7 L of fluid on the day of surgery, leading to a 3- to 6-kg weight gain.[61] This is done to replace assumed preoperative deficits, as well as insensible perspiration, "third space" losses, and urine output. Chappell and colleagues[62] reviewed the evidence and suggested that losses via insensible perspiration have been grossly exaggerated and are probably no more than 1 mL/kg/h during major abdominal surgery. Additionally, a third space, as it was originally described, does not exist.[62] There is no evidence for a nonfunctional space in which fluid is sequestered. Fluid is simply shifted perioperatively from the intravascular space toward the interstitium.

Brandstrup and colleagues[63] found that a combination of crystalloid and colloid designed to avoid fluid overloading and maintain fluid balance, guided by body weight, significantly reduced postoperative complications and length of hospital stay after colorectal surgery. In the postoperative period, water and salt restriction to less than 2 L and 70 mmol, respectively, per day caused earlier return of bowel function and reduced weight gain and length of stay.[64]

In noncardiac surgical patients the administration of HES 450 was associated with less edema, postoperative nausea, vomiting, and antiemetic use than the administration of LR solution.[65]

Superior gut function in patients who receive a combined crystalloid and colloid fluid regimen for intraoperative volume resuscitation might be explained by the presence of less intestinal edema than in patients who receive crystalloids alone. More severe periorbital edema was observed after the administration of LR than after intraoperative HES administration in patients who underwent major abdominal surgery.[65] It seems likely that edema may also occur in the gastrointestinal tract and that this may influence gut function in patients undergoing gastrointestinal and nongastrointestinal surgery. Indeed, more intestinal edema was seen in patients undergoing a Whipple operation who received LR solution rather than HES 450/NS or 20% albumin/NS for intraoperative fluid replacement.[66]

Several other trials have compared restrictive and liberal fluid or sodium regimens.[67-69] The results are not uniform, and comparison is difficult because administered volumes and electrolytes in both arms differed substantially, which reflects nonuniform standard practice. Therefore it has been suggested that "future studies should focus on the effects of individualized 'goal-directed' fluid administration strategies rather than fixed fluid amounts on postoperative outcome."[69]

Goal-Directed Fluid Therapy

Goal-directed fluid therapy (GDFT) is a term that refers to the use of an algorithmic approach to fluid management, whereby tissue oxygenation and intravascular volume status is optimized by assessing and responding to each patient's individual hemodynamic response to fluid boluses.[70-72] GDFT has been associated with improved outcomes after moderate to major surgery, with shorter hospital stays, fewer ICU admissions, and earlier return of bowel function[73-78] (Table 27-3). Most studies use crystalloids and colloids in combination, with background crystalloid infusions to replace extracellular losses augmented by colloid boluses to maintain central euvolemia. A recent meta-analysis suggests that this approach reduces morbidity and mortality rates for high-risk surgical patients.[79]

GDFT is frequently performed as part of enhanced recovery after surgery (ERAS) programs. ERAS pathways integrate a range of evidence-based perioperative interventions to facilitate postoperative recovery.[80] The patient's journey is viewed as a continuum, and preoperative, intraoperative, and postoperative care are of equal importance.

Preoperatively, the avoidance of routine bowel preparation, a preoperative carbohydrate drink, and tolerance of clear fluids until 2 hours before the operation can help avoid hypovolemia and bring the patient to surgery in a fed state. This, in turn, aids intraoperative fluid management. Postoperatively, early enteral nutrition can enable IV fluid therapy to be discontinued within 24 hours and normal homeostasis to resume.

TABLE 27-3 **Impact of Goal-Directed Fluid Therapy on Perioperative Outcomes: Prospective, Randomized Clinical Trials Using Minimally Invasive Cardiac Output Monitors**

Author, Year	Device	Type of Surgery	*N*	Outcome
Mythen,[83] 1995	Esophageal Doppler	Cardiac	60	↓ gastric acidosis in GDFT ↓ complications in GDFT ↓ LOS (3.5 days) in GDFT
Sinclair,[77] 1997	Esophageal Doppler	Neck of femur fracture	40	↓ time FFD (5 days) in GDFT ↓ LOS (8 days) in GDFT
Conway,[84] 2002	Esophageal Doppler	Major bowel	57	↑ ICU admissions in control No difference in LOS
Gan,[74] 2002	Esophageal Doppler	Major general	100	↑ PONV in control ↓ time to tolerating oral intake in GDFT ↓ LOS (2 days) in GDFT
Venn,[78] 2002	Esophageal Doppler	Neck of femur fracture	90	↓ time FFD (6.2 days) in GDFT (versus control) ↓ time FFD (3.9 days) in CVP (versus control)
McKendry,[85] 2004	Esophageal Doppler	Cardiac surgery	174	↓ LOS (2.5 days) in GDFT No difference in complications
Wakeling,[86] 2005	Esophageal Doppler	Colorectal	128	↓ morbidity (GI and overall) in GDFT ↓ time to full diet (1 day) in GDFT ↓ LOS (1.5 days) in GDFT
Noblett,[87] 2006	Esophageal Doppler	Colorectal	108	↓ morbidity in GDFT ↓ time to tolerating diet (2 days) in GDFT ↓ LOS (2 days) in GDFT
Lopes,[88] 2007	Arterial waveform analysis	Major general	33	↓complications in GDFT ↓ LOS (10 days) in GDFT
Buettner,[89] 2008	Arterial waveform analysis	Major abdominal	80	No difference in complications No difference in LOS
Kapoor,[90] 2008	Arterial waveform analysis	Cardiac	30	↓ days with a ventilator in GDFT ↓ days given inotropes in GDFT ↓ ICU stay (2 days) in GDFT ↓ LOS (3 days) in GDFT
Senagore,[91] 2009	Esophageal Doppler	Colorectal	64	↑ complications in GDFT with colloid ↑ LOS (9 hr) in GDFT
Benes,[92] 2010	Arterial waveform analysis	Major abdominal	120	↓ complications in GDFT ↓ lactate at the end of surgery in GDFT No difference in LOS
Forget,[93] 2010	Pulse oximeter analysis	Major abdominal	82	↓ perioperative lactate levels in GDFT No difference in complications or LOS
Challand,[94] 2012	Esophageal Doppler	Colorectal	179	No difference in complications No difference in LOS

CVP, central venous pressure; *FFD,* fitness for discharge; *GDFT,* goal-directed fluid therapy; *GI,* gastrointestinal; *ICU,* intensive care unit; *LOS,* length of stay; *PONV,* postoperative nausea and vomiting.

CONTROVERSIES

The safety of HES, particularly in patients with sepsis or septic shock, is currently the main controversy in IV fluid administration. As already mentioned, it is hoped that large RCTs currently under way in this population will provide robust evidence to guide future practice.

GUIDELINES

The British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP) were published by a consensus group online in 2009 and revised in 2011. They recommended that

- the use of BS solutions should replace NS, except in cases of hypochloremia from, for example, vomiting or gastric drainage
- in patients undergoing some forms of orthopedic and abdominal surgery, intraoperative treatment with IV fluid to achieve an optimal value of stroke volume should be used when possible because this may reduce complication rates and the duration of the hospital stay

The European Society of Intensive Care Medicine task force on colloid volume therapy in critically ill patients recently released a consensus statement. They recommended not to use HES with a molecular weight of 200 kDa or greater and a degree of substitution of more than 0.4 in patients with severe sepsis or risk of acute kidney injury and suggested not to use 6% HES 130/0.4 or gelatin in these populations. They also recommended not to use colloids in patients with head injuries, not to administer gelatins and HES in organ donors, and suggested not to use hyperoncotic solutions for fluid resuscitation.[81]

AUTHORS' RECOMMENDATIONS

It is clear from this review that the evidence regarding the impact of intraoperative IV fluid administration on postoperative clinical outcomes in patients undergoing major surgery is limited. The principal constraint is the small number of published studies large enough to detect significant differences in clinically relevant outcome measures. There is an obvious need to conduct large, prospective, randomized clinical trials to further delineate the effect of intraoperative fluid therapy on clinical outcomes.

The data that are available raise several interesting points. First, it is evident that fluids should no longer be merely classified into crystalloids or colloids. The nature of the solution, that is, normal saline (NS) based or balanced salt (BS) based, has a bearing on the impact of the fluid on various organ systems. Second, not all colloids are the same. Various colloids, even when prepared in similar solutions, may have different clinical effects. Third, the impact on clinical outcome is dependent on the type of surgery and the clinical condition of the patient. Last, intriguing questions are raised as to the potential mechanisms by which clinical outcomes may be influenced by intraoperative IV fluid administration. Is the putative NS-induced renal dysfunction observed in some surgical patients mediated by a similar mechanism, possibly vasoconstriction, as the decrease in splanchnic perfusion observed in elderly surgical patients treated with NS-based fluids?[2]

Does the choice of fluid matter in major surgery? Based on the evidence presented here, the answer is yes, with the caveats already stated. Because no single fluid or fluid type is superior in all ways to all others, it may be that best practice involves the administration of combinations of these fluids to attain the maximum benefit while minimizing possible adverse effects. This can be accomplished with goal-directed fluid therapy and advanced hemodynamic monitoring to optimize each patient's individual hemodynamic status.

A growing body of evidence suggests that acid–base status and renal function are adversely affected by NS. Except in traumatic brain injury, it therefore seems prudent to avoid the use of large volumes of NS and NS-based fluids when BS-based fluid preparations are available.

HES 670 appears to be associated with more bleeding and renal dysfunction than other IV fluids. In patients at risk of bleeding or renal dysfunction, the intraoperative administration of HES 670 should be avoided when possible. This view is supported by the findings of an FDA review panel that recommended the addition of a warning to the HES 670 label stating the risk of bleeding associated with the intraoperative administration of HES 670 during cardiac surgery.

HES 130 may have less effect on coagulation than the older starches, although compared with non-HES fluids, HES 130 has been shown to weaken clot strength as measured by thromboelastography. However, in the available studies, this does not appear to be associated with a clinically significant risk of bleeding. The effect of HES 130 on renal function is unclear, as adequate studies have not been performed to demonstrate safety. Until results from the large studies currently ongoing are published, it currently seems prudent to avoid HES 130/0.4 in patients at risk of renal dysfunction.

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CHAPTER 28

What Works in a Patient with Acute Respiratory Distress Syndrome?

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a common phenomenon encountered by anesthesiologists in the operating room and intensive care unit (ICU) setting. It is also a feared complication of aspiration of gastric contents. ARDS is a syndrome of pathologic changes, caused by a variety of toxic and infectious agents that evolve over time from endothelial injury and alveolar consolidation to fibroblast proliferation and collagen deposition.[1] In 1994, the American–European Consensus Conference on ARDS (AECC) defined ARDS to include bilateral infiltrates on a chest radiograph consistent with pulmonary edema; PaO_2/FiO_2 ratio of less than 200 mm Hg (PaO_2/FiO_2 ratio less than 300 mm Hg defines acute lung injury [ALI]); and a pulmonary artery occlusion pressure less than or equal to 18 mm Hg, or no evidence of left atrial hypertension.[2] Many mediators have been implicated in its pathophysiology, including complement, cytokines, oxygen radicals, arachidonic acid products, nitric oxide, and proteases. Multiple insults incite the syndrome. Direct causes are those that directly injure the lungs such as aspiration, pneumonia, pulmonary contusion, thermal inhalation, amniotic fluid embolism, and particle inhalation. Indirect causes injure the lungs via mediator release and include pancreatitis, sepsis, and bacteremia. The presence of multiple insults increases the risk of ARDS.

The true incidence and mortality rates of ARDS remain somewhat unclear because many studies completed before the AECC did not use a standard definition. A study at Harborview Medical Center in Seattle, Washington reported an incidence of ARDS of 12.6/100,000 per year and an incidence of 18.9/100,000 per year for ALI.[3] Recent work at the Mayo Clinic demonstrated that the incidence decreased over an 8-year period (2001-2008) from 82.4 to 38.9 per 100,000 person years, despite a higher severity of acute illness, a greater number of comorbidities, and an increased prevalence of major predisposing conditions for ARDS.[4] Factors cited included heightened awareness of the adverse effects of high-tidal volume ventilation, implementation of transfusion protocols, and the addition of 24-hour ICU physician coverage. The hospital mortality rate has been reported to be between 40% and 60% in most studies but has decreased over the past three decades.[5] An older age, higher Acute Physiology and Chronic Health Evaluation (APACHE) score, transfusion of blood cells, and the use of steroids before the development of ARDS predict a higher mortality rate.[6]

OPTIONS/THERAPIES

Therapeutic interventions have been either directed at a specific phase of the syndrome or are more general and supportive in nature. Most deaths associated with ARDS are due to sepsis, rarely from the inability to provide adequate ventilatory support.[5] Here we will discuss the evidence supporting or dismissing certain ventilatory strategies including low lung volumes, positioning, and oxygenation; antiinflammatory therapies such as corticosteroid administration; hemodynamic management; and other supportive techniques.

Evidence for Lower Tidal Volume Ventilation in Acute Respiratory Distress Syndrome

Traditional ventilatory strategy in ARDS included the use of tidal volumes in the 10- to 15-mL/kg range in an effort to normalize $PaCO_2$ and pH. This mode of ventilation has been implicated as contributing to additional lung injury and multisystem organ failure.[7] The repetitive opening and closing of recruitable alveoli with traditional ventilation may alter endothelial permeability, increase edema, and release inflammatory mediators that may contribute to extrapulmonary organ failure and a worsened outcome.

Amato and colleagues[8] randomly assigned 53 patients between December 1990 and July 1995 with ARDS to either a conventional or protective mechanical ventilation strategy. The mortality rate at 28 days was 38% in the protective strategy group and 71% in the conventional mechanical ventilation group. Amato and colleagues also found a lower incidence of barotrauma in the protective ventilation group. The rate of survival to hospital discharge was not different between the groups. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network (ARDSNet) studied patients at 10 university centers

between 1996 and 1999.[9] A total of 861 patients were enrolled and equally randomly assigned to either traditional (initial tidal volume 12 mL/kg ideal body weight [IBW]) or low tidal volume ventilation (6 mL/kg tidal volume). The mortality rate at 28 days was reduced from 40% to 30%, the death rate before hospital discharge was reduced, ventilator-free days were higher, and the number of days without failure of nonpulmonary organs or systems was increased. Interleukin-6 levels were lower, possibly indicating less lung inflammation. Kallet and colleagues[10] applied the ARDSNet protocol to 292 patients with ALI or ARDS and found an overall mortality rate of 32% when compared with historical control subjects (51%). Work by Determan and colleagues[11] demonstrated that the implementation of lower tidal volume in patients without ARDS results in lower release of inflammatory mediators and a lower incidence of ALI.

The benefits of a lower tidal volume strategy in patients with ALI extend beyond improved survival rates and reduction in multisystem organ failure. Cooke and colleagues[12] suggest cost effectiveness and a savings of $22,566 per life saved, despite an early investment of $9482 to assure adherence.

Permissive hypercapnia is the elevation of $PaCO_2$ to levels above normal in the setting of tidal volume limitation. It is a consequence of ventilation management strategies that permit lower minute volumes in an attempt to reduce ventilator-induced lung injury and generally appears well-tolerated.[13] Additional work is needed to determine whether permissive hypercapnia is detrimental or perhaps even beneficial.

The ARDSNet compared high levels of positive end expiratory pressure (PEEP) to lower levels in patients with early ARDS while maintaining a plateau pressure less than 30 mm Hg in both groups. The hypothesis of the study was that higher levels of PEEP would improve oxygenation and decrease ventilator-induced lung injury.[14] No benefit was noted in terms of overall mortality, ventilator-free days, ICU-free days, or organ-failure free days. Meade and colleagues[15] studied higher levels of PEEP and found a trend toward a lower mortality rate with higher levels of PEEP, but this did not reach statistical significance. The conclusion further supported the finding that ventilation with lower tidal volumes and inspiratory pressures improved outcomes and that increasing PEEP levels further added little benefit.

Overall, current evidence supports ventilation strategies that include lower tidal volumes (approximately 6 mL/kg IBW), lower plateau airway pressures (less than 30 cm H_2O), higher levels of PEEP to maintain alveolar recruitment, even at the expense of elevated $PaCO_2$ levels, and decreased pH. Increasing PEEP beyond the recommended levels does not appear to improve outcome (Table 28-1).

Evidence for Additional Respiratory Strategies in Acute Respiratory Distress Syndrome

Multiple strategies have been suggested as adjuvants to traditional ventilation, including prone positioning, inhaled nitric oxide, extracorporeal membrane oxygenation (ECMO), recruitment maneuvers, and noninvasive positive pressure ventilation (NIPPV).

Prone and vertical positioning often improves oxygenation.[16,17] The improvement with prone positioning is believed to be due to a more uniform distribution of tidal volume and an improvement in ventilation–perfusion matching. The issue is whether a temporary improvement in oxygenation from prone positioning improves overall outcome. Gattinoni and colleagues[18] randomly assigned 304 patients with acute respiratory failure to either intermittent prone positioning or continual supine positioning. The PaO_2 measured each morning was higher in the prone position patients, but no survival benefit was observed at 10 days, at ICU discharge, or after 6 months' follow-up. Although their study indicated that prone positioning can be done safely, the authors cautioned that routine use of the prone position in patients with acute respiratory failure was not justified. Prone positioning risks include facial edema, accidental extubation, and displacement of catheters.

Vertical positioning involves raising the head 45 degrees and lowering the legs by 45 degrees. The PaO_2 level increases significantly in a high number of patients and is likely due to a time-dependent increase in lung volume, suggestive of alveolar recruitment.[17]

Inhaled nitric oxide (iNO) has been suggested as an adjunctive therapy for ARDS because of its ability to improve the intrapulmonary right-to-left shunting characteristic of ARDS and decrease pulmonary artery pressure. Multiple trials of iNO have been performed in patients with ARDS; most show a transient improvement in PaO_2 level without any outcome benefit.[19-23]

ECMO accompanied by a limited ventilation strategy has been reported as a possible therapeutic modality in severe ARDS.[24] Zapol and colleagues[25] randomly assigned 90 patients to either conventional ventilation or partial venoarterial bypass. They reported no survival benefit but did document that ECMO could support respiratory gas exchange in patients with severe respiratory failure. An uncontrolled trial by Gattinoni and colleagues[26] reported improved survival rates in those patients receiving ECMO. A subsequent randomized trial performed by Morris and colleagues,[27] however, failed to show any benefit. Peek et al[28] performed an efficacy and economic assessment of ECMO versus conventional ventilation. Patients with severe respiratory failure treated with ECMO at a specialized center had a higher survival rate and quality of life compared with conventional but generally low tidal-volume ventilation (4 to 8 mL/kg body weight). ECMO is complicated, labor intensive, not widely available, and of questionable benefit. Its routine use cannot be justified in ARDS, but highly select patients able to be treated at centers skilled in ECMO might be candidates. The results of a large randomized clinical trial may finally resolve this issue.[29]

NIPPV has many benefits compared with traditional intubation for the management of respiratory insufficiency. Benefits include a lower incidence of nosocomial pneumonia, lower intubation rates, less sinusitis, and easier communication with the patient. It is also an alternative for patients who refuse intubation. Disadvantages

TABLE 28-1 **Ventilator/Extracorporeal Membrane Oxygenation/Inhaled Nitric Oxide Trials**

Parameter	Study (Year)	Type	Results	Outcomes
Extracorporeal membrane oxygenation (ECMO)	Zapol (1979)[25]	Randomized	ECMO can support respiratory gas exchange	No difference in survival
High-frequency jet ventilation (HFJV)	Carlon (1983)[34]	Randomized	Oxygenation, ventilation maintained at lower peak pressure and tidal volume with HFJV	No difference in survival of intensive care unit (ICU) stay
ECMO	Morris (1994)[27]	Randomized	Survival similar in both groups	Extracorporeal support not recommended in acute respiratory distress syndrome (ARDS)
High-frequency oscillatory ventilation (HFOV)	Fort (1997)[35]	Prospective, clinical	Improvement in PaO_2/FiO_2 ratio; no change in cardiac output, O_2 delivery	HFOV is safe and effective; additional studies needed
Protective ventilation versus conventional ventilation	Amato (1998)[8]	Randomized	28-day mortality 38% (protective) versus 71% (conventional); less barotrauma	No difference in survival to discharge
Inhaled nitric oxide (iNO)	Dellinger (1998)[21]	Randomized, double-blind, placebo-controlled	Improvement in oxygenation after 4 hr and at 4 days	No improvement in mortality rate
iNO	Michael (1998)[20]	Randomized	PaO_2/FiO_2 improved at 1 hr, 12 hr, 24 hr	Benefits do not persist; no survival benefit
iNO	Troncy (1998)[19]	Randomized	Oxygenation improved in first 24 hr	No benefit after 24 hr; similar mortality
Lower tidal volume versus traditional tidal volume	ARDS Network (2000)[9]	Randomized	28-day mortality 30%; higher ventilator free days, lower interleukin-6; death before hospital discharge reduced	Mortality reduced, but long-term benefits need to be studied
Continuous positive airway pressure (CPAP)	Declaux (2000)[30]	Randomized, concealed, unblinded	Subjective response to CPAP greater than standard O_2	No difference in intubation rate, mortality, ICU stay
Prone position	Gattinoni (2001)[18]	Randomized	Increased PaO_2/FiO_2; similar complication rate	No improvement in survival
Recruitment maneuvers	Oczenski (2004)[39]	Randomized	Recruitment maneuvers improved PaO_2/FiO_2 ratio	Benefits of recruitment did not persist beyond 30 min
High versus lower positive end expiratory pressure (PEEP)	Brower (2004)[14]	Randomized	PaO_2/FiO_2 was higher in the "high PEEP" group	No significant difference in mortality rate, ventilator-free days, or organ failure–free days
Lower tidal volume ventilation	Kallet (2005)[10]	Retrospective, uncontrolled	Mortality rate lower in ARDS patients subject to ARDSNet protocol (32% versus 51%)	Adoption of ARDSNet protocol for acute lung injury/ARDS reduced mortality compared with historical controls
Lung recruitment	Gattinoni (2007)[38]	Observational study	Percentage of recruitable lung varied among patients. On average, 24% of the lung could not be recruited. Patients with a lower respirator-system compliance, higher $PaCO_2$, and lower PaO_2:FiO_2 at the beginning demonstrated more recruitability	This observational trial did not address outcome
iNO	Angus (2006)[23]	Randomized	Hospital costs, length of stay, were similar in the iNO group	No difference in survival at 1 yr
iNO	Adhikari (2007)[22]	Meta-analysis	iNO may increase oxygenation until up to 4 days	No overall mortality benefit with iNO
Higher PEEP levels	Meade (2008)[15]	Randomized controlled trial	Lower incidence of hypoxemia; lower use of rescue therapies	No difference in overall mortality
ECMO	Peek (2009)[28]	Multicenter randomized controlled	Higher survival rate to 6 mo in ECMO patients (63% versus 47%), higher quality of life, less disability	Improved survival rate with ECMO at specialized centers

include increased nursing time, poor airway protection, inability to deliver high levels of PEEP, and difficulty with implementation in the combative or delirious patient. Declaux and colleagues[30] randomly assigned 123 patients (102 with ALI and 21 with cardiac disease) with acute hypoxemic respiratory failure to either continuous positive airway pressure (CPAP) or standard oxygen therapy. They found that subjective responses to treatment were greater with CPAP, but there was no reduction in intubation rate, ICU length of stay, or hospital mortality. Antonelli and colleagues[31] studied NIPPV in patients with ARDS and found that early implementation may avoid intubation in up to 54% of the patients. The trial was more likely to fail and patients were more likely to require intubation if they had a higher Simplified Acute Physiology Score (SAPS) and could not improve their PaO_2/FiO_2 ratio within an hour. Because ARDS is rarely a short-term problem and rarely a single organ abnormality, it is difficult to recommend NIPPV as a first step in all patients with ARDS, but it may be a viable option in select patients or when intubation is not desirable.

High-frequency oscillatory ventilation (HFOV) has been suggested as a possible management strategy in ARDS. The advantages of HFOV are lower tidal volumes and higher mean airway pressure for a given peak pressure, minimizing the risk of overdistention and maintaining end-expiratory lung volume and alveolar recruitment. HFOV has been reported to improve the clinical outcome in premature infants with respiratory distress syndrome compared with conventional ventilation.[32,33] In adult patients, Carlon and colleagues[34] randomly assigned 309 patients to either volume-cycled ventilation (VCV) or high-frequency jet ventilation (HFJV). They found that VCV provided a slightly improved PaO_2 level at equivalent PEEP, but with HFJV, oxygenation and ventilation were maintained with lower peak inspiratory pressures and smaller tidal volumes. There was no improvement in the overall survival rate or ICU length of stay. Fort and colleagues[35] performed a prospective clinical study in 1997 on 17 patients with ARDS. They reported that 13 of 17 had an improvement in their PaO_2/FiO_2 ratio, without decrements in blood pressure, cardiac output, or oxygen delivery. A large randomized controlled trial is needed to assess the benefits of HFOV.

Lung collapse is a major contributing factor to the hypoxemia of ALI and ARDS. The repeated cyclic opening and closing of individual alveoli contribute to ventilator-associated lung injury. Recruitment maneuvers involve the application of high levels of PEEP and have been demonstrated in early lung injury and ARDS to reverse hypoxemia.[36] The ability to recruit alveoli has been demonstrated in ARDS caused by both primary pulmonary and secondary pulmonary causes.[37] The percentage of lung tissue that can be "recruited" varies among individual patients but may sometimes actually be greater in those with more severe lung injury.[38] Unfortunately these maneuvers generally do not result in a sustained improvement in oxygenation.[39] Complications associated with recruitment may include barotrauma and hemodynamic compromise. No study has yet effectively demonstrated long-term benefits attributed to a particular recruitment strategy (Table 28-2).

TABLE 28-2 **Pharmacologic/Steroid Trials**

Parameter	Study (Year)	Type	Results	Outcomes
Prostaglandin E_1 (PGE_1)	Bone (1989)[41]	Randomized, double blind	PGE_1 increased heart rate, stroke volume, and cardiac output	PGE_1 did not increase survival rate
Corticosteroids	Meduri (1991)[54]	Prospective clinical	Improvement in lung injury score and in PaO_2/FiO_2	Larger randomized controlled trial needed
Corticosteroids	Meduri (1994)[55]	Prospective clinical	Improved lung injury score, decreased positive end expiratory pressure, improved chest radiograph score	Larger randomized controlled trial needed
Aerosolized surfactant	Anzueto (1996)[45]	Randomized, placebo-controlled	No improvement: oxygenation, duration of mechanical ventilation, or survival	Aerosolized surfactant not beneficial in acute respiratory distress syndrome (ARDS)
Corticosteroids	Meduri (1998)[56]	Randomized, double-blind, placebo-controlled	Lung injury score improved, PaO_2/FiO_2 improved, Multiple Organ Dysfunction score improved; mortality: 12% versus 62% (control)	Survival rate improved with methylprednisolone; ARDSNet performing larger trial
Ketoconazole	ARDS Network (2000)[44]	Randomized, placebo-controlled	No differences in organ failure–free days, adverse events, or pulmonary function	Ketoconazole did not reduce mortality rate or improve outcome
Lisophylline	ARDS Network (2002)[43]	Randomized, double-blind, placebo-controlled	No difference in organ failure, ventilator-free days, or infections	Lisophylline did not improve mortality rate
Corticosteroids	ARDS Network (2006)[50]	Randomized	Mortality: 28.6% in placebo group, 29.2% in treated group; higher number of ventilator and shock free days in treated group	No improvement in overall mortality; possibly higher mortality in patients who had steroids started later
Corticosteroids	Meduri (2007)[53]	Randomized, controlled	Mortality reduced in treated patients (20.6% versus 42.9%); duration of mechanical ventilation and infections reduced	Mortality reduced

Evidence for Pharmacologic Strategies in Acute Respiratory Distress Syndrome

The pharmacologic interventions that have been tested in ARDS generally are directed at blocking the inflammatory mediators released after the inciting event has occurred. Interventions have included cytokine blockers, monoclonal antibodies against endotoxins or interleukins, antioxidants, activated protein C, nonsteroidal antiinflammatory drugs, and prostanoids.[40]

Although many of these interventions have shown benefit in initial trials and some animal studies, few benefits have been realized in human trials. Studies of prostaglandin $E_{1,}$[41] procysteine,[42] lisophylline,[43] and ketoconazole[44] have not shown a survival benefit.

Reduced surfactant production and function leads to increased surface tension, alveolar collapse, and decreased parenchyma compliance. Airway pressures needed to open these alveoli are exceedingly high. Anzueto and colleagues[46] studied the efficacy of artificial aerosolized surfactant in ARDS patients. They found no improvement in oxygenation, ventilation, or mortality.[45] Work continues on improved techniques of surfactant administration; however, it is unclear whether its pulmonary effects would be sufficient to alter clinical outcome (see Table 28-2).

Evidence for Hemodynamic Manipulation

The goals of hemodynamic management in ARDS are still an area of controversy. The ARDSNet has addressed the benefits of pulmonary versus central venous catheters and "conservative" versus "liberal" fluid management strategies in its Fluid and Catheter Treatment Trial (FACTT).

The Pulmonary Artery Catheter Consensus Conference in 1997 noted that there was inadequate evidence from existing clinical trials and case series to definitively determine benefit or harm from pulmonary artery catheter (PAC) use in patients with respiratory failure.[47] The benefits of PACs were evaluated in 100 patients with ALI through the ARDSNet.[48] Compared with patients managed with a central venous catheter no difference in lung or renal function, incidence of hypotension, ventilator settings, dialysis rate, or use of vasopressors was noted. The survival rate was not improved at 60 days. The incidence of complications related to catheterization was higher in the PAC group, particularly with regard to ventricular and atrial arrhythmias. The routine use of a PAC for management of patients with ARDS to improve organ function and survival rates cannot be recommended.

It is clear that increased permeability is responsible for the accumulation of alveolar fluid in ARDS. This accumulation occurs at lower pulmonary capillary wedge pressures than normal. It has been argued that diuresis and fluid restriction may benefit the ARDS patient by limiting or preventing edema. Mitchell and colleagues[49] studied patients with ARDS who had pulmonary artery catheters in place. Those with lower extravascular lung water had shorter periods of mechanical ventilation and shorter ICU stays, but the mortality rate was not different. It is unclear, however, whether overly aggressive fluid restriction may worsen extrapulmonary organ failure. The FACTT trial compared liberal versus conservative fluid management strategies.[50] Patients randomly assigned to the conservative arm of the clinical trial received nearly 7 L less fluid in the first 7 days of the study. Benefits were noted in oxygenation, lung injury score, and ventilator-free days without an increase in organ failure or need for dialysis. No difference was noted in the 60-day mortality rate. Accordingly, current evidence suggests that clinicians observe a more conservative management strategy for patients with ARDS (Table 28-3).

TABLE 28-3 **Nutrition/Position/Sedation/Monitoring/Fluid/Bundle Trials**

Parameter	Study (Year)	Type	Results	Outcomes
Enteral feeding with specific nutrients and antioxidants	Gadek (1999)[64]	Prospective, multicentered, double-blind, randomized controlled trial	Deceased number of neutrophils in alveolar tissue, improvement in oxygenation, fewer days of ventilator support, decreased length of intensive care unit (ICU) stay, lower rate of development of new organ failure	No significant difference in mortality
"Sedation vacation" in ventilated patients (not acute respiratory distress syndrome [ARDS])	Kress (2000)[61]	Randomized control	Decreased median duration of mechanical ventilation (4.9 days versus 7.3 days) and duration of ICU stay (6.4 versus 9.9 days)	No difference in in-hospital mortality
Prone position	Gattinoni (2001)[18]	Randomized	Increased PaO_2/FiO_2, similar complication rate	No improvement in survival rate

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TABLE 28-3 **Nutrition/Position/Sedation/Monitoring/Fluid/Bundle Trials** (Continued)

Parameter	Study (Year)	Type	Results	Outcomes
Ventilator bundles in ventilated patients	Resar (2005)[67]	Historical control	44.5% reduction in ventilator-associated pneumonia in intubated patients	Increased adherence to ventilator bundle
Vertical positioning	Richard (2006)[17]	Prospective observational physiologic study	Vertical positioning significantly improved PaO_2 and lung recruitment.	Study was not designed to compare outcomes
Conservative versus liberal fluid management trials	ARDS Network (2006)[50]	Randomized	Patients treated with a conservative fluid management protocol demonstrated improved oxygenation, increased ventilator-free days, and greater number of days out of the ICU	No difference in overall 60-day outcome
Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury (Fluid and Catheter Treatment Trial [FACTT])	ARDS Network (2006)[48]	Randomized	No significant difference in pulmonary or renal function, rate of hypotension, dialysis, or use of vasopressors	The pulmonary artery catheter did not improve clinical outcome; patients had a higher number of complications
Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation	NHLBI Clinical Trials Network (2011)[65]	Randomized, double-blind, placebo-controlled, multicenter	Patients receiving supplemental nutrition with omega-3 fatty acids, gamma-linolenic acid, and antioxidants had fewer ventilator-free days, organ failure–free days, and more diarrhea	No benefit to supplementation with fatty acids, gamma-linolenic acid, and antioxidants; mortality rate higher
Neuromuscular blockers in ARDS	ACURASYS study investigators (2010)[60]	Multicenter-double blind	Lower mortality at 28 days and 90 days (crude) in patients receiving cisatracurium	Early administration of neuromuscular blocking agents improved 90-day mortality without increasing muscle weakness

CONTROVERSIES

Corticosteroid treatment remains a major area of controversy in the management of both early and late ARDS. Early studies failed to show any benefit from the use of corticosteroids in early ARDS.[51,52] A more recent randomized, double-blind, placebo-controlled trial showed a reduction in mechanical ventilation, ICU stay, and ICU mortality in patients receiving methylprednisolone.[53] It has been postulated that corticosteroids may inhibit release of proinflammatory or profibrotic cytokines and reduce collagen deposition and fibrosis in the injured lung. Meduri and colleagues[54] initially studied eight patients with ARDS without an obvious site of infection. Methylprednisolone was administered as a bolus of 2 mg/kg followed by 2 to 3 mg/kg/day divided in every-6-hour dosing. Six of eight patients survived to discharge and had lower lung injury scales. A small follow-up study also suggested a survival benefit in those patients treated with steroids.[55,56] The ARDSNet performed a large trial evaluating the effectiveness of methylprednisolone in persistent ARDS.[57] Steroids were initiated 7 to 28 days after the onset of ARDS. Despite improvements in respiratory system compliance, blood pressure, and ventilator-free days, there was no improvement in overall mortality rates. Indeed, mortality at 60 and 180 days was significantly higher in the group receiving steroids compared with the group receiving placebo. Some potential benefit has been shown when steroids are administered to patients with septic shock and adrenal insufficiency[58] or with sepsis syndrome and adrenal insufficiency associated with ARDS.[59] Overall, however, corticosteroid treatment of ARDS remains controversial at best and may be harmful (see Table 28-2).

AREAS OF UNCERTAINTY

Supportive and Preventive Care

The systemic manifestations of ARDS must not be neglected. Sedation must balance patient comfort and the

ability to assess neurologic status. Nutritional needs must be met. Secondary injury to skin and other tissue must be avoided.

Complications of sedation include hypotension, slow ventilator weaning, and the inability to assess neurologic status. Complications of the addition of neuromuscular blocking agents include worsening of critical care myopathy; thus most practitioners continue to avoid their routine use. A French multicenter study,[60] however, randomly assigned 340 patients with severe ARDS to receive cisatracurium (37.5 mg/kg for 48 hours) or placebo early in the course of the disease. Cisatracurium use was associated with an improved adjusted survival rate, faster resolution of respiratory failure, decreased barotrauma, and no change in the frequency of neuromuscular weakness. Although this study raises many questions concerning drug selection, dose, duration of therapy, and mechanism of action, it suggests that use of neuromuscular blockade early in the course of ARDS may not be as harmful as previously thought and, indeed, may be of benefit. Although no specific sedation technique is clearly superior to another, daily interruption of sedative infusions (stopping an infusion until the patient is awake, then restarting the drug, commonly called a "sedation vacation") has been reported to decrease the duration of mechanical ventilation and length of stay in the ICU.[61] It is recommended that protocols be developed for the sedation of ICU patients requiring mechanical ventilation that address pain control, comfort, and patient safety.

Patients commonly do not receive adequate nutrition in both medical and surgical ICUs.[62] Fortunately, nutritional support protocols increase the proportion of patients who are adequately fed.[63] Gadek and colleagues[64] demonstrated that enteral feeding with certain nutrients and antioxidants improved gas exchange, lowered the requirement for mechanical ventilation, decreased the length of ICU stay, and reduced the incidence of new organ failure. Rice and colleagues,[65] however, recently completed a double-blind multicenter trial of twice-daily enteral supplementation of omega-3 fatty acid, gamma-linolenic acid, and antioxidants compared with isocaloric control enteral feeding in patients with ALI. The supplemented diet did not improve clinical outcomes but was found to be associated with fewer ventilator-free and nonpulmonary organ failure–free days and increased diarrhea. It is recommended that units implement protocols for early enteral feeding in patients with ARDS. Initial "trophic" feeding for up to the first 6 days may produce less gastrointestinal intolerance compared with full feeding in patients with ALI.[66]

The implementation of a small set of evidenced-based interventions referred to as "ventilator bundles" may decrease the incidence of complications common in patients receiving mechanical ventilation. These include peptic ulcer disease (PUD) prophylaxis, deep venous thrombosis (DVT) prophylaxis, elevation of the head of the bed, and a daily interruption of sedative infusions. Implementation of such bundles has been reported to decrease the incidence of ventilator-associated pneumonia (see Table 28-3).[67]

GUIDELINES

The diagnosis of ARDS should be established. An early onset of respiratory failure, $PaO_2/FiO_2 \leq 200$ mm Hg (300 mm Hg for ALI), bilateral patchy infiltrates on chest radiographs, and no evidence of a cardiogenic cause of pulmonary edema defines the syndrome.

The original insult responsible for inciting ARDS must be identified and treated. Pneumonia, sepsis, and bacteremia must be treated with antibiotics, and surgical drainage should be used, when indicated. Further injury must be prevented.

Close monitoring of fluid balance is imperative. The administration of excessive amounts of fluid in attempts to maintain hemodynamic stability imparts no clear outcome benefit. A conservative strategy to fluid management may shorten the duration of intubation without contributing to nonpulmonary organ failure.[45]

The adoption of sedation protocols that include a daily sedation vacation reduces the duration of mechanical ventilation and allows assessment of neurologic status.

Protocols established for the early initiation of enteral nutrition decrease the rate of underfeeding.

The integration of ventilator bundles that routinely provide prophylaxis for PUD and DVT, and require elevation of the head of the bed, decreases the incidence of ventilator-associated pneumonia.

Mechanical ventilation according to the protocols published by the National Institutes of Health ARDSNet is recommended.[68] This protocol has become the gold standard against which methods of management of ARDS can be tested (Box 28-1).

BOX 28-1 Acute Respiratory Distress Syndrome Clinical Network Mechanical Ventilation Protocol Summary

Inclusion Criteria—Acute Onset of:

1. $PaO_2/FiO_2 \leq 300$ (corrected for altitude)
2. Bilateral (patchy, diffuse, or homogeneous) infiltrates consistent with pulmonary edema
3. No clinical evidence of left atrial hypertension

Part I: Ventilator Setup and Adjustment

1. Calculate PBW.
   Males = 50 + 2.3 [height (inches) – 60]
   Females = 45.5 + 2.3 [height (inches) – 60]
2. Select any ventilator mode.

Continued on following page

BOX 28-1 Acute Respiratory Distress Syndrome Clinical Network Mechanical Ventilation Protocol Summary (Continued)

3. Set ventilator settings to achieve initial V_T= 8 mL/kg PBW.
4. Reduce V_T by 1 mL/kg at intervals ≤ 2 hr until V_T = 6mL/kg PBW.
5. Set initial rate to approximate baseline minute ventilation (not > 35 beats/min).
6. Adjust V_T and RR to achieve pH and plateau pressure goals below.

Oxygenation Goal: PaO_2 55-80 mm Hg or SpO_2 88%-95%

Use a minimum PEEP of 5 cm H_2O. Consider use of incremental FiO_2/PEEP combinations such as shown below (not required) to achieve goal.

Lower PEEP/Higher FiO_2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
FiO_2	0.7	0.8	0.9	0.9	0.9	1.0		
PEEP	14	14	14	16	18	18-24		

Higher PEEP/Lower FiO_2

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16
FiO_2	0.5	0.5-0.8	0.8	0.9	1.0	1.0		
PEEP	18	20	22	22	22	24		

Plateau Pressure Goal: ≤ 30 cm H_2O

Check P_{plat} (0.5 second inspiratory pause), at least q4h and after each change in PEEP or V_T.

If P_{plat} > 30 cm H_2O: decrease V_T by 1mL/kg steps (minimum = 4 mL/kg).

If P_{plat} < 25 cm H_2O and V_T< 6 mL/kg, increase V_T by 1 mL/kg until P_{plat} > 25 cm H_2O or V_T = 6 mL/kg.

If P_{plat} < 30 and breath stacking or dys-synchrony occurs: may increase V_T in 1 mL/kg increments to 7 or 8 mL/kg if P_{plat} remains ≤ 30 cm H_2O.

pH Goal: 7.30-7.45

Acidosis management: (pH < 7.30)

If pH 7.15-7.30: Increase RR until pH > 7.30 or $PaCO_2$ < 25 (maximum set RR = 35).

If pH < 7.15: Increase RR to 35.

If pH remains < 7.15, V_T may be increased in 1 mL/kg steps until pH > 7.15 (P_{plat} target of 30 may be exceeded).

May give $NaHCO_3$.

Alkalosis management: (pH > 7.45) Decrease vent rate if possible.

I:E Ratio Goal:

Recommend that duration of inspiration be less than or equal to duration of expiration.

Part II: Weaning

A. Conduct a Spontaneous Breathing Trial Daily When:

1. FiO_2 ≤ 0.40 and PEEP ≤ 8
2. PEEP and FiO_2 ≤ values of previous day
3. Patient has acceptable spontaneous breathing efforts (may decrease vent rate by 50% for 5 min to detect effort)
4. Systolic blood pressure ≥ 90 mm Hg without vasopressor support
5. No neuromuscular blocking agents or blockade

B. Spontaneous Breathing Trial:

If all above criteria are met and subject has been in the study for at least 12 hr, initiate a trial of *up to* 120 min of spontaneous breathing with FiO_2 ≤ 0.5 and PEEP ≤ 5:

1. Place on T-piece, trach collar, or CPAP ≤ 5 cm H_2O with PS ≤ 5.
2. Assess for tolerance as below for up to 2 hr.
   a. SpO_2 ≥ 90: and/or PaO_2 ≥ 60 mm Hg
   b. Spontaneous V_T ≥ 4 mL/kg PBW
   c. RR ≤ 35/min
   d. pH ≥ 7.3
   e. No respiratory distress (distress = 2 or more)
      - Heart rate > 120% of baseline
      - Marked accessory muscle use
      - Abdominal paradox
      - Diaphoresis
      - Marked dyspnea
3. If tolerated for at least 30 min, consider extubation.
4. If not tolerated, resume preweaning settings.

Definition of UNASSISTED BREATHING

(DIFFERENT FROM THE SPONTANEOUS BREATHING CRITERIA AS PS IS NOT ALLOWED)

1. Extubated with face mask, nasal prong oxygen, or room air, *or*
2. T-tube breathing, *or*
3. Tracheostomy mask breathing, *or*
4. CPAP ≤ 5 cm H_2O *without pressure support or intermittent mandatory ventilation assistance*

CPAP, continuous positive airway pressure; *PBW*, predicted body weight; *PEEP*, positive end expiratory pressure; *PS*, pressure support; *RR*, respiratory rate.

Reproduced with permission from NHLBI ARDS Network. Lower tidal volume/higher PEEP reference card, <www.ardsnet.org/system/files/Ventilator%20Protocol%20Card.pdf> [accessed 11.06.12].

Rescue therapies, including prone positioning, inhaled vasodilators, high-frequency ventilation, and ECMO, continue to be implemented in patients with severe oxygenation deficits who have not responded to traditional management. Walkey and Weiner[69] reviewed the clinical outcomes associated with rescue therapy use in patients enrolled in trials conducted by the ARDSNet. Cox proportional hazards analysis of propensity score-matched subjects showed no differences in survival. These therapies should not be routinely used but may continue to have specialized applications.

AUTHORS' RECOMMENDATIONS

- Establish the diagnosis of acute respiratory distress syndrome (ARDS)
- Institute low tidal volume ventilation according to ARDS Clinical Trials Network protocol
- Position patient with the head of the bed at 45 degrees
- Implement early enteral nutritional support
- Implement standard "ventilator bundles"
  a. Deep venous thrombosis prophylaxis
  b. Stress ulcer prophylaxis
- Institute a periodic "sedation vacation"
- Establish ventilation protocols that mandate lower tidal volumes in patients at risk of ARDS
- Consider extracorporeal membrane oxygenation (ECMO) for patients with isolated respiratory failure at centers with an established ECMO program
- Consider rescue therapies, including neuromuscular blockade, for select patients for whom traditional therapy has failed

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CHAPTER 29

What Actions Can Be Used to Prevent Peripheral Nerve Injury?

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INTRODUCTION

Perioperative peripheral nerve injury is a significant source of morbidity for patients, and the second most frequent cause of professional liability for anesthesiologists, accounting for 16% of claims in the American Society of Anesthesiologists (ASA) closed claims project database.[1] The incidence of postoperative peripheral nerve dysfunction is estimated at 0.1% to 0.15%, or 1 in 1000 to 1500 anesthetics.[2-4] A more recent study of more than 380,000 anesthetics observed an incidence of 0.03% for postoperative nerve injuries.[5]

The etiology of perioperative nerve damage is largely unknown. Injuries to the nerves of the brachial plexus or sciatic nerve may be secondary to stretching and/or compression with malpositioning of the patient. In contrast, ulnar nerve injury may occur despite protective padding and careful positioning. Direct trauma from needles or instruments and chemical toxicity of injected local anesthetics or vasoconstrictors may be implicated in nerve damage after regional anesthetic techniques.[6] However, there are very few prospective studies on the genesis or prevention of perioperative neuropathy. None of these is randomized and blinded. The relationship between conventional perioperative care and development of postoperative neuropathy is poorly understood.

Because of the absence of randomized controlled trials and a paucity of epidemiologic studies, the evidence on which practice patterns for prevention of perioperative peripheral neuropathy are based is largely consensus opinion. Using expert consensus, the ASA Task Force on Prevention of Perioperative Peripheral Neuropathies[7] formed guidelines regarding perioperative positioning of the patient, use of protective padding, and avoidance of contact with hard surfaces or supports to reduce perioperative neuropathies. These guidelines were revised in 2011 (Box 29-1).[8] However, even with close adherence to these recommendations, many peripheral neuropathies, especially those involving the ulnar nerve, may not be preventable.

THERAPIES/OPTIONS AVAILABLE TO REDUCE PERIPHERAL NEUROPATHY

Understanding the etiology and pathogenesis of neuropathy is essential for formulating ways of preventing or minimizing its occurrence. A lack of understanding regarding the development of postoperative peripheral nerve dysfunction is the major impediment in developing preventive steps.

Based on current knowledge of the pathogenesis of perioperative neuropathy, several recommendations have been made to prevent its occurrence. These include a preoperative screening to detect any subclinical neuropathy, preoperative history and physical examination directed at defining the comfortable range of stretching and movement at different joints, meticulous attention to avoiding intraoperative compression of superficial nerves, padding of the extremities and points at which nerves may get compressed, measures aimed at reducing stretching of the nerves, periodic intraoperative checking for optimal positioning of the extremities, and performing regional blocks with a nerve stimulator while the patient is awake. However, there is no definitive scientific evidence that these maneuvers are effective in preventing perioperative neuropathy.

EVIDENCE

When studying the evidence for causation and prevention of peripheral neuropathy, one must consider the different criteria used to diagnose neuropathy in each of the studies. Although transient sensory neurologic dysfunction lasting less than 2 weeks is not uncommon after anesthesia and surgery, permanent disabling nerve injuries are infrequent.

Upper Extremity Neuropathies

Postoperative neuropathies involving brachial plexus nerves and ulnar nerve are observed more commonly as compared with lower extremity neuropathies. As a result, they have been studied to a larger extent.

Ulnar Neuropathy

The ulnar nerve is the most common site of postoperative peripheral nerve damage, accounting for 28% of claims for anesthesia-related nerve injuries in the ASA closed claims database.[1] The incidence of ulnar nerve dysfunction is estimated to be between 0.26% and 0.5% in prospective studies of postsurgical patients (Table 29-1).[2,9-14] Ulnar neuropathy has been documented not only in surgical patients but also in medical inpatients and

BOX 29-1 Summary of Advisory Statements

Preoperative History and Physical Assessment

When judged appropriate, it is helpful to ascertain that patients can comfortably tolerate the anticipated operative position.

Specific Positioning Strategies for the Upper Extremities

Arm abduction in supine patients should be limited to 90 degrees.

Patients who are positioned prone may comfortably tolerate arm abduction greater than 90 degrees.

Supine Patient with Arm on an Arm Board

The upper extremity should be positioned to decrease pressure on the postcondylar groove of the humerus (ulnar groove).

Either supination or the neutral forearm positions facilitates this action.

Supine Patient with Arms Tucked at Side

The forearm should be in a neutral position.

Flexion of the elbow may increase the risk of ulnar neuropathy, but there is no consensus on an acceptable degree of flexion during the perioperative period.

Prolonged pressure on the radial nerve in the spiral groove of the humerus should be avoided.

Extension of the elbow beyond the range that is comfortable during the preoperative assessment may stretch the median nerve.

Periodic perioperative assessments may ensure maintenance of the desired position.

Specific Positioning Strategies for the Lower Extremities

Stretching of the Hamstring Muscle Group

Positions that stretch the hamstring muscle group beyond the range that is comfortable during the preoperative assessment may stretch the sciatic nerve.

Limiting Hip Flexion

Because the sciatic nerve or its branches cross both the hip and the knee joints, extension and flexion of these joints, respectively, should be considered when determining the degree of hip flexion.

Neither extension nor flexion of the hip increases the risk of femoral neuropathy.

Prolonged pressure on the peroneal nerve at the fibular head should be avoided.

Protective Padding

Padded Arm Boards

Padded arm boards may decrease the risk of upper extremity neuropathy.

Chest Rolls

The use of chest rolls in the laterally positioned patient may decrease the risk of upper extremity neuropathy.

Padding at the Elbow

Padding at the elbow may decrease the risk of upper extremity neuropathy.

Padding to Protect the Peroneal (Fibular) Nerve

The use of specific padding to prevent pressure of a hard surface against the peroneal nerve at the fibular head may decrease the risk of peroneal neuropathy.

Complications from the Use of Padding

The inappropriate use of padding (e.g., padding too tight) may increase the risk of perioperative neuropathy.

Equipment

The use of properly functioning automated blood pressure cuffs on the arm (i.e., placed above the antecubital fossa) does not change the risk of upper extremity neuropathy.

The use of shoulder braces in a steep head-down position may increase the risk of perioperative neuropathies.

Postoperative Assessment

A simple postoperative assessment of extremity nerve function may lead to early recognition of peripheral neuropathies.

Documentation

Documentation of specific perioperative positioning actions may be useful for continuous improvement processes and may result in improvements by: (1) helping practitioners focus attention on relevant aspects of patient positioning and (2) providing information on positioning strategies that eventually leads to improvements in patient care.

Used with permission from Practice advisory for the prevention of perioperative peripheral neuropathies: an updated report by the American Society of Anesthesiologists Task Force on Prevention of Perioperative Peripheral Neuropathies. Anesthesiology 2011;114:741–54 [Appendix 1].

outpatients,[12] irrespective of whether general anesthesia, regional anesthesia, or sedation-monitored anesthesia care was administered.[1]

Male gender, extremes of body habitus, and prolonged hospitalization are important risk factors for perioperative ulnar neuropathy.[9-11] The male predisposition may be explained by gender-related anatomic variations in the cubital tunnel at the elbow that render the ulnar nerve more sensitive to injury. Men have a 50% larger tubercle of the ulna, thicker retinaculum, and a shallow cubital tunnel, whereas women have 2 to 9 times more fat content in the cubital tunnel.[15] It is speculated that these anatomic differences may predispose the ulnar nerve to ischemia, by either direct compression or a reduction in blood flow by compression of the ulnar collateral artery and vein. Patients with perioperative neuropathy have a high incidence of contralateral nerve conduction dysfunction, suggesting that a subclinical neuropathy may become symptomatic as a result of manipulations during the perioperative period.[9]

The risk of ulnar nerve injury may be increased by flexion of the elbow[16] and pronation of the forearm[16] (see Table 29-1).[2,9-14] The ASA task force concluded that flexion of the elbow may increase the risk of ulnar

TABLE 29-1 **Ulnar Neuropathy**

Author, Year	Anesthesia Technique	Study Design	Incidence of Neuropathy	Comment
Dhuner, 1950[2]	GA/spinal	Retrospective review of 30,000 cases	Ulnar neuropathy in 8 patients	Transient paresis lasting a few weeks in 7 cases
Alvine, 1987[9]	GA for orthopedic, cardiac, urology, general surgical procedures	Prospective study in 6538 patients	Ulnar neuropathy in 0.26% patients	Subclinical ulnar neuropathy may become symptomatic secondary to perioperative maneuvers and manipulations
Warner, 1994[10]	GA, sedation, regional	Retrospective review of 1,129,692 cases	Ulnar neuropathy in 1 per 2729 patients (0.04%)	No correlation with anesthetic technique or patient position; males, extremes of body habitus, prolonged hospital stay had higher incidence
Warner, 1999[11]	GA, sedation, regional	Prospective study in 1502 patients	Ulnar neuropathy in 7 per 1502 patients (1 in 215 patients) (0.5%)	More frequent in men 50-75 yr of age; signs and symptoms develop 2-7 days after surgery
Warner, 2000[12]	Medical inpatients	Prospective study in 986 patients	Ulnar neuropathy in 2 of 986 patients (0.2% incidence)	Prolonged bed rest in supine position and elbow flexion may be causative
Lee, 2002[13]	GA	Prospective study in 203 orthopedic patients	Six cases (3% incidence) of ulnar neuropathy	Higher incidence in tilted patients in the lowermost adducted arm
Navarro-Vicente, 2012[14]	Open and laparoscopic colorectal surgeries	Prospective study in 2304 patients	Upper extremity neuropathy in 5 patients (0.2% incidence)	Adoption of tucked position and vacuum bags instead of shoulder braces has eliminated neuropathies thus far

GA, general anesthesia.

neuropathy,[7] but there is no consensus on an acceptable degree of flexion during the perioperative period.[8] This opinion is supported by anatomic evidence of a reduction in the cross-sectional contour of the cubital tunnel and a sevenfold increase in pressure within the tunnel, to a range that can compromise the intraneural circulation.[17] Pronation of the forearm increases the pressure over the ulnar groove.[16] Supination of the forearm produces the least amount of pressure, whereas a neutral position results in an intermediate value. Supination also "lifts" the cubital tunnel and ulnar nerve away from a contact surface. Almost half of the men who experience pressure on their nerve sufficient to impair the electrophysiologic function do not perceive symptoms.[16] A higher incidence of ulnar neuropathy is also found in tilted patients in the lowermost adducted arm, which is speculated to occur because internal rotation of the shoulder rotates the ulnar nerve toward compressive forces at the elbow.[13]

The ASA Task Force on Prevention of Perioperative Peripheral Neuropathies (see Box 29-1) made the following recommendations to prevent ulnar nerve injury: (1) position arms to decrease pressure on the ulnar groove, (2) use a neutral forearm position when arms are tucked at the sides, (3) use supination or a neutral forearm position when the arms are abducted on armboards, and (4) use padded armboards and padding at the elbow.[7,8] The task force advised that flexion of the elbow may increase the risk of ulnar neuropathy, but the acceptable degree of elbow flexion remains unclear. Periodic checking and documentation were also recommended. Properly functioning blood pressure cuffs on the upper arms do not affect the risk of upper extremity neuropathy.[7,8]

Despite the theoretical value of these precautions in positioning the arms, there is no evidence that these practices decrease the risk of postoperative ulnar neuropathy. To the contrary, the evidence suggests that ulnar nerve damage may occur despite padding and placement of the patient's arms in supination.[18]

Brachial Plexus Injury

Injury to the brachial plexus is the second most common nerve injury, responsible for 20% of claims for anesthesia-related nerve injuries in the ASA closed claims analysis.[1] The perioperative incidence of brachial plexus neuropathy is estimated at 0.2% to 0.6%.[2,14,19,20] Injury to the brachial plexus is most commonly reported after procedures involving a median sternotomy, especially with dissection of the internal mammary artery[20-22]; Trendelenburg position, especially with shoulder braces for support[2]; and after surgery in the prone position.[23]

Most brachial plexus nerve injuries are caused by stretching and traction on the plexus.[2,4,19,23,24] The anatomic features that make the brachial plexus most susceptible to injury include the following: (1) the nerve roots of the brachial plexus run a long, mobile, and superficial course between two firm points of fixation—the intervertebral foramina above and the axillary fascia below, (2) its close anatomic relationships with a number of freely movable bony prominences, and (3) the plexus runs its course through the limited space between the first rib and the clavicle.[23,25] The first two features make the brachial plexus more susceptible to stretch-induced injury, whereas the third one (along with

fracture and/or displacement of the first rib) is generally implicated in a direct or compression injury after cardiac surgery.

Arm Position. Brachial plexus neuropathy has been reported after arm abduction equal to or greater than 90 degrees.[2,25] Positions that induce stretching of the brachial plexus include extension and lateral flexion of the head to one side, allowing the arm to sag off the operating table,[2] or use of a shoulder roll or gall bladder rest to "bump" the patient to one side.[24] Contralateral cervical lateral flexion, lateral rotation of the shoulder, fixation of the shoulder girdle in a neutral position, and wrist extension also stretch the brachial plexus.[26] Simultaneous application of these positions has a cumulative effect. Ninety-six percent of ASA members felt that limiting the arm abduction to 90 degrees in supine patients may reduce the risk of brachial plexus injury.[7] Navarro-Vicente et al report elimination of brachial plexus injuries during laparoscopic surgeries when they adopted the practice of tucking arms by the side and using vacuum bags (bean bags) instead of shoulder braces.[14] The ASA Task Force on Prevention of Perioperative Peripheral Neuropathies concluded that arm abduction should be limited to 90 degrees in supine patients (see Box 29-1).[7,8]

Shoulder Braces. The use of shoulder braces to stop patients from sliding down when placed in a steep Trendelenburg position has been associated with development of postoperative brachial plexus damage.[2,7,19] Shoulder braces can compress the brachial plexus against the numerous bony and rigid structures within the shoulder complex. The danger is even greater when the arm is abducted, which causes the brace to act as a fulcrum and stretch the plexus. Fixation of the shoulder (caused by use of shoulder braces even in the recommended position over the acromioclavicular joints) loads the nerves of the upper extremity and reduces the range of elbow extension in the brachial plexus tension test.[26] The ASA Task Force on Prevention of Perioperative Peripheral Neuropathies concurred that shoulder braces in a steep head-down position may increase the risk of brachial plexus neuropathies (see Box 29-1).[7,8]

Prone Position. Placement of a patient into the prone position can also be accompanied by a stretch injury to the brachial plexus. Once a prone position is established, the arms may be positioned either alongside the torso or extended above the head. In the presence of symptoms suggestive of thoracic outlet syndrome (i.e., paresthesia, numbness, or pain on raising hands above the head), arms should be restrained by the side of the body to avoid stretching of the brachial plexus.[27] Closure of retroclavicular space in the prone position can occur as a result of dorsal and caudal displacement of the clavicle by the chest roll, causing compression of the brachial plexus between the thorax and clavicle. The ASA Task Force on Prevention of Perioperative Peripheral Neuropathies concluded that patients who are positioned prone may comfortably tolerate arm abduction greater than 90 degrees (see Box 29-1).[7,8]

Lateral Decubitus Position. Compression of the brachial plexus between the thorax and the head of the humerus of the downside extremity can also occur in the lateral decubitus position.[19] This can possibly be reduced by placing a roll under the chest wall just caudad to the axilla, with the aim of elevating the rib cage off the table and freeing the dependent shoulder.[7,27] The ASA Task Force on Prevention of Perioperative Peripheral Neuropathies recommended use of chest rolls in laterally positioned patients to reduce the risk of upper extremity neuropathies (see Box 29-1).[7,8]

Other Upper Extremity Neuropathies

Radial Nerve Injury

The radial nerve is susceptible to compression injury as it passes dorsolaterally around the middle and lower thirds of the humerus in the musculospiral groove. The nerve can be compressed approximately 5 cm above the lateral epicondyle of the humerus between an external object, such as the vertical bar of an anesthesia screen, an improperly positioned tourniquet, or the distal edge of a blood pressure cuff, and the underlying bone.[7,28] The ASA Task Force on Prevention of Perioperative Peripheral Neuropathies recommended that prolonged pressure on the radial nerve in the spiral groove of the humerus should be avoided (see Box 29-1).[7,8]

Median Nerve Dysfunction

Isolated median nerve damage in the perioperative setting is relatively uncommon, and the mechanism is poorly understood.[1,29] Needle trauma during venipuncture or intravenous cannulation in the antecubital fossa is possible. Median nerve dysfunction is predominantly seen in muscular men, in the 20- to 40-year-old age group, who are unable to fully extend their elbows because of their large biceps and relatively inflexible tendons. The ASA Task Force on Prevention of Perioperative Peripheral Neuropathies concluded that extension of the elbow beyond a comfortable range may stretch the median nerve (see Box 29-1).[7,8]

Long Thoracic Nerve Damage

Long thoracic nerve dysfunction is an infrequent neuropathy.[1,30] The absence of any apparent mechanism of injury in most of these cases has led to the postulation that a coincidental infectious neuropathy may be responsible for the postoperative long thoracic nerve dysfunction.[31]

Lower Extremity Neuropathy

Postoperative nerve lesions in the lower extremity occur infrequently and are poorly studied (Table 29-2).[14,32-38] In the analysis of closed claims for nerve damage, Cheney et al[1] reported 23 cases of sciatic nerve injuries, of which 10 were associated with the use of the lithotomy position and two with the frog-leg position for surgery. Warner et al[37] prospectively studied 991 patients undergoing

TABLE 29-2 **Lower Extremity Neuropathy**

Author, Year	Study Design	Incidence of Neuropathy	Comment
Burkhart, 1966[32]	Retrospective analysis of 2526 vaginal surgical procedures	0.2% incidence of sciatic neuropathy	Stretch injury and not compression injury
McQuarrie, 1972[33]	Vaginal hysterectomy in 1000 patients	0.3% incidence of sciatic neuropathy	Sciatic and common peroneal nerves are anatomically fixed at the sciatic notch and neck of the fibula, making them susceptible to stretch
Keykhah, 1979[34]	488 cases of neurosurgery in sitting position	1% incidence of peroneal neuropathy	—
Warner, 1994[35]	Retrospective review of 198,461 patients in lithotomy position	Persistent motor deficit in lower extremity for >3 mo in 55 patients (1 per 3608 cases)	Association with prolonged duration in lithotomy, very thin body habitus, and smoking in preoperative period
Nercessian, 1994[36]	7133 consecutive total hip arthroplasties	45 cases (0.63%) of neuropathy: 34 (0.48%) in lower extremity and 11 (0.15%) in upper limb	Common peroneal and ulnar nerves usually involved; females more likely to develop neuropathy
Warner, 2000[37]	Prospective study in 991 patients in lithotomy position	Lower extremity neuropathy in 15 patients (1.5% incidence)	Sensory neuropathy, developing within 4 hr; complete recovery within 6 mo; direct correlation with time in lithotomy position
Anema, 2000[38]	Prospective study in 185 male patients undergoing urethral reconstruction in high lithotomy position	12 cases of neuropathy (6.5% incidence)	Duration of lithotomy position was significant risk factor; height, weight, type of stirrups were not associated with increased risk
Navarro-Vicente 2012[14]	Prospective study in 2304 open and laparoscopic colorectal surgeries	Three cases of neuropathy (0.13% incidence of lower extremity neuropathies)	Adoption of Allen type for elective and urgent cases has eliminated further cases of nerve damage in lower limbs

surgery in a lithotomy position and observed a 1.5% incidence of lower extremity neuropathies. Of the 15 patients who developed neuropathies, the obturator nerve was involved in five patients, the lateral femoral cutaneous nerve in four patients, the sciatic nerve in three patients, and the peroneal nerve in three patients, which indicates that multiple nerves are affected with similar frequency. All the neuropathies were purely sensory.

The risk of developing lower extremity neuropathy increases with the duration of lithotomy position,[35,37,38] and limiting the duration of lithotomy may decrease the incidence of postoperative lower extremity nerve dysfunction.

Sciatic Neuropathy

Perioperative sciatic nerve injury is relatively uncommon but may occur from stretching, compression, ischemia, or a combination of these mechanisms. A stretching injury to the sciatic nerve could occur if the patient is placed in some variant of a lithotomy position, especially those with simultaneous hyperflexion of the hip and extension of the knee or external rotation of the thigh.[23,32,33] Case reports of left-sided sciatic neuropathy after cesarean section in patients with left lateral tilt[39,40] suggest that pressure on the sciatic nerve in this position may cause sciatic nerve injury. Because the same forces stretch the sciatic nerve and the hamstring group of muscles, eliminating the stretch (tautness) of knee flexor muscles in a surgical position helps reduce the incidence of stretch-related injury to the sciatic nerve.[7,23]

The ASA Task Force on Prevention of Perioperative Peripheral Neuropathies recommended that flexion of the hip and extension of the knee should be jointly considered to reduce the amount of stretching on the hamstring when a patient is placed in the lithotomy position (see Box 29-1).[7,8]

Peroneal Nerve Dysfunction

The common peroneal nerve (common fibular nerve) wraps superficially around the neck of the fibula before dividing into the sensory superficial peroneal nerve and predominantly motor deep peroneal nerve. The common peroneal nerve is vulnerable to compression between the head of the fibula and external hard objects, particularly in the lithotomy and sitting positions[34,35,37] and after hip surgery.[36] Warner et al[37] observed only sensory deficits in their patients who developed peroneal neuropathy after prolonged duration in lithotomy positions, which suggests that only the superficial peroneal nerve was affected either because of compression distal to the fibular head or by stretching secondary to plantar flexion of the foot. The ASA Task Force on Prevention of Perioperative Peripheral Neuropathies recommended use of protective padding at the fibular head to decrease the risk of peroneal neuropathy (see Box 29-1).[8]

Femoral Neuropathy

Postoperative femoral neuropathy is relatively uncommon and is often associated with surgical factors, such as

the use of self-retaining retractors for abdominopelvic operations,[41] ischemia after aortic cross-clamping, and compression caused by a hematoma.[42] Femoral nerve ischemia may also result from extreme abduction and external rotation of thighs in the lithotomy position.[43]

Obturator Neuropathy

The obturator nerve lies deep within the pelvis and medial thigh and is relatively well-protected. The nerve is particularly at risk during total hip arthroplasty and pelvic surgery.[44]

Nerve Damage after Peripheral Nerve Block

The incidence of persistent neuropathy after peripheral nerve block is estimated at 0.2%, although transient sensory deficits and paresthesia are relatively common, occurring in up to 7% to 14% of patients (Table 29-3).[45-57] In a review of all studies investigating neurologic complications after regional anesthesia, Brull et al[58] found that the rate of transient neuropathy after peripheral nerve blockade was less than 3% and that permanent nerve damage was rare. The etiology of nerve injury is thought to be secondary to needle trauma, intrafascicular injection, local anesthetic neurotoxicity, ischemia, or a combination of these factors.[59,60] Hematomas, intraneural edema, and direct neuronal toxicity may result in an immediate injury. Formation of perineural edema, inflammation, and microhematomas around the nerve may account for the 2- to 3-week delay sometimes seen from performance of a regional block to the onset of neurologic symptoms. A tissue reaction or scar formation in response to mechanical or chemical trauma may also be responsible for delayed neurologic dysfunction.[59]

Risk factors for neurologic dysfunction after peripheral nerve blocks have been speculated to include elicitation of paresthesia, use of a multiple injection technique, use of a long-bevel needle, use of continuous block techniques, performance of blocks under general anesthesia, and performance of regional blocks in anticoagulated patients. The scientific quality of evidence in support of these risk factors is relatively poor, relying mostly on small clinical series, case reports, and editorials. In contrast, tourniquet inflation pressures of greater than 400 mm Hg have been demonstrated to be associated with the development of postoperative neurologic dysfunction.[50]

An analysis of risk factors for the development of neurologic complications after axillary blocks[51] found no association of neuronal dysfunction with elicitation of paresthesia, nerve stimulator response, use of epinephrine, or use of long-beveled needles. The multiple injection technique is also not associated with an increased incidence of postoperative neurologic dysfunction.[50] Continuous nerve block techniques may theoretically increase the risk of nerve injury; however, the risk of neurologic complications with continuous axillary blocks is similar to that of single-dose techniques.[56]

Commonly used endpoints used for successful localization of nerve(s) to be blocked include elicitation of paresthesia, motor stimulation of the muscles innervated, and ultrasound guidance. Although an early study[45] suggested that searching for paresthesia increased the incidence of nerve injury, more recent studies[47,51] have not demonstrated this relationship. Some experts believe that the use of a peripheral nerve stimulator reduces the risk of nerve injury, but this claim remains unproved and warrants further study. In a French survey of anesthesiologists, Auroy et al[55] found that a nerve stimulator was used in nine of 12 peripheral nerve blocks that resulted in a neurologic complication. Ultrasound guidance for performing peripheral nerve blocks is becoming popular worldwide. Animal studies have shown that ultrasound may prove useful in detecting intraneural injection, whereas a motor response above 0.5 mA may not exclude intraneural needle placement.[61] On the other hand, Robards et al[62] noted that the absence of motor response to nerve stimulation also does not exclude intraneural needle placement and may lead to additional unnecessary attempts at nerve localization. Furthermore, in their report of 24 sciatic nerve blocks, low-current stimulation was associated with a high frequency of intraneural needle placement. Liu et al[63] found that the incidence and severity of postoperative neurologic symptoms at 4 to 6 weeks were similar, whether nerve stimulation or ultrasound was used to perform interscalene blocks.

Bigeleisen[64] reported that puncturing of the peripheral nerves and apparent intraneural injection during axillary plexus block did not necessarily lead to a postoperative neurologic injury. Sala-Blanch et al[65] observed that nerve stimulator–guided sciatic nerve block at the popliteal fossa often results in intraneural injection. In a series of 16 intraneural injections, they did not observe any clinical or electrophysiologic evidence of nerve injury at 1 and 3 weeks postoperatively.

Perlas et al[66] noted that paresthesia was 38.2% sensitive and motor response was 74.5% sensitive for detection of needle-to-nerve contact via ultrasound. Performance of peripheral nerve blocks under general anesthesia is also controversial. No neurologic sequelae were noted in a prospective study of more than 4000 peripheral nerve blocks in pediatric patients.[48] Several case reports and editorials point out potentially serious complications of placing nerve blocks in anesthetized patients,[67,68] yet brachial plexus and other blocks are frequently performed in anesthetized patients and neurologic sequelae are uncommon.[69]

Data on neurologic injury after peripheral nerve blocks in patients receiving anticoagulation therapy are scanty and are in the form of isolated case reports. The consensus statements on neuraxial anesthesia and systemic anticoagulation, including oral anticoagulants, heparin, and thrombolytic–fibrinolytic therapy published by the American Society of Regional Anesthesia,[70] can be applied to any regional anesthetic technique. Placement of blocks and removal of catheters in patients receiving these anticoagulation therapies may increase the risk of hematoma and neurologic dysfunction. Close monitoring of anticoagulated patients undergoing peripheral nerve blocks for early signs of neural compression such as pain, weakness, and numbness and timely intervention may prevent

TABLE 29-3 **Neuropathy after Regional Nerve Blockade**

Author, Year	Anesthesia Technique	Study Design	Incidence of Neuropathy	Comment
Selander, 1979[45]	AxB	Prospective study in 533 patients	Nerve lesions in 10 of 533 patients attributed to block	Searching for paresthesia increased incidence of nerve lesions from 0.8% to 2.8% (not significant statistical difference)
Urban, 1994[46]	AxB and ISB AxB	Prospective study in 508 patients: 242 AxB and 266 ISB	Incidence of paresthesia at 2 wk postblock was 3% with ISB and 7% with AxB	All but one patient in each group made complete recovery in 4 wk with AxB and 6 wk with ISB
Stan, 1995[47]	AxB by transarterial approach	Prospective study in 966 patients	Transient sensory neuropathy in 2 of 996 patients (0.2% incidence)	Direct needle trauma believed to be cause; complete recovery within 1 mo
Giaufré, 1996[48]	Regional anesthetics	Prospective study in pediatric patients	No complications in 4090 peripheral nerve blocks	Demonstrated safety of peripheral nerve blocks over central blocks in pediatric anesthesia
Auroy, 1997[49]	Regional anesthesia	Prospective study, 103,730 regional anesthetics including 21,278 peripheral nerve blocks	Nerve damage in 34 patients	Paresthesia during needle placement or pain during injection in all patients with nerve injury; complete recovery in 19 patients within 3 mo
Fanelli, 1999[50]	Sciatic-femoral, AxB and ISB using nerve stimulator	Prospective study in 3996 patients, using multiple-injection technique	69 patients (1.7% incidence) developed neurologic dysfunction in the first month	Tourniquet inflation to >400 mm Hg associated with nerve injury; complete recovery in all but one patient in 4-12 wk
Horlocker, 1999[51]	Repeated AxBs	Retrospective study of 1614 AxBs in 607 patients	1.1% incidence of anesthesia-related neurologic dysfunction	Repeated AxBs did not increase risk of neurologic complications
Borgeat, 2001[52]	ISB for shoulder surgery	Prospective study in 520 patients, followed up for 9 mo	Severe long-term complication (persistent dysesthesias at 9 mo) rate of 0.2%; no incidence of motor weakness	Need to exclude sulcus ulanaris syndrome, carpal tunnel syndrome, or complex regional pain syndrome in cases of persistent dysesthesias after regional block
Grant, 2001[53]	Continuous peripheral nerve block	Prospective study in 228 patients	No incidence of postoperative neurologic dysfunction	Safety of using insulated Touhy catheter system for continuous blocks
Klein, 2002[54]	Peripheral nerve blocks	Prospective study of 2382 blocks with ropivacaine	6 cases (0.25% incidence) of paresthesia at 7 days postoperatively	Neurologic recovery in all patients over 6 mo
Auroy, 2002[55]	AxB	Prospective study 11,024 patients	2 cases of neurologic deficits	Follow-up beyond 6 mo not available
Auroy, 2002[55]	Femoral nerve block	Prospective study 10,309 patients	3 cases	Follow-up beyond 6 mo not available
Auroy, 2002[55]	Sciatic nerve block	8507 patients	2 cases	Follow-up beyond 6 mo not available
Auroy, 2002[55]	ISB	3459 patients	1 case	Follow-up beyond 6 mo not available
Bergman, 2003[56]	Continuous AxBs	Retrospective study in 405 patients with axillary catheters	2 cases (0.5% incidence) of anesthesia-related neurologic deficits	Use of continuous AxB does not increase risk of nerve damage
Liu, 2011[57]	ISB and supraclavicular blocks	Prospective study in 257 patients, all blocks with ultrasound guidance; 17% had intraneural injection	No neurologic deficits at 4-6 wk, even in the intraneural injection patients	

AxB, axillary block; *ISB,* interscalene block.

neurologic sequelae from compression caused by a hematoma.

AREAS OF UNCERTAINTY

Many peripheral neuropathies occur in the absence of a definite mechanism of nerve injury. Some of the areas of uncertainty in the causation and prevention of perioperative peripheral neuropathy are as follows:

1. *Padding of superficial nerves:* conventional wisdom dictates that the superficial peripheral nerves can be protected from injury by the use of protective padding (e.g., foam sponges, towels, blankets, or soft gel pads); however, there are no data to suggest that any of these materials are more protective than the others or that any of them are better than none at all.
2. *Frequent change of position:* prolonged duration in one position is associated with increased risk of neurologic injury,[35,37] and limiting the time spent in one position decreases this risk.[38] The ASA Task Force on Prevention of Perioperative Peripheral Neuropathies recommended periodic perioperative assessments of the position of extremities to ensure maintenance of the desired position and to reduce the incidence of neuropathies (see Box 29-1).[7,8]
3. *Electrophysiologic monitoring:* electrophysiologic studies, such as somatosensory-evoked potentials (SSEPs) and electromyography, can detect changes in nerve function in the perioperative period.[71] The nonspecificity and poor sensitivity of SSEPs in predicting postoperative neurologic deficits, combined with time, cost, and personnel issues involved in SSEP monitoring, make the role of SSEPs questionable as a routine method of monitoring.
4. *Elicitation of paresthesia for regional blocks:* although an early study[45] suggested an increased risk of postblock neurologic dysfunction with elicitation of paresthesia, this relationship has not been subsequently proven[47,51] and requires further study.
5. *Ultrasound guidance for regional blocks:* ultrasound guidance may be more sensitive than elicitation of paresthesia or obtaining a motor twitch to electrical stimulation for localization of peripheral nerves.[66] Although ultrasound may help in reducing the incidence of intraneural injection, the clinical significance of intraneural injection in causation of nerve dysfunction remains debatable.[62,64,65]

GUIDELINES

An updated practice advisory by the ASA Task Force on Prevention of Perioperative Peripheral Neuropathies is summarized in Box 29-1.[8] However, the protective effect of these recommendations on the development of postoperative neuropathies reflects the consensus opinion of anesthesiologists, not randomized controlled trials, and remains unproved.

AUTHORS' RECOMMENDATIONS

Many peripheral neuropathies, especially ulnar neuropathy, are not currently preventable. Further scientific research may shed more light on the genesis of postoperative nerve dysfunction and measures aimed at preventing this complication. Based on available evidence, specific steps should be taken to minimize compression, stretching, ischemia, and trauma to the peripheral nerves (see Box 29-1).[8] During positioning and padding of the extremities, direct compression of the superficial peripheral nerves should be avoided, and the limbs should be positioned so that any compressive forces that must be placed on the nerves will be distributed over as large an area as possible. It is advisable to define the patient's preoperative condition and the normally tolerated limits of stretching in the limbs. Any stretching over these limits should then be avoided while the patient is anesthetized. A description of the intraoperative positioning and measures aimed at preventing peripheral nerve dysfunction should be documented in the anesthetic record. We are in agreement with the ASA Practice Advisory for the Prevention of Perioperative Peripheral Neuropathies.

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CHAPTER 30

What Is the Best Means of Preventing Perioperative Renal Injury?

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ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is a clinical syndrome that reflects the clinical manifestation of isolated or multiple insults to the kidney. The degree of renal damage ranges from the trivial, that is, a transient increase in serum creatinine (SCr) or a decrease in urine output, to the profound, that is, established acute renal failure (ARF) requiring renal replacement therapy (RRT). A consensus definition of AKI by a multinational expert panel, the Acute Dialysis Quality Initiative Group (ADQI),[1] attempts to standardize the classification and reporting of AKI (Table 30-1). The classification is based on the degree of elevation of SCr or calculated glomerular filtration rate (GFR), severity and duration of oliguria, and the requirement for RRT. The acronym *RIFLE* serves to organize a hierarchy of severity of AKI into risk of injury (R), acute injury (I), established failure (F), sustained loss of function (L) and end-stage renal disease (E).

A consensus definition of ARF in critically ill patients such as RIFLE is long overdue, given that more than 30 different definitions can be found in the literature. However, there are some important caveats. RIFLE does not take into consideration that about three quarters of ARF is nonoliguric in nature,[2] that abrupt changes in GFR may not be reflected by rapid changes in SCr,[3] or that SCr may increase slowly and subtly in patients with depleted muscle mass.[4] It was also not designed to examine the specific AKI associated with surgery and may not be as useful for anesthesiologists as a criterion such as peak percentage change in postoperative SCr.[5] Nonetheless, there have been several investigations of the predictive ability, internal validity, robustness, ease of application, and clinical relevance of RIFLE in a variety of settings.[6-12] These retrospective and prospective studies do demonstrate a broad correlation between the RIFLE severity and overall mortality from AKI. It does appear that the RIFLE classification is easy to use, identifies patients with early signs of dysfunction that may progress to more severe renal disease, and can identify patients of different mortality risk. However, the RIFLE criteria have yet to be used in large multicenter randomized controlled clinical trials in a wide variety of patient populations.

Perioperative AKI, characterized by postoperative elevation of SCr, is generally uncommon. However, it has a predilection for certain surgical procedures, particularly vascular surgery involving aortic manipulation, in which the incidence is between 10% and 25%.[13-15] One study demonstrated a relatively static incidence over a 12-year period.[15] The risk of AKI is enhanced by nephrotoxic factors such as obstructive jaundice or exposure to radiocontrast agents (Box 30-1).[16] Regardless of its etiology, pathogenesis, or requirement for RRT, postoperative AKI is associated with increased length of hospital stay, an increased mortality rate, and impaired quality of life.[13,14,17-19]

A considerable research effort has been marshaled to evaluate perioperative interventions to protect the kidneys when they are placed at risk by pre-existing impairment, nephrotoxins, renal ischemia, and the inflammatory process. Preventive strategies have focused on preoperative optimization of renal function, judicious perioperative fluid balance, and "renoprotective" pharmacologic agents. However, given the wide variety of renal insults that contribute to perioperative AKI, outcome studies of therapeutic interventions have addressed only a limited territory of perioperative renal protection.

These strategies appear to have had some benefit because, although the incidence of postoperative AKI has been increasing over the last two decades, the mortality rate of ARF requiring RRT is decreasing. For example, a study on coronary artery bypass grafting (CABG) in a sample of 20% of U.S. hospitals revealed an increase in incidence of postoperative ARF from 1% to 4% between 1988 and 2003.[20] However, the proportion of cases requiring RRT declined from about 16% to less than 9%, and the mortality rate declined from nearly 40% to less than 18%. These figures may be influenced by less stringent criteria for the diagnosis of ARF, but the proportion of survivors requiring special care after discharge almost doubled from 35% to 65%, emphasizing the increasing burden of perioperative AKI on our health care system.

Perioperative Risk Factors for Acute Kidney Injury

An isolated risk factor or insult rarely induces AKI. Inevitably, AKI is the consequence of the complex, often

TABLE 30-1 Risk, Injury, Failure, Loss, and End-Stage Kidney (RIFLE) Classification

Class	SCr Increase	GFR Decrease	Oliguria (UO < 0.5 mL/kg/hr)
Risk	×1.5	>25%	>6 hr
Injury	×2	>50%	>12 hr
Failure	×3 (or >4 mg/dL, with an abrupt increase >0.5 mg/dL)	>75%	>24 hr (or anuria >12 hr)
Loss	ARF >4 wk		
ESRD	ARF >3 mo		

ARF, acute renal failure; *ESRD,* end-stage renal disease; *GFR,* (calculated) glomerular filtration rate; *SCr,* serum creatinine; *UO,* urine output.

RIFLE class is determined based on the worst of either SCr, GFR, or UO criteria. SCr change is calculated as an increase of SCr above baseline SCr. Acute kidney injury should be both abrupt (within 1-7 days) and sustained (>24 hr). When the baseline SCr is not known and patients are without a history of chronic kidney insufficiency, it is recommended that a baseline SCr be calculated with the use of the Modification of Diet in Renal Disease (MDRD) equation for assessment of kidney function, assuming a GFR of 75 mL/min/1.73M^2. When the baseline SCr is elevated, an abrupt increase of at least 0.5 mg/dL to greater than 4 mg/dL is all that is required to achieve the class of Failure.

Data from Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204–12.

BOX 30-1 Risk Factors for Developing Perioperative Renal Failure

- Cardiac surgery
  - Pre-existing renal insufficiency
  - Emergency procedures
  - Sepsis
  - Prolonged cardiopulmonary bypass
  - Postoperative cardiac dysfunction
- Vascular surgery
  - Pre-existing renal insufficiency
  - Postoperative dye studies
  - Sepsis
  - Aortic cross clamp
    - Direct renal ischemia
    - Myocardial ischemia, low cardiac output
    - Declamping hypotension
  - Renal artery atheromatous embolization
  - Ruptured aortic aneurysm
  - Biliary tract and hepatic surgery including liver transplantation
- Kidney transplantation
- Urogenital surgery
- Complicated obstetrics
- Major trauma
  - Direct renal trauma
  - Hemorrhagic shock
  - Massive blood transfusion
  - Elevated intra-abdominal pressure
  - Rhabdomyolysis
  - Sepsis and multiorgan dysfunction syndrome

Data from Sladen RN, Prough DS. Perioperative renal protection. Problems in Anesthesia 1997;9:314–31.

sequential interaction of multiple factors. Indeed, AKI may be the final common pathway of a confluence of factors such as pre-existing renal insufficiency or a genetic predisposition, high-risk surgery, compromised hemodynamic function, nephrotoxic insults, and acute inflammation. It is little wonder that no single intervention has been shown to be the magic bullet that prevents AKI.

Patient Factors

Patient factors demonstrated to be associated with an increased risk of the development of postoperative AKI include advanced age, hypertension, diabetes mellitus, ventricular dysfunction, sepsis, hepatic failure, and chronic kidney disease (CKD). Because CKD also has various definitions, the association between preoperative CKD and postoperative AKI is difficult to quantify accurately, but it is strong.[21-23] Poorly controlled diastolic hypertension is an established risk factor for AKI, but wide pulse pressure hypertension (isolated systolic hypertension) is independently associated with worsened renal function after cardiac surgery.[24]

Genetic polymorphisms may also play a role in the predisposition to AKI. The Duke University group demonstrated a negative association between the possession of the apolipoprotein E4 allele and postoperative increases in SCr levels in a prospective study of 564 patients undergoing CABG.[25] This renal protective effect is interesting because the same polymorphism is associated with atherosclerotic disease and an increased risk of perioperative neurologic impairment.[25,26]

Intraoperative Factors

Ischemia and Inflammation

Ischemia–Reperfusion Injury. Ischemia compromises the supply of oxygen to the tissues and can interfere with normal physiologic function. Re-establishment of the oxygen supply, while essential for minimizing ischemia, can also contribute to cell injury and subsequent death. The etiology of the reperfusion injury is multifactorial, including interstitial edema, capillary obstruction, and inflammatory cell infiltration.

Although the renal medulla receives less than 10% of renal blood flow (RBF), the medullary process of urinary concentration has a high metabolic requirement. Any compromise to RBF increases the regional perfusion imbalance and renders the medulla ischemic. Compromise may result from aortic occlusion, atheromatous embolism, hypotension, low blood flow states, and hypovolemia.

Suprarenal aortic cross-clamping creates an ischemia–reperfusion injury and self-limited acute tubular necrosis (ATN) that takes up to 48 hours to recover.[3] Injury is exacerbated by the proinflammatory cytokine liberation that follows reperfusion. Infrarenal aortic cross-clamping

also significantly compromises RBF, most likely through reflex renal vasoconstriction.[27]

Atheromatous renal artery embolism is a devastating complication that may be provoked by trauma as trivial as coughing, aortic and renal angiography, manipulation of the renal arteries by the proximate application of the cross-clamp, or by placement of an endovascular graft. Patchy or confluent renal infarction that is usually irreversible can occur.

Cardiorenal Syndrome. Besides local factors, renal perfusion is manifestly affected by global changes in intravascular volume, renal perfusion pressure, and RBF. Deleterious changes in cardiac function in the perioperative period (such as after cardiopulmonary bypass [CPB]), in addition to any preoperative cardiac impairment, can more than additively affect perfusion variables for the kidney. Cardiorenal syndrome broadly describes the bidirectional negative influences of impairment or failure of either the kidney or the heart on the other.[28]

The Inflammatory Response. Ischemia–reperfusion injury provokes an inflammatory response that may be more detrimental than the original ischemic insult itself. Major surgery itself provokes inflammation. A cascade of stress responses is elicited, mediated by the release of various cytokines and stress hormones, culminating in the systemic inflammatory response syndrome. The kidneys sequester proinflammatory cytokines and may be damaged by them. Systemic inflammatory response syndrome is activated to a variable degree in all patients who undergo CPB and in many who undergo major operations.[29,30]

Gut ischemia and portal endotoxemia frequently complicate major aortic surgery. The insult appears to be more frequent in patients who undergo surgery via the intraperitoneal abdominal aorta rather than with the endovascular approach.[31] Endotoxin and other activated cytokines cause afferent arteriolar constriction, mesangial contraction, and direct tubular injury that diminish RBF, GFR, sodium excretion, and urine flow.[32] Compared with open aortic repair, endovascular techniques require shorter aortic occlusion times and are associated with a diminished early-phase response and proinflammatory surge.[33]

Glucose Homeostasis. Abnormal glucose homeostasis (hyperglycemia) is characteristic of the acute inflammatory response and is exacerbated by the perioperative administration of high-dose steroids (e.g., in patients undergoing transplantation). Strict perioperative glycemic control has been advocated in the intensive care setting on the basis of data indicating improved survival rates with a concomitant decrease in the incidence of ARF.[34-36] In one study evaluating persistent intraoperative hyperglycemia despite an insulin protocol, hyperglycemia was associated with worsened renal outcomes.[37] However, in another randomized, controlled trial in patients undergoing cardiac surgery, tight glucose control did not reduce the incidence of perioperative ARF.[38] Presently, it is unclear whether intraoperative hyperglycemia is simply a marker of acute illness or whether it is a reversible, treatable, and independent effector of renal outcome.

Nephrotoxins

Renin–Angiotensin System Blocking Drugs. Drugs that block the renin–angiotensin system include the angiotensin-converting enzyme (ACE) inhibitors and the selective angiotensin II receptor antagonists. These groups of drugs have become well-established in the treatment of hypertension and promote beneficial cardiac remodeling in congestive heart failure (CHF). As such, they may prevent the progression of chronic renal disease.

However, angiotensin release is an important protective mechanism that induces efferent renal arteriolar constriction in states of decreased RBF or perfusion pressure. The presence of ACE inhibitors or angiotensin II receptor antagonists may impair the maintenance of RBF and GFR when renal perfusion is compromised. In one prospective study of 249 patients undergoing aortic surgery, long-term preoperative ACE inhibitor administration was the only factor independently associated with a 20% decline in GFR after surgery.[39]

Aprotinin. Aprotinin is an inhibitor of endogenous serine proteases such as kallikrein and plasmin. Its effectiveness in decreasing bleeding after CPB—through its antifibrinolytic action and platelet stabilization—was established more than 20 years ago.[40] Numerous observations have suggested that aprotinin administration is associated with elevations in postoperative SCr levels,[41-43] likely mediated through its effects on kinin pathways and subsequent alteration of intrarenal hemodynamics.[44,45] Aprotinin may cause vasoconstriction of the afferent arteriole, which reduces glomerular perfusion pressure and renal excretory function. Indeed, there may be a deleterious interaction of ACE inhibitors and aprotinin on renal function when neither drug alone has any effect.[46]

Two retrospective observational reports published in 2006 evoked much debate.[47,48] They indicated that significant increases in adverse postoperative events, including renal failure, occurred with aprotinin, whereas the reduction in blood loss was no better than simpler, safer antifibrinolytic agents such as epsilon aminocaproic acid or tranexamic acid. In contrast, meta-analyses of 13 randomized controlled trials that reported data on AKI published before these observational studies failed to show an adverse effect of aprotinin on renal or other organ function.[49,50] A large Canadian randomized controlled trial of antifibrinolytic drugs in high-risk cardiac surgery was halted after a higher mortality rate was seen in patients randomly allocated to receive aprotinin, although there appeared to be no difference in renal outcomes between the different antifibrinolytic agents.[51]

Nonsteroidal Antiinflammatory Drugs. Nonsteroidal antiinflammatory drugs (NSAIDs) exert multiple renal effects. Their inhibition of cyclooxygenase suppresses the formation of endogenous prostaglandins that induce afferent arteriolar vasodilatation during situations of renal stress. Thus administration of NSAIDs causes little harm when renal circulation is normal[52] but may exacerbate renal injury during low flow states or in conjunction with other nephrotoxic agents. Administration of NSAIDs has also been implicated in interstitial and membranous nephritis and minimal change protein leak

disease. NSAIDs may be harmful in conditions such as cirrhosis, CKD, and CHF, in which maintenance of RBF is dependent on precapillary vasodilation.

Calcineurin Inhibitors. In the early 1980s, the introduction of supplemental immunosuppression by the calcineurin phosphatase inhibitor, cyclosporine A, revolutionized solid organ transplantation. It soon became apparent that its benefit was limited by dose-dependent acute nephrotoxicity, induced by afferent arteriolar vasoconstriction.[53] Subsequently, the importance of chronic nephrotoxicity was also appreciated, but the mechanisms are more complex, involving the renin–angiotensin system, endothelin, nitric oxide, and inflammatory activation.[54] Another widely used calcineurin inhibitor, tacrolimus, shares the propensity for nephrotoxicity, and its actions on growth factor may promote fibrogenesis as a component of chronic renal impairment.[55] Strategies of altering the timing of calcineurin introduction, minimizing calcineurins, or replacing calcineurins with other immunosuppressives have no conclusive evidence of minimizing renal injury and may carry a higher rejection risk.[56]

Myoglobin. In the presence of acidic urine, myoglobin and uric acid precipitate and form obstructive casts within the tubules. Furthermore, at a urinary pH less than 5.6, myoglobin dissociates into the nephrotoxic ferrihematin with further potentiation of ATN. Myoglobin appears less nephrotoxic in the absence of intravascular hypovolemia and acidic urine.

Radiocontrast Media. The mechanism of nephrotoxicity of radiocontrast media is multifactorial. They cause direct cytotoxic injury, whereas their hyperosmolality crenates red cells and causes microcirculatory obstruction. They induce an imbalance of renal oxygen supply and demands, by promoting acute vasoconstriction that impairs renal medullary perfusion, whereas the osmotic load they induce increases medullary oxygen consumption.[57] Contrast material filtered through the glomerulus precipitates in the renal tubules and liberates damaging free oxygen radicals. The risk of radiocontrast nephropathy (RCN) is greatly exacerbated by dehydration and hypovolemia and the concomitant administration of other nephrotoxic agents.

TABLE 30-2 **Levels of Evidence**

Level	Type of Evidence
1a	Systematic review (with homogeneity*) of RCTs
1b	Individual RCT (with narrow confidence interval)
1c	All or none†
2a	Systematic review (with homogeneity*) of cohort studies
2b	Individual cohort study (including low-quality RCT)
2c	"Outcomes" research
3a	Systematic review (with homogeneity*) of case-control studies
3b	Individual case-control studies
4	Case series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

RCT, randomized, controlled trial.
*Homogeneity of both direction and degree of results between the individual studies.
†When all patients developed renal failure before the therapy was available, but now some do not; or when some patients developed renal failure before therapy was available, but now none do.
Adapted from Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, et al. Levels of evidence (March 2009), Oxford Centre for Evidence Based Medicine, <www.cebm.net/index.aspx?o=1025>; 2012 [accessed 02.10.12].

TABLE 30-3 **Grades of Recommendations**

Grade	Criteria
A	Consistent Level 1 studies
B	Consistent Level 2 or 3 studies *or* extrapolations* from Level 1 studies
C	Level 4 studies *or* extrapolations from Level 2 or 3 studies
D	Level 5 evidence *or* troubling inconsistent or inconclusive studies of any level

*Extrapolations are from data regarding renal failure obtained from studies with a different clinical focus.

OPTIONS AND THERAPIES

- Optimize renal function preoperatively and minimize nephrotoxic insults.
- Minimize hemodynamic insults to the kidney
  - Avoid prolonged aortic cross-clamping.
  - Maintain RBF and perfusion pressure.
  - Avoid pharmacologic agents that may compromise RBF or increase the metabolic demand of the kidney.
- Consider pharmacologic renoprotective strategies.

EVIDENCE

Overall, studies on prophylactic and therapeutic interventions in patients at high risk of developing perioperative AKI are limited. The majority of studies have concentrated on RCN, and their findings may not be applicable to perioperative AKI. Tables 30-2, 30-3, and 30-4 summarize and grade the evidence using established criteria.[58]

A Cochrane Database review of 53 studies of the protective renal effects of perioperative administration of dopamine, diuretics, calcium channel blockers (CCBs), ACE inhibitors, or simple hydration concludes that certain interventions show some benefit but that all the results suffer from significant heterogeneity.[59] The authors deemed the evidence from available literature too unreliable for any conclusions to be drawn about the effectiveness of these interventions in protecting the kidneys from damage during surgery.

TABLE 30-4 **Summary of Renal Protective Strategies in Humans for High-Risk Surgery**

Study	Level of Evidence	Patient Group	Comments
Dopamine, Diuretics, Calcium Channel Blockers, Angiotensin-Converting Enzyme Inhibitors, Hydration Fluids			
Zacharias et al[59]	1a	Systematic review	Cochrane Database Systematic review of 53 studies indicated that certain interventions showed some benefits, but all the results suffered from significant heterogeneity. There is no reliable evidence from available literature to suggest that interventions during surgery can protect the kidneys from damage.
Perioperative Optimization			
Brienza et al[62]	2a	Systematic review	Twenty studies suggested that perioperative optimization in elective and emergency surgical patients was effective in reducing renal injury. No guidance of methods or goals of therapy could be promoted.
Remote Ischemic Conditioning			
Desai et al[79]	2a	Systematic review	Four vascular surgical studies involving 115 patients (remote ischemic preconditioning) and 117 patients without. Small numbers led to inconclusive results. No difference in mortality or renal failure.
Dopamine			
Kellum[83]	1a	Systematic review	Routine use of diuretics or dopamine for the prevention of acute renal failure cannot be justified on the basis of available evidence.
Kellum and Decker[84]	1a	Systematic review	No justification for the use of low-dose dopamine for the treatment or prevention of acute renal failure.
Marik[85]	1a	Systematic review	Dopamine demonstrates no renoprotective effect in patients at high risk of developing renal failure.
Bellomo et al[81]	1b	Critically ill	Large placebo-controlled RCT ($n = 328$) of dopamine in critically ill patients with signs of sepsis. No differences in peak creatinine, need for RRT, or mortality.
Fenoldopam			
Halpenny et al[87]	2b	Cardiac surgery	Small placebo-controlled RCT ($n = 31$) of fenoldopam during cardiac surgery with cardiopulmonary bypass. The fenoldopam group was spared decline in postoperative creatinine clearance.
Halpenny et al[88]	2b	Vascular surgery	Small placebo-controlled RCT ($n = 28$) of fenoldopam in aortic surgical patients undergoing infrarenal cross-clamping. Fenoldopam was associated with postoperative maintenance of creatinine clearance and prevention of deterioration of serum creatinine.
Cogliati et al[89]	2b	Cardiac surgery	Single center, double-blind RCT ($n = 193$). Fenoldopam infusion for 24 hr after cardiac surgery associated with less AKI, decreased need for RRT, and lower postoperative rise in serum creatinine.
Landoni et al[94]	2b	Cardiac surgery	Meta-analysis of 1059 patients in 13 studies was associated with less need for RRT, less in-hospital death, and shorter ICU stay.
Dopamine versus Fenoldopam			
Bove et al[90]	2b	Cardiac surgery	Prospective single-center, randomized, double-blind trial ($n = 80$). Fenoldopam or dopamine after the induction of anesthesia for a 24-hr period. No difference in clinical outcome.
Oliver et al[91]	2b	Vascular surgery	Single center, randomized, double-blind trial ($n = 60$). Fenoldopam or dopamine with nitroprusside after the induction of anesthesia in patients undergoing aortic cross-clamping. No difference in clinical outcome.
Furosemide			
Lassnigg et al[97]	1b	Cardiac surgery	Prospective ($n = 126$) RCT of cardiac surgical patients that received either "renal dose" of dopamine or furosemide or placebo until 48 hr postoperatively. Furosemide administration was associated with greater creatinine deterioration, lower creatinine clearance, and more need for RRT with the conclusion of a possible negative treatment effect.
Kellum[83]	1a	Systematic review	Level 1 evidence exists against the use of diuretics for prevention of perioperative renal failure after vascular surgery.
Mannitol			
Tiggeler et al[100]	2b	Renal transplantation	Prospective ($n = 61$) study of cadaveric renal transplant recipients receiving restricted fluids (1.1 L), or restricted fluids (1.5 L) plus mannitol, or moderate fluids (2.5 L) plus mannitol. The incidence of ATN was 43%, 53%, and 4.8%, respectively.

Continued on following page

TABLE 30-4 **Summary of Renal Protective Strategies in Humans for High-Risk Surgery** (Continued)

Study	Level of Evidence	Patient Group	Comments
Nicholson et al[103]	2b	Vascular surgery	Prospective ($n = 28$) study of mannitol or placebo for aortic surgery with infrarenal aortic cross-clamping. No differences in BUN, SCr, or creatinine clearance. Mannitol group had lower urinary albumin and *N*-acetyl glucosaminidase.
Ip-Yam et al[104]	2b	Cardiac surgery	Prospective ($n = 23$) study of hypothermic CPB, normothermic CPB, or normothermic CPB plus mannitol in bypass prime. No significant differences between groups in markers of renal function.
Homsi et al[105]	4	Rhabdomyolysis	Retrospective case series ($n = 24$) of saline versus saline plus bicarbonate plus mannitol for rhabdomyolysis (CK >500 U/L). No additive benefit with the addition of bicarbonate or mannitol.
Gubern et al[106]	2b	Obstructive jaundice	Prospective RCT ($n = 31$) of mannitol in postoperative patients with obstructive jaundice. Mannitol had no beneficial effects on renal function.
Urinary Alkalinization			
Haase et al[109]	2b	Cardiac surgery	Prospective RCT ($n = 100$) of $NaHCO_3$ (4 mmol/kg) versus saline. Bicarbonate group had lower markers of renal dysfunction.
Heringlake et al[110]	2b	Cardiac surgery	Prospective observational cohort study comparing 280 patients (4 mmol $NaHCO_3$/kg) versus 304 patients (control). Bicarbonate group had more hypotension and needed more fluids but no improvement in postoperative renal function.
Antioxidants			
Haase et al[117]	1b	Cardiac surgery	Placebo-controlled RCT ($n = 60$) of a 24-hr infusion of *N*-acetylcysteine. No difference in creatinine change, peak creatinine, urine output, or serum cystatin C.
Wijnen et al[118]	2b	Vascular surgery	Small RCT ($n = 44$) of standard therapy plus antioxidants (allopurinol, vitamins E and C, acetylcysteine, mannitol) versus standard therapy only. No difference in urine albumin/creatinine ratio but antioxidant group had higher creatinine clearance at postoperative day 2.
Burns et al[116]	1b	Cardiac surgery	CABG patients. Randomized, quadruple-blind, placebo-controlled trial ($n = 295$) of intravenous *N*-acetylcysteine or placebo over 24 hr. No difference in the proportion of patients with postoperative renal dysfunction. A post hoc subgroup analysis of patients (baseline creatinine level >1.4 mg/dL) showed a nonsignificant trend toward fewer patients experiencing postoperative renal dysfunction in the *N*-acetylcysteine group compared with the placebo group.
Calcium Channel Blockers			
Shilliday et al[125]	1a	Renal transplantation /systematic review	Cochrane Database Systematic Review. Ten trials included. Treatment with calcium channel blockers in the peritransplant period was associated with a significant decrease in the incidence of post-transplant ATN and delayed graft function. There was no difference between control and treatment groups in graft loss, mortality, or requirement for hemodialysis.
van Riemsdijk et al[124]	2b	Renal transplantation	Placebo-controlled RCT ($n = 210$) of isradipine after renal transplantation. Isradipine was associated with better renal function at 3 and 12 mo without changes in acute rejection or delayed graft function.
Antonucci et al[126]	2b	Vascular surgery	Small RCT ($n = 16$) of nifedipine or dopamine for aortic surgery with infrarenal cross-clamping. Immediate postoperative GFR was maintained in the nifedipine group (but not dopamine group).
Young et al[127]	4	Cardiac surgery	Case series of perioperative diltiazem infusion ($n = 271$) and control ($n = 143$). Diltiazem was associated with higher SCr rise and greater need for dialysis (4.4% versus 0.7%).
Statins			
Prowle et al[134]	2b	Cardiac surgery	Prospective, double-blind, randomized, placebo-controlled study ($n = 100$). Patients with normal renal function randomly assigned to atorvastatin or placebo. No difference in incidence of postoperative AKI or urinary neutrophil gelatinase–associated lipocalin.
Liakopoulos et al[132]	2a	Cardiac surgery	Meta-analysis of studies of preoperative statins and postoperative complications of cardiac surgery suggested renoprotective benefit.
Mithani et al[135]	1b	Cardiac surgery	Single-center prospective RCT of 2104 patients undergoing CABG or valve surgery. Statins (high or low dose) had no influence on postoperative AKI or need for hemodialysis.

TABLE 30-4 **Summary of Renal Protective Strategies in Humans for High-Risk Surgery** (Continued)

Study	Level of Evidence	Patient Group	Comments
Natriuretic Peptides			
Sward et al[166]	2b	Postcardiac surgery	Prospective, double-blind, randomized, placebo-controlled study ($n = 61$). Patients with normal preoperative renal function post cardiac surgery randomly assigned to receive recombinant h-ANP or placebo when serum creatinine increased by >50% from baseline. Significant reduction in the proportion of patients requiring dialysis before or at day 21 and significant reduction in the proportion of patients with the composite endpoint of dialysis or death before or at day 21 compared with placebo.
Sward et al[138]	4	Postcardiac surgery	Case series ($n = 11$) of longer than 48-hr infusion of ANP in postcardiac surgical patients with acute renal impairment needing pharmacologic support. ANP was associated with increased urine flow, GFR, and renal blood flow.
Sezai et al[148]	2b	Cardiac surgery	RCT ($n = 504$) of carperitide (0.02 then 0.01 mcg/kg/min) versus placebo in elective CABG with normal renal function. Less increase in creatinine and less need for RRT.
Sezai et al[147]	2b	Cardiac surgery	RCT ($n = 303$) of carperitide versus placebo in cardiac surgical patients with chronic kidney disease. Lower postoperative creatinine and need for RRT in carperitide group. No difference in 1-yr mortality.
Mitaka et al[152]	1a	Cardiovascular surgery	Systematic review and meta-analysis of 11 studies of ANP analog (carperitide) and four studies of BNP analog (nesiritide). ANP analog associated with lower peak creatinine, reduced need for RRT, and reduced ICU and hospital stay. BNP analog associated with decreased ICU and hospital stay.
Langrehr et al[139]	2b	Liver transplantation	Placebo-controlled RCT ($n = 70$) of ularitide immediately after liver transplantation. No difference in course of urea or creatinine. There was no difference in urine flow or need for dialysis. Less diuretic use in the ularitide group.
Weibe et al[140]	2b	Cardiac surgery	Small placebo-controlled RCT ($n = 14$) of 7 days of ularitide in postcardiac surgical patients with anuric acute renal failure. No patients taking ularitide needed hemodialysis (compared with 6 of 7 in control group).
Brenner et al[141]	2b	Cardiac surgery	Small placebo-controlled RCT ($n = 24$) of 6 days of ularitide immediately after cardiac transplantation. Equal numbers of each group (50%) required hemodialysis, although the duration and frequency were less in the ularitide group.
Prostaglandins			
Manasia et al[156]	2b	Liver transplantation	Small ($n = 21$) placebo-controlled RCT of PGE_1 for 5 days immediately after liver transplantation in patients with an immediate postoperative GFR less than 50 mL/min. No difference in GFR or effective renal plasma flow.
Klein et al[157]	2b	Liver transplantation	Larger ($n = 118$) placebo-controlled multicenter RCT of PGE_1 immediately after liver transplantation. PGE_1 associated with lower peak creatinine, "severe renal dysfunction," need for dialysis, and ICU length of stay.
Abe et al[159]	4	Cardiac surgery	Small ($n = 10$) case-control study of PGE_1 during cardiopulmonary bypass. Rise in *N*-acetyl-glucosaminidase less, and no change in free water clearance in PGE_1 group.
Abe et al[160]	2b	Cardiac surgery	Small ($n = 20$) placebo-controlled RCT of PGE_1 during cardiopulmonary bypass. PGE_1 group had better results for *N*-acetyl-glucosaminidase, free water clearance, and beta-2 microglobulin.
Feddersen et al[161]	4	Cardiac surgery	Small ($n = 36$) case-control study of prostacyclin during cardiopulmonary bypass. Prostacyclin was associated with a postoperative increase in GFR but more hypotension than control group.
Insulin-like Growth Factor-1			
Franklin et al[165]	2b	Vascular surgery	Small ($n = 54$) placebo-controlled RCT of 72 hr IGF-1 with primary endpoint as change in creatinine clearance within 72 hr after surgery involving suprarenal aorta or renal arteries. Fewer patients with IGF-1 had postoperative decline in creatinine clearance (22% versus 33%).

AKI, acute kidney injury; *ANP,* atrial natriuretic peptide; *ATN,* acute tubular necrosis; *BNP,* brain natriuretic peptide; *BUN,* blood, urea, nitrogen; *CABG,* coronary artery bypass graft; *CK,* creatinine kinase; *CPB,* cardiopulmonary bypass; *GFR,* glomerular filtration rate; *ICU,* intensive care unit; *IGF-1,* insulin-like growth factor-1; *PGE1,* prostaglandin E_1; *RCT,* randomized controlled trial; *RRT,* renal replacement therapy; *SCr,* serum creatinine.

Perioperative Hemodynamic Optimization

Perioperative hemodynamic optimization refers to the manipulation of hemodynamic variables reflecting intravascular volume status (by crystalloids, colloids, hematocrit), perfusion pressure (vasopressors), and cardiac output (inotropes). High-risk surgical patients may benefit from hemodynamic optimization in terms of lower mortality and morbidity rates,[60,61] but not much evidence exists on renal outcomes specifically. A meta-analysis of 20 studies (4220 emergency and elective surgical patients) suggested that renal dysfunction could be broadly reduced with perioperative optimization.[62] However, no recommendations could be made regarding the techniques of such optimization, the monitoring required, or to which endpoints the optimization should be titrated.

Hypotheses regarding the impact of hydration on the prevention of perioperative AKI—either a liberal versus conservative strategy or the superiority of one type of crystalloid or colloid over another—have not been subjected to randomized controlled trials.

However, there is considerable evidence that the single-most important protective measure to ameliorate RCN is fluid loading and hydration before intravascular administration of radiocontrast media.[63-68] There is no agreement on the minimal duration, optimal rate, and composition of intravenous fluid administered. Administration of intravenous isotonic saline for several hours before, during, and after radiocontrast media injection is usually advocated. One significant randomized controlled trial[69] demonstrated a more favorable impact on the incidence of RCN by the infusion of isotonic sodium bicarbonate than by the infusion of sodium chloride.

The mainstay of the prevention of AKI as a consequence of rhabdomyolysis and myoglobinemia is the early, aggressive administration of large quantities of fluids. It is advocated that intravenous access be obtained in the field in cases of traumatic crush injury and that saline at 1.5 L/hr be infused.[70]

In critically ill patients with acute lung injury, conservative fluid management (as opposed to traditional liberal fluid management) did not influence the development of AKI.[71] Interestingly, a trend of increased dialysis need was noted in the traditional liberal fluid group.

Hematocrit has emerged as a consideration with a retrospective review suggesting that renal dysfunction was more prevalent in cardiac surgical patients if the hematocrit was less than 21% or the patient had been transfused.[72] The concern of extreme hemodilution with consequent low hematocrit level has been replicated by others.[73]

Some initial studies suggested that fluid therapy guided by invasive hemodynamic monitoring via a pulmonary artery catheter could provide renal protection during open aortic aneurysm resection[74,75]; however, subsequent controlled studies failed to confirm this benefit.[74-77] On the other hand, mannitol and dopamine appear to be no better than saline hydration in the amelioration of the transient decline in GFR after infrarenal aortic cross-clamping.[78]

Remote Ischemic Preconditioning

Remote ischemic preconditioning describes a technique of brief repeated cycles of nonlethal organ ischemia followed by reperfusion. The ischemic preconditioning may affect the same organ bed to be protected (direct) or in a vascular bed distant from the one to be protected (remote). The mechanism of how remote ischemic preconditioning contributes to organ protection is not clear but may involve biochemical messengers, perhaps neurally or humorally inducing lower oxidative stress and mitochondrial preservation. Unfortunately, the majority of the studies have had small patient numbers. The authors of a systematic review of these studies believed that the paucity of data could only lead to equivocal conclusions regarding remote ischemic preconditioning.[79]

Dopaminergic Agents

Dopamine

Dopamine is an endogenous catecholamine with a broad range of activity on dopaminergic, beta-adrenergic, and alpha-adrenergic receptors. "Low dose" dopamine, that is, less than 3 mcg/kg/min, was long considered a useful agent for renal protection by virtue of its dopaminergic actions on the kidney, both in inducing renal vasodilation and in blocking tubular sodium reabsorption (natriuresis). However, the pharmacokinetics of dopamine vary so widely in the general population such that there may be a 30-fold variability in the plasma concentration.[80] This may, in part, explain why multiple trials have been unable to demonstrate a beneficial effect of prophylactic low-dose dopamine on renal outcome, and the consensus today is that it has no role in this regard.[81-86] The impact of therapeutic intervention with dopamine as an inotropic agent to enhance cardiac function and RBF has not been subjected to randomized controlled trials.

Fenoldopam

Fenoldopam is a phenolated derivative of dopamine that has several pharmacologic advantages over the parent compound. It is a selective dopaminergic-1 receptor agonist that induces dose-dependent renal vasodilation, increases in RBF, and natriuresis. The pharmacokinetics are very predictable, and there is a close relationship between dose and plasma concentration. It lacks any beta- or alpha-adrenergic effects that could induce unwanted tachycardia or vasoconstriction and, as such, is safe to administer by a peripheral catheter.

Preliminary observations suggested a renoprotective effect of fenoldopam infusion during CPB[87] and infrarenal cross-clamping.[88] Infusion of low-dose fenoldopam (0.1 mcg/kg/min) in cardiac surgery patients was associated with no change in the creatinine clearance and a significantly smaller increase in postoperative serum creatinine level.[89] However, two other randomized, prospective studies were unable to detect a difference in renal function between fenoldopam and dopamine

prophylaxis during cardiac surgery or vascular surgery with aortic cross-clamping.[90,91] After a preliminary study suggested that fenoldopam may confer greater renal protection against RCN than saline,[92] a large, prospective controlled study failed to confirm a benefit over simple hydration.[93]

Despite these somewhat conflicting data, a meta-analysis of 1059 patients undergoing cardiovascular surgery from 13 randomized studies demonstrated that fenoldopam infusion was associated with decreased risk of RRT, intensive care unit (ICU) length of stay, and in-hospital mortality.[94] The authors concluded, appropriately, that large randomized controlled outcome studies are needed to confirm these findings and fully define the role of fenoldopam in protection against AKI.

Loop Diuretics

The so-called loop diuretics include furosemide, bumetanide, torsemide (all structurally related to the sulfonylureas) and ethacrynic acid. They act as potent blockers of active sodium, potassium, and chloride transport at the medullary thick ascending limb (mTAL) of the loop of Henle, causing diuresis and natriuresis. Theoretically, mTAL blockade enhances tubular oxygen balance by decreasing tubular energy requirements and oxygen consumption. However, the loop diuretics also induce renal cortical vasodilatation that could "steal" blood flow from the already oligemic medulla, which could undermine this benefit.

There is little or no evidence to support the use of loop diuretics as renoprotective agents, either by bolus or continuous infusion. A number of systematic reviews of undifferentiated patients at risk of ARF concluded that the addition of diuretics confers no benefit over fluids alone.[83,95,96] In patients with chronic renal impairment, prevention of RCN was accomplished better with saline hydration alone than hydration plus furosemide, which actually appeared to increase the risk of AKI.[68] Diuretic administration that results in intravascular hypovolemia may actually worsen renal function. In an effort to evaluate renal protection during cardiac surgery, a double-blind randomized study was performed in which 126 patients received continuous infusions of dopamine (2 mcg/kg/min), furosemide (0.5 mcg/kg/min, or about 2 mg/hr), or saline placebo from anesthetic induction to 48 hours after surgery. The effect of dopamine was no different than placebo, but patients who received furosemide had AKI, which was reflected by increases in SCr and decreases in creatinine clearance and by the fact that two patients required RRT.[97]

Mannitol

Mannitol is an inert sugar that is widely used as an osmotic diuretic. There is considerable experimental evidence in animals that mannitol attenuates ischemia–reperfusion injury by multiple mechanisms, including maintaining glomerular filtration pressure, preventing tubular obstruction by cellular casts, scavenging hydroxyl free radicals, and preventing cellular swelling.[98,99]

Although confirmatory evidence from clinical studies is scarce, mannitol has been widely used for renal protection during renal transplantation, CPB, aortic surgery, and rhabdomyolysis. Its routine use (with hydration) in renal transplantation was established by studies showing a renal protective effect almost three decades ago.[100,101] Animal models of suprarenal aortic cross-clamping revealed that neither mannitol nor dopamine nor both together prevented a persistent decrease in GFR and RBF after cross-clamp release.[102] Human studies on patients undergoing infrarenal cross-clamping have revealed that infusions of mannitol, dopamine, or both induce more diuresis but are no more effective than saline hydration at attenuating a transient decrease in GFR,[78] although there is evidence of attenuated biochemical glomerular and tubular injury in patients who received mannitol.[103] There is no evidence from randomized controlled trials that mannitol decreases AKI in patients with traumatic rhabdomyolysis or in those who receive radiocontrast media, undergo CPB, vascular surgery, or biliary tract surgery.[104-107]

Urinary Alkalinization

There is animal evidence that alkalinization of the urine to a pH greater than 6.0 can prevent the conversion of myoglobin to toxic ferrihematin in the renal tubules and further ameliorates the risk of AKI. Although there is reasonable evidence that a sodium bicarbonate–based hydration regimen is beneficial in preventing RCN,[108] the limited studies involving cardiac surgical patients have yielded conflicting results.[109-110]

Antioxidants

N-acetylcysteine (NAC) is an antioxidant that directly scavenges reactive oxygen species and has received intense study as a potential renal protective agent. A seminal study of 83 patients with severe CKD (mean SCr, 2.4 mg/dL) showed a decrease in the incidence of RCN, defined as an SCr increase of more than 0.5 mg/dL, from 21% to 2% by the preprocedure administration of 600 mg twice daily oral NAC.[111] Subsequent larger studies disputed these results, suggesting that the dose of contrast medium is a greater determinant of RCN than NAC administration[112] or that NAC confers no greater protection than fenoldopam or saline loading.[113] Moreover, there is evidence that NAC administration decreases creatinine production, thus rendering uncertain any studies using SCr or derived creatinine clearance as endpoints.[114] In contrast, a large prospective placebo-controlled study evaluated NAC in 354 patients with acute myocardial infarction undergoing primary angioplasty.[115] Patients were randomly assigned to standard-dose NAC (600 mg intravenous bolus before angioplasty and 600 mg orally twice daily for 48 hours), high-dose NAC (1200 mg with an identical regimen), or saline placebo. AKI, defined as greater than a 25% increase in SCr, occurred in 33% of control patients, 15% of patients receiving standard-dose NAC, and 8% of patients after high-dose NAC; moreover, a significant decrease was also seen in in-hospital mortality (i.e., 11%, 4%, and 3%, respectively).

In other settings, notably cardiac surgery with CPB and major vascular surgery, randomized controlled trials[116-118] and a systematic review[119] have demonstrated no benefit to the perioperative infusion of NAC in the prevention of postoperative AKI. In conclusion, although evidence supports the prophylactic administration of NAC for the amelioration of RCN, there is no evidence to recommend NAC outside this setting.

Calcium Channel Blockers

CCBs promote renal vasodilation, increase RBF, and GFR. They appear to confer protection against intracellular calcium injury in ischemia–reperfusion injury,[120] inhibit angiotensin action in the glomerulus, and decrease circulating interleukin-2 receptors.[121] Their role in treating chronically hypertensive patients with or without CKD appears beneficial to the kidney.[122]

CCBs specifically protect the kidney against the nephrotoxic effects of calcineurin inhibitors, cyclosporine, and tacrolimus, which induce renal injury in part by causing increased sympathetic tone and renal arteriolar vasoconstriction. In a prospective randomized study in patients undergoing cadaveric kidney transplantation, diltiazem was added to preservative solution and infused into the recipient for 2 days. Patients who received diltiazem had a significantly lower incidence of graft ATN (10% versus 41%) and a lower requirement for postoperative RRT. Moreover, they tolerated higher cyclosporine blood levels with better graft function and fewer episodes of rejection. Diltiazem also appeared to delay cyclosporine elimination, which allowed a 30% decrease in dose with comparable immunosuppressive blood levels.

This benefit appears to continue with long-term (5-year) follow-up,[123] but a study with another CCB, the dihydropyridine isradipine, demonstrated improved SCr without improved early allograft dysfunction.[124] A subsequent systematic review of CCBs in cadaveric kidney transplantation concluded that graft ATN is significantly decreased but that there is no significant difference in treatments for graft loss, mortality, or postoperative RRT requirement.[125]

Studies on CCBs in other situations have been more equivocal. A small placebo-controlled trial of patients undergoing aortic surgery with infra-aortic cross-clamping showed that nifedipine prevented the postoperative decline in GFR.[126] A retrospective study of cardiac surgical patients suggested that prophylactic diltiazem infusion increased the incidence of AKI,[127] but prospective studies have indicated that it is not harmful and may confer some benefit as evidenced by decreased biochemical urinary markers of tubular injury.[128-130]

Statins

Statins have been suggested to have renoprotective properties in AKI by preserving glomerular filtration, maintaining intrarenal blood flow, and producing anti-inflammatory effects. A number of retrospective studies have yielded conflicting data.[130-134] A meta-analysis of preoperative statin therapy suggested a renoprotective benefit in cardiac surgical patients,[132] but a large prospective randomized controlled trial in cardiac surgical patients failed to demonstrate any lower incidence of AKI or need for hemodialysis.[135]

Natriuretic Peptides

The natriuretic peptides are a family of endogenous compounds of varying sizes (28 to 32 amino acids) with a similar active core and actions.[136] They act on specific receptors to induce activation of guanosine cyclase, which converts guanosine triphosphate to cyclic guanosine monophosphate. Through this pathway, natriuretic peptides oppose the vasoconstrictor, salt-retaining actions of catecholamines and the renin–angiotensin–aldosterone axis. They promote renal afferent arteriolar dilation, thereby increasing GFR and natriuresis. In addition to the diuretic and natriuretic actions, natriuretic peptides have vasodilatory properties in both the systemic and pulmonary circulations.

Atrial natriuretic peptide (A-type natriuretic peptide, ANP) is secreted in response to stretching of cardiac atrial cells.[137] Brain natriuretic peptide (B-type natriuretic peptide, BNP) is released by ventricular stretching, C-type natriuretic peptide is released from the endothelium of the great vessels, and urodilatin is elaborated in the kidney itself. Analogs of ANP (anaritide, carperitide), BNP (nesiritide), and urodilatin (ularitide) have been produced in human recombinant form for intravenous administration.

In a small series of patients who had heart or liver transplantation or cardiac surgery, it was suggested that ularitide had beneficial effects on urine flow and RBF[138] and decreased requirements for RRT.[138-141] However, in patients with established ARF, ularitide neither decreased RRT requirements or the mortality rate.[142]

On the basis of animal studies and preliminary human studies, anaritide (atrial natriuretic factor prohormone) infusion engendered considerable interest as a "rescue" agent for established ATN.[143] A randomized controlled study of anaritide infusion at 200 ng/kg/min in 504 patients with ATN showed no difference in RRT-free days.[2] However, a subanalysis of the 76% of patients with nonoliguric ATN (>400 mL/day urine) and the 24% of patients with oliguric ATN demonstrated a significant decrease in RRT-free days in the latter group. Subsequently, a prospective study of 222 patients with oliguric ATN showed no benefit on RRT-free days, ICU length of stay, or mortality.[144] Of note, patients who received anaritide sustained a significantly greater incidence of systemic hypotension, which suggests that the vasodilatory, hypotensive effects of the natriuretic peptide negated its benefit on renal recovery. This hypothesis is reinforced by a perioperative study of cardiac surgery patients in which a lower dose of anaritide (50 ng/kg/min) resulted in a halving of the RRT-free days and RRT-free survival.[138] Anaritide infusion had previously been shown to prevent elevations in renin, angiotensin II, and aldosterone induced by CPB and also had been shown to maintain GFR.[145] Subsequent studies have also indicated that continuous infusion during thoracic aortic surgery with

CPB increased urine output and decreased diuretic requirements.[146]

Carperitide (human natriuretic peptide precursor A or hNPPA) is another ANP analog that has undergone clinical study. It is currently available in Japan, and many of the supporting studies have been at single centers with small sample sizes. Two larger studies looking at cardiac surgical patients both with and without CKD suggested renoprotective effects.[147,148]

Nesiritide is a natriuretic peptide approved for clinical use in the United States and a few other countries. It is indicated for the parenteral treatment of patients with acutely decompensated congestive heart failure (ADCHF) who have dyspnea at rest or with minimal activity. Although initial prospective studies revealed no adverse effect in patients with ADCHF and renal insufficiency,[149] a meta-analysis suggested that nesiritide infusion is associated with an increased risk of elevated SCr in patients with ADCHF.[150] However, a randomized prospective study of 279 patients with an ejection fraction less than 40% undergoing cardiac surgery demonstrated that infusion of 0.01 mcg/kg/min nesiritide starting at anesthetic induction until 24 to 96 hours after surgery was associated with a significant decrease in postoperative elevation of SCr, as well as a significantly decreased 6-month mortality rate.[151]

Unfortunately, the literature regarding natriuretic peptides has largely focused on changes in serum creatinine and urine output and only secondarily on outcome measures of RRT and mortality. In this frame, a systematic review and meta-analysis of 15 studies involving carperitide and nesiritide in cardiovascular surgical patients suggested preservation of postoperative renal function, as demonstrated by urine output and creatinine clearance.[152] Carperitide reduced the need for RRT, and both drugs reduced the ICU stay and hospital stay.

Intraoperative Glucose Control

A large single-center study of critically ill patients (63% of whom had cardiac surgery) suggested that a strategy of intensive insulin therapy to achieve tight glucose control was associated with survival benefits and reductions in the development of AKI and the requirement for dialysis.[36] A subsequent meta-analysis failed to demonstrate benefits in survival or a reduced need for dialysis.[153] Specifically, in cardiac surgical patients, tight glucose control had no benefit in dialysis rates but did show a worrisome trend toward increased mortality and stroke rates.[38]

Prostaglandins

Prostaglandins PGE_2 and PGD_2 and prostacyclin are endogenous eicosanoids that act as intrarenal vasodilators. They are released during renal stress and may protect the kidneys by preserving intrarenal hemodynamics and medullary perfusion and increasing natriuresis.[16,154] Alprostadil (synthetic PGE_1), which has been used for many years for ductus arteriosus dilation in the treatment of congenital heart disease, has been evaluated for renal protection. In patients with CKD undergoing radiocontrast angiography, PGE_1 limited the increase in SCr but without a change in measured creatinine clearance.[155] In studies of PGE_1 or PGE_2 infusion after orthotopic liver transplantation, beneficial effects on renal function have been inconsistent.[156-158] In cardiac surgery, PGE_1 and prostacyclin have been infused during CPB only, without any demonstrated renal benefit.[159-161] The limiting factor appears to be prostaglandin-induced hypotension, particularly with the loss of renal autoregulation during anesthesia and hypothermic CPB.

Growth Factors

Growth factors improve regeneration and repair of damaged nephrons in ischemic ATN and may speed renal recovery after AKI. Acidic fibroblast growth factor-1 has been protective in an animal model, perhaps mediated by the antiinflammatory and vasodilating effects of nitric oxide.[162] Results with insulin-like growth factor-1 (IGF-1) have been similarly encouraging.[163] In humans with end-stage CKD, administration of IGF-1 improved renal function,[164] and in a small clinical trial, high-risk vascular surgical patients given IGF-1 had less renal dysfunction.[165] However, as yet evidence is insufficient to recommend IGF-1 for clinical use.

GUIDELINES

At present, guidelines of measures to prevent perioperative AKI have not been published.

AUTHORS' RECOMMENDATIONS

Although numerous definitions of acute kidney injury (AKI) remain and the lack of consensus has hampered research in the area thus far, perioperative AKI is an ominous development for the individual patient. We look forward to the RIFLE criteria (i.e., risk of injury [R], acute injury [I], established failure [F], sustained loss of function [L] and end-stage renal disease [E]) being used in perioperative clinical trials. Currently, no magic bullets exist to prevent development of acute renal failure, and despite vigorous research, evidence for therapeutic strategies is very limited (Table 30-5).

TABLE 30-5 **Authors' Recommendations for Perioperative Interventions**

Intervention	Evidence	Effect	Grade[58]
Minimize radiocontrast media exposure	Nil		D
Maintain renal blood flow	Extrapolated	Beneficial	C
Maintain renal perfusion pressure	Extrapolated	Beneficial	C
Minimize duration of aortic cross-clamping	Nil		D
Maintain intravascular volume	Extrapolated	Beneficial	C
Avoid perioperative nephrotoxins	Nil		D
Pharmacologic Strategies			
Dopamine	Yes	No benefit	A
Fenoldopam	Some subgroups	May be of benefit	C
Furosemide	Some subgroups	May be harmful	B
Mannitol	Some subgroups	May be of benefit	C
Antioxidants (*N*-acetylcysteine)	Some subgroups	May be of benefit	B
Calcium channel blockers	Some subgroups	May be of benefit	C
Natriuretic peptides	Some subgroups	May be of benefit	B
Prostaglandins	Some subgroups	No benefit	C

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CHAPTER 31

Does Nitrous Oxide Affect Outcomes?

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INTRODUCTION

No anesthetic agent has been administered more often than nitrous oxide. Since its first demonstration in 1845, nitrous oxide has been administered to billions of patients for general anesthesia, sedation for diagnostic and therapeutic procedures, labor analgesia, and the pain of trauma. It remains one of the most widely available and widely used anesthetic agents worldwide.

Nitrous oxide is one of the simplest and smallest of anesthetic molecules (N≡N–O). Its anesthetic actions occur via noncompetitive inhibition of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors,[1] as well as at additional targets.[2] Although nitrous oxide is not very potent (minimum alveolar concentration [MAC], 104%) and is not used alone to produce general anesthesia, it significantly reduces the doses of potent anesthetic agents required to produce hypnosis.[3,4] NMDA receptor antagonism may also lead to hypothalamic release of corticotropin-releasing hormone and activation of opioidergic neurons in the periaqueductal gray matter. Nitrous oxide's analgesic action has been attributed to this mode of action,[5] and inhalation of nitrous oxide is favored when rapidly reversible analgesia is required.

Many of the unwanted effects of nitrous oxide are attributed to its inhibition of methionine synthetase, via its oxidation of the cobalt atom on vitamin B_{12} (a cofactor for methionine synthetase). The result is impaired conversion of homocysteine to methionine and hyperhomocysteinemia. Because methionine synthetase also catalyzes the conversion of 5-methyltetrahydrofolate to tetrahydrofolate, deoxyribonucleic acid (DNA) synthesis is disrupted after administration of nitrous oxide (Figure 31-1). Significant inhibition of methionine synthetase by nitrous oxide occurs after about 1 hour of administration and may persist for some time after administration has ceased.[6] Other unwanted effects of nitrous oxide result from its physical characteristics and its ability to increase the volume, pressure, or both in gas-filled spaces.[7]

The host of mechanistic studies on the physiologic and pathologic effects of nitrous oxide administration has added greatly to our understanding of nitrous oxide pharmacology.[8] However, it is the study of real endpoints that are most meaningful and important to patients.[9] In particular, patients want to know *who* will be at risk of important complications, not just what those complications are. Recent large randomized trials and systematic reviews provide this kind of evidence and have provoked a re-evaluation of nitrous oxide use. This chapter reviews the evidence regarding the safety of nitrous oxide as part of the gas mixture for general anesthesia in adult nonobstetric patients and suggests a more selective evidence-based approach to its administration.

OPTIONS/THERAPIES

Nitrous oxide is commonly administered as 50% to 75% of the gas mixture for anesthesia. If nitrous oxide is omitted, three decisions must be made.

What Gases Will Make Up the Gas Mixture?

When nitrous oxide is omitted, the inhaled gas mixture chosen is usually oxygen (25% to 100%) with the balance, where required, composed of nitrogen. The percentage of inhaled oxygen has significant implications for patients, and the benefits and risks of higher inspired concentrations are currently hotly debated.[10-13]

How Will Hypnosis Be Achieved?

Nitrous oxide significantly reduces propofol and the volatile anesthetic agent requirement for hypnosis.[3,4] Doses of these agents therefore need to be increased if nitrous oxide is omitted, and those practitioners unfamiliar with the increased doses required could put their patients at risk of awareness.[7]

How Will Intraoperative Analgesia Be Achieved?

The relatively mild analgesic action of nitrous oxide will need to be replaced with other antinociceptive agents intraoperatively, and additional early postoperative analgesics may be necessary. Even though more volatile anesthetic and opioid medication may be administered, omission of nitrous oxide should result in the requirement for fewer antiemetic agents.[14]

EVIDENCE

Cardiovascular Outcomes

One of the most active areas of research in recent years has been the effect of nitrous oxide on cardiovascular

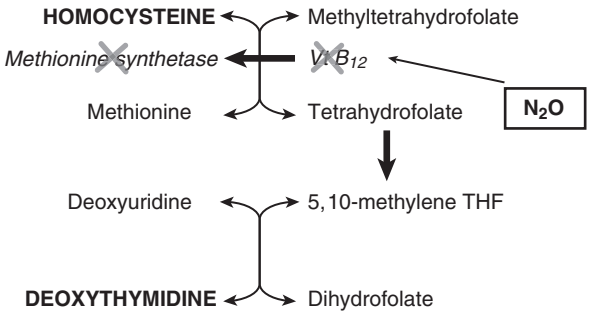

FIGURE 31-1 ■ Nitrous Oxide *(N_2O)* Oxidizes the Cobalt Atom on Vitamin B_{12}, Inhibiting Methionine Synthetase and Causing Accumulation of Homocysteine and Disruption of Deoxythymidine Synthesis. *THF,* tetrahydrofolate.

outcomes after surgery. As mentioned previously, nitrous oxide administration increases plasma homocysteine concentrations.[6,15,16] In a study of 394 noncardiac surgery patients randomly assigned to nitrous oxide–based or nitrous oxide–free anesthesia, plasma homocysteine concentrations were increased postoperatively in patients receiving nitrous oxide (11.1 [standard deviation, 3.8] versus 8.5 [4.0] mmol/L; $p = 0.0005$), and there was a significant association between the duration of nitrous oxide administration and the relative change in plasma homocysteine concentration ($r = 0.42$; $p = 0.001$).[15] Small studies suggest that 1 week of preoperative oral treatment with vitamin B_{12} may ameliorate nitrous oxide's effect on homocysteine concentrations,[17] whereas an infusion of vitamin B_{12} immediately before induction of anesthesia may not.[18]

Some patients are more likely to develop hyperhomocysteinemia after nitrous oxide exposure than others. Patients who are homozygous for polymorphisms in the methylenetetrahydrofolate reductase gene develop higher plasma homocysteine concentrations than patients with the wild-type or heterozygous allele and may reach homocysteine concentrations considered abnormal (>15 micromoles) during nitrous oxide administration.[19] Preexisting elevated homocysteine concentrations, which are common in elderly patients and those with cardiovascular disease,[20,21] may cause frank hyperhomocysteinemia after exposure to nitrous oxide.

Hyperhomocysteinemia promotes endothelial dysfunction and is associated with vascular disease in the nonoperative setting.[20] Endothelial dysfunction may lead to a failure of flow-mediated vasodilation and an impaired response to increased oxygen requirement. In a recent study of 59 noncardiac surgery patients with cardiovascular disease, nitrous oxide administration was associated with an increase in plasma homocysteine concentrations (mean difference, 4.9 micromoles; 95% confidence interval [CI], 2.8 to 7.0 micromoles; $p < 0.0005$) and a decrease in flow-mediated dilation (mean difference, 3.2%; 95% CI, 0.1 to 5.3%; $p = 0.001$).

Nitrous oxide-induced hyperhomocysteinemia is also associated with an increased incidence of myocardial ischemia and cardiovascular complications.[15,16,22] In 90 patients seen for carotid endarterectomy, hyperhomocysteinemia was reported in patients receiving nitrous oxide, and they experienced a higher incidence of myocardial ischemia on Holter monitoring (46% versus 25%; $p < 0.05$) and more ischemic events (82 versus 53; $p = 0.02$) in the first 48 hours postoperatively than patients who did not receive nitrous oxide.[16] In the aforementioned study of 394 noncardiac surgery patients, postoperative hyperhomocysteinemia was associated with an increased risk of cardiovascular events (relative risk, 5.1; 95% CI, 3.1 to 8.5; $p < 0.0005$), including myocardial infarction, thromboembolism, and stroke. Strategies to reduce plasma homocysteine concentrations, which are not proved to reduce the incidence of cardiac events in nonoperative settings,[23] have not be evaluated for this outcome perioperatively.

The Evaluation of Nitrous oxide in the Gas Mixture for Anaesthesia (ENIGMA) trial randomized 2050 noncardiac surgery patients having surgery of more than 2 hours' duration to a nitrous oxide–based or nitrous oxide–free general anesthetic.[24] The primary outcome, hospital length of stay, was not significantly different in patients in the nitrous oxide–based group than in the nitrous oxide–free group (7.1 [interquartile range, 4.0 to 11.8] days versus 7.0 [4.0 to 10.9] days; hazard ratio, 1.09; 95% CI, 1.00 to 1.19; $p = 0.06$). Trends of increased incidence of myocardial infarction (13 versus 7 events) and death (9 versus 3 events) during the 30-day follow-up period were reported in patients who received nitrous oxide. These patients were not enrolled on the basis of their cardiovascular risk profile, although 79% of them had at least one significant pre-existing medical condition. In addition, the inspired oxygen concentration was not equal in the two groups (30% in the nitrous oxide–based group versus 80% in the nitrous oxide–free group), which is a confounding factor that was emphasized in subsequent commentary as an alternative explanation for the results.[8,25]

In contrast, a trend toward a decreased 30-day risk of major adverse cardiovascular events in patients receiving nitrous oxide intraoperatively was reported in a retrospective analysis of a 49,016-patient administrative database.[13] Propensity-matching was used to adjust for the fact that nitrous oxide was administered to lower risk patients in this institution. The incidence of cardiac events was 1.8% in the nitrous oxide–based group and 2.2% in the nitrous oxide–free group (odds ratio, 0.82; 95% CI, 0.64 to 1.05; $p > 0.05$).

Long-term follow-up of the ENIGMA trial patients revealed an increased long-term risk of myocardial infarction but not death or stroke in patients who received nitrous oxide.[26] The median follow-up time was 3.5 years (range, 0 to 5.7), during which time 380 patients (19%) had died, 91 (4.5%) had had a myocardial infarction, and 44 (2.2%) had had a stroke. Nitrous oxide did not significantly increase the risk of death (hazard ratio, 0.98; 95% CI, 0.80 to 1.20; $p = 0.82$) or stroke (odds ratio, 1.01; 95% CI, 0.55 to 1.87; $p = 0.97$) but did increase the risk of myocardial infarction (odds ratio, 1.59; 95% CI, 1.01 to 2.51; $p = 0.04$). In patients with myocardial infarction, postoperative plasma homocysteine and folate concentrations were significantly increased when compared with preoperative values, and more of them had postoperative hyperhomocysteinemia. These authors and others called

for a specifically designed randomized trial in high-risk patients.[8,13,26,27]

Such a trial is nearly complete at this time (the ENIGMA-II trial, NCT00430989, www.enigma2.org.au; accessed May 23, 2012).[28] In ENIGMA-II, 7000 patients with or at risk of ischemic heart disease will be randomly assigned to 70% nitrous oxide or 70% nitrogen, both supplemented by 30% oxygen. Cardiac biomarkers and electrocardiographs will be collected in the early postoperative period, and telephone interviews will be conducted at 30 days and 1 year after surgery. Assessors unaware of group assignments will evaluate all events. The primary outcome is a composite of death and major nonfatal events (i.e., myocardial infarction, cardiac arrest, pulmonary embolism, and stroke) at 30 days after surgery.

Neurologic Outcomes

Speed of Emergence

The inclusion of nitrous oxide with a volatile agent in the gas mixture may speed early recovery from anesthesia.[29] This has been attributed to both the "second gas effect" and the "MAC-sparing effect."[30,31] To determine the relative importance of these effects, investigators randomly assigned 20 patients to 33% oxygen and either nitrous oxide or air (the control group).[30] Five minutes after cessation of nitrous oxide administration, arterial sevoflurane partial pressure was 39% higher in the control group than in the nitrous oxide-based group ($p = 0.04$). Times to eye opening (8.7 versus 10.1 minutes) and extubation (11.0 versus 13.2 minutes) also were shorter ($p = 0.04$). The authors concluded that more than half of the reduction of volatile agent concentration resulted from the diffusion effect, and the remainder was due to the MAC-sparing effect. In contrast, times to eye opening were similar in the nitrous oxide-based and nitrous oxide-free groups in the ENIGMA trial, although propofol-based maintenance was used in 20% of these patients; thus a less dramatic effect of nitrous oxide would be expected.[24]

Awareness

The risk of awareness when nitrous oxide is omitted is controversial. In a systematic review to determine the effect of the omission of nitrous oxide on postoperative nausea and vomiting (PONV), the number needed to treat for intraoperative awareness with nitrous oxide–free anesthetic was 46.2 (95% CI, 24.1 to 581).[14] This was attributed by others to unfamiliarity with nitrous oxide–free techniques.[7] In the ENIGMA-I trial, two cases of awareness were reported in the nitrous oxide–based group and none in the nitrous oxide–free group; however, ENIGMA-I was not powered for this outcome.[24] A comprehensive review of reported cases up to 2009 concluded that avoidance of nitrous oxide did not increase the risk of awareness.[32]

Neurotoxicity

Although numerous cases of neurotoxicity associated with nitrous oxide have been published, especially in folate-deficient or overexposed patients,[33] very few data from randomized controlled trials are available.[34] In 228 elderly patients seen for noncardiac surgery under volatile-based general anesthesia, the omission of nitrous oxide did not alter the incidence of delirium (41.9% versus 43.8%; $p = 0.78$) or cognitive impairment (14.8% versus 18.6%; $p = 0.59$) within 48 hours of surgery.[35] Similarly, in post-hoc analyses of the International Hypothermia for Aneurysm Surgery Trial,[36] no difference was demonstrated at 3 months postoperatively between patients who received nitrous oxide and those who did not in terms of any outcome variable. In a further subgroup who were treated with temporary parent artery occlusion during surgery, the use of nitrous oxide was associated with an increased risk of deficits due to vasospasm. However, at 3 months postoperatively, no demonstrable difference was found between the two groups.[37]

Respiratory Outcomes

The high solubility of nitrous oxide may potentially promote absorption atelectasis (when compared with nitrogen but not oxygen), but the importance of this phenomenon to real outcomes for patients is unclear.[7,38] In the ENIGMA-I trial, pneumonia (1.5% versus 3.0%; odds ratio, 0.51; 95% CI, 0.27 to 0.91; $p = 0.04$) and atelectasis (7.5% versus 13%; odds ratio, 0.55; 95% CI, 0.40 to 0.75; $p = 0.001$) were less commonly associated with nitrous oxide–free anesthesia than nitrous oxide–based anesthesia (Table 31-1).[24] However, as mentioned previously, the inspired oxygen concentration was higher in nitrous oxide–free patients. In contrast, the aforementioned retrospective analysis of a 49,016-patient administrative database revealed a lower incidence of pulmonary/respiratory complications in patients receiving nitrous oxide (1.6% versus 2.7%; odds ratio, 0.60; 95% CI, 0.47 to 0.77). In this study, nitrous oxide–free patients also received a higher inspired concentration of oxygen. The ENIGMA-II randomized controlled trial, conducted in higher risk patients and with equal inspired oxygen concentration in each group, may illuminate this issue further.[28]

Gastrointestinal Outcomes

Nitrous oxide may increase the volume, pressure, or both in gas-filled spaces.[39] Recently, a randomized controlled trial conducted in 344 colorectal surgery patients confirmed that nitrous oxide–based anesthesia was associated with more moderate to severe bowel distention than nitrous oxide–free anesthesia (25% versus 9%; absolute risk reduction, 14%; 95% CI, 8% to 21%) and scores at 2 hours postoperatively on a 100-mm visual analog scale were greater in the nitrous oxide–based compared with nitrous oxide–free group (43 [standard deviation, 30] mm versus 35 [31] mm; $p = 0.018$).

PONV is a miserable experience for patients and may necessitate additional in-patient treatment, increasing the cost of care.[40] Nitrous oxide is firmly established as a significant cause of PONV,[14,41] and guidelines recommend the avoidance of nitrous oxide to reduce the baseline risk of this complication.[42] A recent systematic

TABLE 31-1 **Postoperative Outcomes in Patients Randomly Assigned to Nitrous Oxide–Based and Nitrous Oxide–Free General Anesthesia in the ENIGMA Trial**

Outcome (within 30 days)	N_2O-free (n = 997)	N_2O-based (n = 997)	Adjusted OR* (95% CI)	p Value
Severe PONV	104 (10%)	229 (23%)	0.40 (0.31-0.51)†	<0.001
Wound infection	77 (7.7%)	106 (10%)	0.72 (0.52-0.98)‡	0.036
Fever	275 (28%)	345 (34%)	0.73 (0.60-0.90)	0.003
Pneumonia	15 (1.5%)	30 (3.0%)	0.51 (0.27-0.97)	0.04
Atelectasis	75 (7.5%)	127 (13%)	0.55 (0.40-0.75)	<0.001
Myocardial infarction	7 (0.7%)	13 (1.3%)	0.58 (0.22-1.50)	0.26
Thromboembolism	16 (1.6%)	10 (1.0%)	1.60 (0.72-3.55)	0.25
Blood transfusion	188 (19%)	202 (20%)	0.96 (0.75-1.21)	0.71
Death	3 (0.3%)	9 (0.9%)	0.33 (0.09-1.22)	0.096
Any pulmonary complication	78 (7.8%)	132 (13%)	0.54 (0.40-0.74)	<0.001
Any major complication§	155 (16%)	210 (21%)	0.70 (0.55-0.89)	0.003

CI, confidence interval; *ENIGMA,* Evaluation of Nitrous oxide in the Gas Mixture for Anaesthesia; *N_2O,* nitrous oxide; *OR,* odds ratio; *PONV,* postoperative nausea and vomiting.
*Adjusted for age, American Society of Anesthesiologists physical status classification, and duration of anesthesia unless otherwise stated.
†Adjusted for postoperative nausea and vomiting risk and intraoperative antiemetic drug use.
‡Adjusted for National Nosocomial Infections Surveillance System score, lowest intraoperative temperature, and smoking status.
§Any major complication includes wound infection, pneumonia, pneumothorax, myocardial infarction, thromboembolism, stroke, awareness, and death within 30 days of surgery.
From Myles P, Leslie K, Chan M, Forbes A, Paech M, Peyton P, et al. Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. Anesthesiology 2007;107:221–31, with permission.

review[43] included thirty studies of the incidence of PONV in adults after general anesthesia with or without nitrous oxide, who were maintained with the same potent hypnotic agent (i.e., propofol or a volatile anesthetic). The relative risk of PONV was significantly reduced when nitrous oxide was omitted (0.80; 95% CI, 0.71 to 0.90; p = 0.0003). When propofol rather than a volatile anesthetic was used to maintain anesthesia, however, the effect of nitrous oxide on the risk of PONV was not significant (relative risk, 0.94; 95% CI, 0.77 to 1.15).

In the ENIGMA-I trial, 16.6% of 2050 patients reported severe PONV (repeated PONV or the need for repeated treatment).[40] Younger age, female sex, abdominal surgery, absence of bispectral index monitoring, longer duration of surgery, and nitrous oxide administration were significant predictors of PONV in a multivariate model. The incidence of PONV in patients receiving nitrous oxide was 23% compared with an incidence of 10% for patients who did not receive nitrous oxide (odds ratio, 2.04; 95% CI, 1.55 to 2.70; $p < 0.0001$).

Acute and Chronic Pain Outcomes

The effect of intraoperative nitrous oxide administration on acute postoperative pain is unclear. Small retrospective studies have reported conflicting results.[44,45] The aforementioned randomized trial of 228 elderly patients seen for noncardiac surgery reported that postoperative 10-mm visual analog scale scores were similar after nitrous oxide–based or nitrous oxide–free anesthesia,[35] and in the ENIGMA trial patients, the incidence of severe acute pain was 8.9% in the nitrous oxide–based group and 12.4% in the nitrous oxide–free group (p = 0.27).[24] However, a randomized trial of 50 patients seen for nasal surgery suggested that nitrous oxide may prevent remifentanil-induced hyperalgesia,[46] and this is supported by animal evidence reporting an antihyperalgesic effect of nitrous oxide.[47]

Preliminary evidence from the ENIGMA trial suggests that nitrous oxide may prevent chronic pain.[48] Nearly 11% of patients had chronic postoperative pain (5.6% in the nitrous oxide–based group and 12.9% in the nitrous oxide–free group (odds ratio, 0.43; 95% CI, 0.23 to 0.83; p = 0.01). Patients with chronic postoperative pain reported a lower quality of life in all domains measured. Suggested mechanisms include not only its action as an NMDA antagonist but also impairment of axonal regeneration due to its effects on DNA synthesis.[5,48] Chronic pain follow-up is part of the long-term follow-up of the ENIGMA-II trial.

Inflammatory and Infectious Outcomes

Through its effects on folate metabolism and DNA synthesis,[49] as well as the obligation to deliver lower inspired oxygen concentrations during nitrous oxide administration,[10] nitrous oxide may impair responses to inflammation and infection. In 418 patients undergoing colon resection, 15% of patients who were randomly assigned to nitrous oxide–based anesthesia and 20% of patients who were randomly assigned to nitrous oxide–free anesthesia were later seen with postoperative wound infection (p = 0.205). In contrast, in the ENIGMA trial, the risk of wound infection was reduced when nitrous oxide was omitted (7.7% versus 10.0%; odds ratio, 0.72; 95% CI, 0.52 to 0.98; p = 0.036), and a similar effect was demonstrated for pneumonia. Because of concern about the effect of inspired oxygen concentration (which was different in the two groups),[25] data from the nitrous oxide–free group (n = 997) were analyzed.[24] There were no

measurable effects of oxygen concentration on wound infection (p = 0.40), which implies that the effect on wound infection was due to nitrous oxide administration. Further data on wound infection will be available when the ENIGMA-II trial is completed.

COST OF CARE

Patients have an interest in making health care more efficient so that services can be spread more evenly and widely throughout the population.[9] It appears that the costs of treating the complications of nitrous oxide administration overcome any savings that can be made by reducing the requirement for more expensive potent hypnotic agents. A recent retrospective cost analysis of the 2050 patients included in the ENIGMA trial reported that total costs were $16,203 in the nitrous oxide–based group and $13,837 in the nitrous oxide–free group (mean difference, $2366; 95% CI, $841 to $3891; p = 0.002).[50] The costs of infrastructure associated with piped nitrous oxide, the costs to the environment, and the costs incurred after 30 days were not included in this analysis but neither were the potential savings associated with a reduction in chronic pain if nitrous oxide administration were omitted.

CONTROVERSIES

"Nitrous oxide is a funny gas."[34] More than 150 years after the first public demonstration of nitrous oxide, nearly every indication and contraindication for its use as part of the gas mixture for anesthesia in adult nonobstetric patients remains controversial.[8,25,27] Even with respect to PONV, the emetic effects of nitrous oxide can simply be overcome by the use of propofol for maintenance of anesthesia or the administration of one additional antiemetic, if the indications for its use are strong enough.[43] The announcement of the results of the ENIGMA trial resulted in a re-evaluation of the place of nitrous oxide in the practice of many anesthesiologists and the abandonment of its use by some. The subsequent publication of mechanistic studies on nitrous oxide's antinociceptive and antihyperalgesic actions, as well as data from the ENIGMA trial suggesting a reduction in chronic pain in patients treated with nitrous oxide, have sparked interest in the use of nitrous oxide for specific indications in adults having general anesthesia.

AREAS OF UNCERTAINTY

Many areas of uncertainty in relation to nitrous oxide have been outlined in the chapter. The most significant area of uncertainty at present remains the effect of nitrous oxide on the risk of major postoperative adverse cardiac events in patients with or at risk of ischemic heart disease and, in particular, whether patients with key genetic polymorphisms or dietary deficiencies are especially at risk. Postoperative myocardial infarction is an important complication of noncardiac surgery with an incidence of approximately 5% and an in-hospital mortality rate of approximately 12%, and no preventive measure has yet proven to be both effective and safe.[51] The ENIGMA-II trial is specifically designed to answer some of these questions.

GUIDELINES

National and international guidelines exist for safe exposure limits to nitrous oxide for workers in manufacturing and health care. The only guideline relating to the use of nitrous oxide in adult nonobstetric patients receiving general anesthesia recommends the avoidance of nitrous oxide in patients at risk of PONV, in particular, women, patients with a past history of PONV or motion sickness, and those who will receive volatile anesthetic agents.[42]

AUTHOR'S RECOMMENDATIONS

Does administration of nitrous oxide make a difference in patient-centered outcomes? On the basis of the evidence presented here, I believe that it does. Nitrous oxide administration should be avoided in patients at high risk of postoperative nausea and vomiting, especially when propofol-based maintenance of anesthesia will not be used. Consideration should also be given to avoiding nitrous oxide during abdominal surgery because of the risk of moderate to severe abdominal distension. The current evidence is insufficient to support recommendations about avoidance of nitrous oxide in patients at risk of major adverse cardiac events, pulmonary atelectasis, infectious complications of anesthesia and surgery, or neurologic deficits. The omission of nitrous oxide is not a risk factor for anesthetic awareness, and its use is not a proved preventive measure. Intriguing new evidence about the potential for nitrous oxide to prevent remifentanil-induced hyperalgesia and severe chronic postoperative pain supports the use of nitrous oxide during general anesthesia in patients at risk of these complications who have no other contraindications to its use. The "nitrous oxide frolics" are not yet over.

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CHAPTER 32

Are Alpha-2 Agonists Effective in Reducing Perioperative Cardiac Complications in Noncardiac Surgery?

J. Devin Roberts, MD • John E. Ellis, MD • Douglas C. Shook, MD

INTRODUCTION

Alpha-2 receptor agonists have many desirable effects such as minimum alveolar concentration (MAC) reduction, analgesia, anxiolysis, sedation, and sympatholysis.[1,2] Adding to this list the possibility of perioperative myocardial protection makes the perioperative use of alpha-2 agonists very appealing in patients with known or suspected coronary artery disease. It is well-known that drugs that positively affect myocardial oxygen supply and demand are beneficial in the perioperative period for myocardial protection.[3] Perioperative beta-blockade is an excellent example of this.[4,5] The ability of alpha-2 agonists to modulate sympathetic tone may similarly offer perioperative myocardial protection.

OPTIONS/THERAPIES

The most widely studied alpha-2 agonists are clonidine, mivazerol, and dexmedetomidine. Clonidine is available in oral, transdermal, and parenteral forms and is a partial agonist. Mivazerol is an intravenous alpha-2 agonist, and dexmedetomidine is a shorter-acting intravenous alpha-2 agonist. The selectivity ratios for all three are shown in Table 32-1.[1] All three alpha-2 agonists have been shown to cause dose-dependent sympatholysis, but clonidine and mivazerol have been most extensively studied with regard to perioperative cardiac protection. Unfortunately, mivazerol is not available in the United States.

EVIDENCE

Several studies have been published investigating alpha-2 agonists and their role in perioperative myocardial protection. In addition, many studies have evaluated the hemodynamic stabilizing effects and sympatholysis produced by alpha-2 agonists. It is important to understand the endpoints in these investigations because many used myocardial ischemia as a surrogate marker for myocardial infarction and cardiac death. Although several studies have linked perioperative myocardial ischemia to subsequent increased cardiac morbidity and mortality rates,[6,7] most of the studies to date have not linked the use of perioperative alpha-2 agonists to decreased rates of myocardial infarction and death.

Randomized Controlled Trials: Clonidine

The perioperative use of clonidine for myocardial protection in noncardiac surgery has been studied in three well-designed small, randomized trials. Ellis and colleagues[8] studied the use of transdermal clonidine combined with oral clonidine in a randomized, double-blind, placebo-controlled clinical trial of 61 patients undergoing elective major noncardiac surgery. The treatment group received premedication with the transdermal clonidine system (0.2 mg/day) the night before surgery, which was left in place for 72 hours, and 0.3 mg oral clonidine 60 to 90 minutes before surgery. The incidence of intraoperative electrocardiographic (ECG) ischemia was diminished in the clonidine group (4% versus 21%, $p = 0.05$). There was no difference, however, between the two groups in the incidence of postoperative ischemia. Later, Stuhmeier and colleagues[9] studied 297 patients scheduled for vascular surgery in a randomized, double-blind fashion. They evaluated the effect of 2 mcg/kg of oral clonidine 90 minutes before induction of anesthesia. Patients receiving oral clonidine demonstrated a decreased incidence of intraoperative myocardial ischemia (24% versus 39%, $p < 0.01$). However, no statistical difference was noted in the number of patients who had a nonfatal myocardial infarction or who died of major cardiac events. In 2004 Wallace and colleagues[10] conducted a prospective, double-blind, randomized clinical trial of 190 patients at risk of coronary artery disease scheduled for noncardiac surgery. All patients in the clonidine group ($n = 125$) received 0.2 mg orally the night before and 1 hour before surgery. A transdermal patch (0.2 mg/day) was placed the night before surgery and removed on postoperative day 4. The incidence of myocardial ischemia in the clonidine group was reduced on days 0 to 3 versus the placebo group (14% versus 31%, $p < 0.01$). Long-term follow-up revealed that the clonidine group had a reduced mortality rate at 30 days (0.8% versus 6.5%, $p = 0.048$) and at

TABLE 32-1 **Specificity of Alpha-2 Agonists for the Alpha-2 Receptor**

Alpha-2 Agonist	Alpha-2:Alpha-1 Specificity
Dexmedetomidine	1300:1
Mivazerol	119:1
Clonidine	39:1

2 years (15% versus 29%, $p = 0.035$), but this benefit lost statistical significance after removing all patients who received preoperative or intraoperative beta-blockers.

Randomized Controlled Trials: Mivazerol

Mivazerol, an intravenous alpha-2 agonist administered by continuous infusion, has been studied in larger trials. A European multicenter group studied mivazerol in a phase II, placebo-controlled, double-blind, randomized trial.[11] Three hundred patients with known coronary artery disease (CAD) were placed into three groups: high-dose mivazerol (1.5 mcg/kg/hr), low-dose mivazerol (0.75 mcg/kg/hr), or placebo. High-dose mivazerol had significantly less intraoperative myocardial ischemia versus placebo (20% versus 34%, $p = 0.026$), but no differences were observed for perioperative myocardial infarction or death. In addition, there was no difference in postoperative myocardial ischemia. In 1999 Oliver and colleagues[12] conducted a large double-blind, randomized, placebo-controlled study of 2854 patients (1897 with known CAD and 957 with risk factors for CAD). Patients received perioperative mivazerol at 1.5 mcg/kg/hr for 72 hours or placebo. On subgroup analysis, in the group of 1897 patients with known CAD, there were fewer cardiac deaths in the mivazerol group versus placebo (13 of 956 versus 25 of 941, $p = 0.037$). The rates of myocardial infarction and all-cause death were not statistically different between the two groups. In the subgroup of patients undergoing vascular procedures ($n = 904$), mivazerol afforded significant myocardial protection. The cardiac death rate was 6% versus 18% ($p = 0.009$), and the combined cardiac death and myocardial infarction rate was 10% versus 14% ($p = 0.02$). The myocardial infarction rate alone was not significantly different.

Randomized Controlled Trials: Dexmedetomidine

No large randomized controlled trials have studied the infusion of dexmedetomidine for reduction of perioperative cardiac morbidity and mortality rates in noncardiac surgical patients. Dexmedetomidine has been investigated in small studies for its hemodynamic effects. Talke and colleagues[13] evaluated the hemodynamic effects of four different doses of dexmedetomidine in 22 vascular surgery patients at risk of CAD. Although patients at the higher doses of dexmedetomidine appeared to have greater hemodynamic stability (less tachycardia and systolic hypertension), they needed more intraoperative vasopressor and fluid support. Because of the study size, no statistical significance could be determined regarding myocardial ischemia and perioperative myocardial infarction. A second study by Jalonen and colleagues[14] looked at 80 patients scheduled for elective coronary artery bypass grafting. Again, dexmedetomidine produced less tachycardia and was associated with lower blood pressures, but the study patients needed more fluid challenges and pharmacologic treatment for hypotension. No statistical significance was determined with respect to myocardial ischemia and infarction. Table 32-2 summarizes all of the randomized controlled trials.

Meta-Analysis of Alpha-2 Agonists

A meta-analysis published by Nishina and colleagues[15] in 2002 looked at the efficacy of clonidine for the prevention of perioperative myocardial ischemia. The study systematically reviewed the randomized controlled trials that tested this endpoint. Seven studies were included in the meta-analysis. Two of them were referenced previously,[8,9] and the other five looked at the use of clonidine for the prevention of ischemia in cardiac surgery. The meta-analysis concluded that clonidine in both cardiac surgery patients and noncardiac surgery patients reduced perioperative myocardial ischemia. Conclusions about preferable endpoints such as myocardial infarction and death could not be drawn because of the low statistical power of the analysis. A more comprehensive meta-analysis by Wijeysundera and colleagues[16] investigated the perioperative cardiac effects of all alpha-2 adrenergic agonists studied through 2002. Twenty-three studies were included, enrolling 3395 patients (cardiac and noncardiac surgical patients). The study concluded that alpha-2 agonists significantly reduced overall mortality rate and reported ischemia but failed to show a statistically significant reduction in myocardial infarction. In vascular surgery patients, alpha-2 agonists significantly reduced mortality rates and myocardial infarction and were associated with a trend toward ischemia reduction. A recent meta-analysis by Biccard and colleagues[17] looked at dexmedetomidine and cardiac protection in noncardiac patients. Twenty studies were included, involving 840 patients. The regimen of dexmedetomidine infusion varied between studies, and most of the studies did not continue the infusion postoperatively. Perioperative cardiac outcomes were not the primary outcome measure in any of the studies included in the analysis. The study concluded that perioperative dexmedetomidine infusion was associated with a trend toward but did not significantly reduce the cardiac mortality rate, myocardial infarction, or myocardial ischemia. Dexmedetomidine was also associated with more hypotension and bradycardia. Table 32-3 summarizes all the meta-analysis studies.

AREAS OF UNCERTAINTY

The endpoints studied in the majority of the randomized, controlled trials are primarily surrogate endpoints, such

TABLE 32-2 **Summary of Randomized Controlled Trials**

Author, Year	Procedure	No. of Subjects	Study Design	Intervention	Ischemia	MI	Cardiac Death
Ellis, 1994	Noncardiac	Control 31 Treated 30	Double-blind placebo	TD clonidine 0.2 mg night prior (72 hr); clonidine 0.3 mg PO preoperatively	D: 1/28 (4%) C: 5/24 (21%) $p = 0.05$		
Stuhmeier, 1996	Vascular	Control 152 Treated 145	Double-blind placebo	Clonidine 2 mcg/kg PO preoperatively	D: 35/145 (24%) C: 59/152 (39%) $p < 0.01$	D: 0/145 (0%) C: 4/152 (3%) NS	D: 2/145 (1%) C: 1/152 (1%) NS
McSPI, 1997	Noncardiac	Control 103 Treated 98	Double-blind placebo	Mivazerol 1.5 mcg/kg/hr (high dose); started 20 min before induction; continued for 72 hr	D: 17/87 (20%) C: 34/99 (34%) $p = 0.026$ (high dose only)	D: 2/98 (2%) C: 6/103 (6%) NS (high dose only)	D: 1/98 (1%) C: 1/98 (1%) NS (high dose only)
Oliver, 1999	Noncardiac with known CAD	Control 941 Treated 946	Double-blind placebo	Mivazerol 1.5 mcg/kg/hr; started 20 min before induction; continued for 72 hr		D: 78/946 (8%) C: 79/941 (8%) NS	D: 13/946 (3%) C: 25/941 (1%) $p = 0.037$
Oliver, 1999	Vascular	Control 450 Treated 454	Double-blind placebo	Mivazerol 1.5 mcg/kg/hr; started 20 min before induction; continued for 72 hr		D: 42/454 (9%) C: 53/450 (12%) NS	D: 6/454 (1%) C: 18/450 (4%) $p = 0.009$
Wallace, 2004	Noncardiac	Control 65 Treated 125	Double-blind placebo	TD clonidine 0.2 mg night prior (4 days); clonidine 0.2 mg PO preoperatively and night prior	D: 18/125 (14%) C: 20/65 (31%) $p = 0.01$	D: 5/125 (4%) C: 3/65 (5%) NS	D: 19/125 (15%) C: 19/65 (29%) $p = 0.035$

C, control; *CAD,* coronary artery disease; *D*, drug; *MI,* myocardial infarction; *NS,* no statistical significance; *PO,* per os (by mouth); *TD,* transdermal.

TABLE 32-3 **Summary of Meta-Analysis Studies**

Author, Year	Procedures (Trials)	No. of Trials	No. of Subjects	Perioperative Interventions (Trials)	Outcome
Nishina, 2002	Cardiac (5) Noncardiac (2)	7	664	Clonidine	Reduced overall ischemia; OR, 0.49; 95% CI, 0.34-0.71
Wijeysundera, 2003	Cardiac (10) Noncardiac (11)	23	3395	Clonidine (15) Dexmedetomidine (6) Mivazerol (2)	Reduced mortality rate (overall); RR, 0.64; 95% CI, 0.42-0.99 Reduced ischemia (overall); RR, 0.76; 95% CI, 0.63-0.91 Reduced mortality rate (vascular); RR, 0.47; 95% CI, 0.25-0.90 Reduced MI (vascular); RR, 0.66; 95% CI, 0.46-0.94
Biccard, 2008	Noncardiac	20	840	Dexmedetomidine	Mortality rate; OR, 0.27; 95% CI, 0.01-7.13 (NS); MI, OR, 0.26; 95% CI, 0.04-1.60 (NS) Ischemia, OR, 0.65; 95% CI, 0.26-1.63 (NS)

CI, confidence interval; *MI,* myocardial infarction; *NS,* no statistical significance; *OR,* odds ratio; *RR,* relative risk.

as myocardial ischemia, rather than more definitive endpoints such as myocardial infarction or death. Two trials looked specifically at mortality and myocardial infarction rates. Oliver and colleagues[12] evaluated endpoints such as myocardial infarction and death and found that the group most affected was patients with known CAD and those undergoing vascular surgery. The validity of this conclusion is limited in that the effect was not seen in the overall group, as originally intended, but only on subsequent subgroup analysis. Wallace and colleagues[10] concluded that perioperative clonidine reduced episodes of ischemia and, more important, reduced the long-term incidence of myocardial infarction and death. Unfortunately, the long-term benefit may have been due to perioperative administration of beta-blockers in both the study and placebo groups.

The studies reviewed demonstrated less intraoperative ischemia with the use of alpha-2 agonists, but alpha-2 agonists did not consistently show the ability to continue this protection into the postoperative period. It is possible that the doses needed for postoperative sympatholysis may be higher than those effective during surgery and anesthesia. Many studies were also underpowered to demonstrate outcome differences, if they, indeed, were to exist. It is widely recognized that the risk of myocardial infarction is greatest over the first 3 postoperative days.[18] Therefore, in addition to questions of dosage, the exact time frame in which to use alpha-2 agonists for myocardial protection remains unclear. No study in this review continued alpha-2 agonists beyond 72 hours postoperatively. Increasing the preoperative dose of clonidine will invariably increase sympatholysis and decrease heart rate and blood pressure. Unfortunately, the effects of clonidine are long-acting and not quickly reversed or stopped if severe hypotension or bradycardia develops. Indeed, several studies suggest increased need for fluid and/or vasopressor support.[9,12-14] Dexmedetomidine, which has a shorter half-life, may be advantageous in this regard. Although evidence supporting the routine use of alpha-2 agonists is not nearly as complete and accepted as that of perioperative beta-blockade, this may change after completion of future large-scale, prospective studies.

GUIDELINES

The American College of Cardiology and American Heart Association updated their practice guidelines in 2007 (with a 2009 supplemental update regarding perioperative beta-blockade) on perioperative cardiovascular evaluation for noncardiac surgery.[19] As a Class IIb recommendation, alpha-2 agonists for the perioperative control of hypertension may be considered in patients with known CAD or at least one clinical risk factor who are undergoing surgery. Perioperative beta-blockers for similar indications are Classes I, IIa, and IIb recommendations because studies of beta-blockade have shown amelioration of clinical endpoints. Similarly designed large-scale, prospective studies of alpha-2 agonists that assess outcomes, not just the surrogate marker of myocardial ischemia, are needed to help further define the role of alpha-2 agonists in the prevention of perioperative cardiac morbidity and mortality.

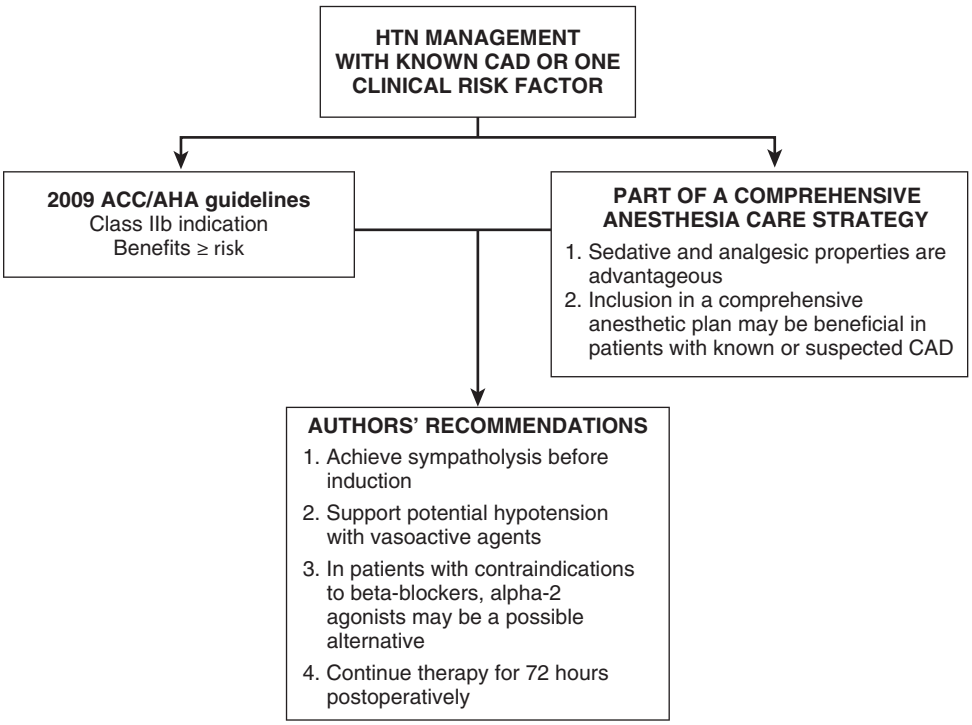

FIGURE 32-1 ■ Alpha-2 Agonist Patient Management. *ACC/AHA,* American College of Cardiology/American Heart Association; *CAD,* coronary artery disease; *HTN,* hypertension.

AUTHORS' RECOMMENDATIONS

Conservative Evidence-Based Pharmacologic Cardiac Management

- Based on the evidence of randomized controlled trials and meta-analysis studies, alpha-2 agonists may have a role as an adjunct in the prevention of perioperative cardiac morbidity and mortality in patients with known or suspected coronary artery disease, especially in patients scheduled for vascular surgical procedures (Figure 32-1).
- Achieving sympatholysis before induction appears to be optimal. This can be done by a number of means, including oral preparations 60 to 90 minutes before induction, transdermal application the night before surgery, or starting an infusion so as to reach effect before induction. However, this may or may not increase the need for vasopressor support.
- If patients have well-established contraindications to beta-blockers, alpha-2 agonists may be a possible alternative.
- Therapy should probably be continued for at least 72 hours postoperatively.

AUTHORS' OPINIONS

Comprehensive Anesthetic Care Strategy

- Alpha-2 agonists have well-established sedative and analgesic properties that have proven advantageous in various clinical scenarios.
- Despite their Class IIb classification, their inclusion in a comprehensive anesthetic plan may be beneficial for patients with cardiac risk factors requiring complex anesthetic management.

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CHAPTER 33

What Is the Role of Ketamine in Perioperative Management?

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INTRODUCTION

More than 40 years ago during the Vietnam War, ketamine, a nonbarbiturate phencyclidine derivative, was considered an ideal "battlefield anesthetic" because it does not alter hemodynamics and has sedative, hypnotic, analgesic, and amnestic properties.[1,2] Its popularity waned, however, because of an undesirable side effect profile: hallucinations, delirium, lacrimation, tachycardia, and the potential for an increase in intracranial pressure (ICP) and coronary ischemia. Recent reports suggest that with lower doses,[3-5] ketamine may not be associated with untoward effects and may reduce perioperative pain, prevent opioid-induced hyperalgesia, decrease inflammation, reduce bronchoconstriction, and improve the quality of life in a palliative care setting.[6-9]

Ketamine binds with the N-methyl-D-aspartate (NMDA) and sigma opioid receptors to produce intense analgesia and a state of "dissociated anesthesia" in which the patient appears calm, does not react to pain, and maintains airway reflexes. Ketamine also interacts with nicotinic and muscarinic acetylcholine receptors, reduces neuronal sodium permeability, and blocks L-type Ca^{2+} channels in the muscle and myocardium.[10] Ketamine possesses a chiral center and exists commonly as a mixture of S(+) and R(–) stereoisomers. S(+) ketamine has greater analgesic potency and a shorter duration of action compared with R(–) ketamine because it has a fourfold greater affinity for the NMDA receptor.[11] The liver metabolizes ketamine (via the cytochrome CYP3A4 and CYP2B6 pathways) into norketamine, a weaker active metabolite that is excreted in the urine.[12]

OPTIONS/THERAPIES

Intravenous (IV) (patient-controlled analgesia [PCA]), intramuscular, sublingual, rectal, and epidural administration of ketamine achieves effective plasma levels. Ketamine is not currently approved for intrathecal administration because of the potential neural toxicity.[13]

General Anesthesia

Ketamine crosses the blood–brain barrier rapidly and reaches maximal effect in 1 minute. A single dose of ketamine (2 mg/kg IV) lasts 10 to 15 minutes and the half-life elimination is 2.5 to 3 hours.[14] Ketamine is used in clinical anesthesia as an induction agent to preserve hemodynamic stability, as an adjunctive anesthetic to spare opioid use, and as a sole anesthetic for painful procedures such as dressing changes.

Intensive Care

Concerns about ketamine's psychotropic effects have limited its use as a sedative-analgesic in the intensive care unit (ICU). Ketamine's potential advantages include preserved heart rate and blood pressure for patients with poor cardiopulmonary reserve, antagonism of the NMDA receptor in patients experiencing short-term and repetitive pain (e.g., suctioning and turning), decreased opioid consumption, and bronchodilation for patients with status asthmaticus.[15-19]

Palliative Care

Ketamine has been used as an analgesic and as an antidepressant in the palliative care setting.[9,20] Reports of "burst doses" of ketamine to relieve symptoms have been published.[21,22] Despite ketamine's potential to relieve refractory cancer and neuropathic pain, a systematic review found insufficient evidence to evaluate ketamine's effectiveness as an adjuvant to opioid treatment in cancer pain.[23]

Organ and Physiologic Responses to Ketamine

Cardiovascular Response

Ketamine acts on the heart via sympathetic-mediated stimulation and inhibition of catecholamine uptake.[24,25] At clinical concentrations, ketamine has a positive inotropic action and induces vasoconstriction, probably by inhibiting endothelial nitric oxide production, which preserves hemodynamic stability even in septic shock.[26-28] Ketamine may act as a myocardial depressant in patients who are catecholamine depleted.[29,30] Its sympathetic activity can be attenuated by concomitant administration of benzodiazepines or alpha-2 agonists.[31] Ketamine has been proposed as an antiarrhythmic agent and an

antiinflammatory agent because it inactivates neutrophils and suppresses cytokines.[32-34]

Respiratory Response

Ketamine causes clinically significant bronchodilation. Potential mechanisms include preventing reuptake of circulating catecholamines to stimulate the beta-2-adrenergic receptor, relaxation of bronchial smooth muscle via vagolysis and reduction of calcium influx, and direct antagonism of histamine.[17,35,36] In contrast to other general anesthetics, ketamine preserves functional residual capacity, minute ventilation, and tidal volume and enhances thoracic compliance.[3-5,37-39]

Neurologic Response

Ketamine increases cerebral metabolism and blood flow in patients breathing spontaneously. In patients whose lungs are mechanically ventilated, it preserves cerebral perfusion pressure without increasing intracranial pressure.[40] Ketamine enhances cortical somatosensory evoked potentials[41] and maintains or increases bispectral index[42] values.[43-46] The potential for neuroprotection against ischemic damage with ketamine is intriguing. During neuronal injury, the NMDA receptor is activated to release Ca^{2+} and glutamate by ischemic neurons, which initiate cell necrosis and apoptosis. Blockade of NMDA receptors may be therapeutic.[40,47,48] Abolition of dysarthria and tremor in patients with Parkinson disease has been observed.[49] Animal studies suggest that ketamine may cause neuronal cell death in newborns.[50-66]

Pain Response

Ketamine decreases acute and chronic pain via the NMDA and opioid receptors. Major surgery, burns, trauma, and painful procedures in the ICU can induce prolonged noxious stimuli. Noxious stimuli cause central sensitization and lead to allodynia (a painful response to an innocuous stimulus), hyperalgesia (an exaggerated response to a painful stimulus), and eventually chronic pain syndromes. Administering short-acting opioids can result in early opioid tolerance and hyperalgesia. Ketamine antagonizes the NMDA receptor to block these responses, reducing windup pain and central hyperexcitability.[67-71] In both animal and human models, subanesthetic ketamine doses prevented these effects from alfentanil, remifentanil, and fentanyl.[6,72-75] Ketamine has the potential to decrease opioid requirements and tolerance and to prevent chronic pain.[75]

Gastrointestinal Response

Ketamine inhibits reuptake of serotonin and may activate the chemoreceptor trigger zone to cause nausea and vomiting. Prolonged infusions of opioids such as fentanyl and morphine inhibit bowel function and promote constipation or even prolonged ileus. Ketamine does not inhibit bowel mobility and may reduce the feeding complications associated with opioids.[76]

EVIDENCE

Opioid Sparing

Table 33-1 summarizes randomized controlled trials of adults receiving IV perioperative ketamine.[15,42,72,77-111] Table 33-2 summarizes meta-analyses of perioperative ketamine use.[112-117] Recent reviews suggest that ketamine spares opioid use in the perioperative period at subanesthetic doses. In a meta-analysis of studies of more than 2000 patients randomly assigned to perioperative ketamine, subanesthetic ketamine administration reduced rescue analgesic requirements, pain intensity, and 24-hour PCA morphine consumption.[113] Similar findings were reported in a review of randomized trials of ketamine in surgical patients.[112] In a meta-analysis of studies of IV ketamine, opioid-sparing effects were greater in procedures associated with high postoperative pain scores (e.g., upper abdominal, orthopedic, and thoracic surgery).[115] Ketamine's opioid-sparing effect may not be uniform because different operations produce different stimuli for sensitization.[114]

The opioid-sparing effect of ketamine may be diminished in children when added to opioid-based PCA. In contrast to studies of adult patients, a recent meta-analysis of pediatric patients suggested that systemic ketamine reduced initial pain scores in the recovery room but did not decrease postoperative opioid requirements.[116] Potential explanations for these findings include lower doses of ketamine, less painful surgeries, and lack of continuous infusions in children during the perioperative period. The addition of a single dose of ketamine during induction did not decrease postoperative morphine requirements in children.[118] A review of studies analyzing the addition of ketamine to opioid-based PCA showed no reduction in pain scores or morphine consumption.[114] Heterogeneous timing of ketamine administration and evaluation of pains scores and investigations of small patient populations limited the analysis.

Preventing Chronic Postsurgical Pain

Studies examining perioperative ketamine use after thoracotomy, hysterectomy, and mastectomy with a follow-up of patients ranging from 4 weeks to 3 months did not show a benefit.[119] In contrast, subanesthetic doses of ketamine (0.5 mg/kg followed by 0.25 mg/kg/hr) administered to patients for rectal cancer surgery decreased postsurgical pain at 2 weeks, 1 month, and 6 months postoperatively.[7] This effect was not observed at lower doses (0.25 mg/kg followed by 0.125 mg/kg/hr), which suggested a dose-dependent effect.

CONTROVERSIES

Ketamine and Premedication with Benzodiazepines

Benzodiazepines are often coadministered with ketamine to prevent emergence agitation.[120-122] A large meta-analysis and two randomized controlled trials studying

TABLE 33-1 **Randomized Controlled Trials of Perioperative Intravenous Ketamine in Adults**

Author	Procedure	Size	Design	Intervention	Outcome
Roytblat et al (1993)[77]	Abdominal	*N* = 22	RDBPCT	Preincision ketamine versus placebo	Reduction of opioid consumption and first 5-hr pain score
Stubhaug et al (1997)[72]	Abdominal	*N* = 20	RDBPCT	Preincision + intraoperative versus placebo	Increased global satisfaction; no difference in opioid consumption or pain scores except in first few postoperative hours
Mathisen et al (1999)[78]	Abdominal (laparoscopic)	*N* = 60	RDBPCT	Preincision versus postoperative versus placebo	Reduction of pain score in postoperative group only; no difference in opioid consumption
Suzuki et al (1999)[79]	Ambulatory	*N* = 140	RPCT	Intraoperative ketamine versus placebo	Reduction of opioid consumption and pain scores
Adriaenssens et al (1999)[80]	Abdominal	*N* = 30	RDBPCT	Postoperative ketamine versus placebo	Reduction of opioid consumption; no difference in pain score
Heinke and Grimm (1999)[81]	Gynecologic	*N* = 39	RPCT	Preincision + intraoperative + postoperative ketamine versus placebo	No difference in total opioid consumption or pain scores
Menigaux et al (2000)[82]	Orthopedic	*N* = 45	RDBPCT	Preincision versus postoperative ketamine versus placebo	Reduction of opioid consumption over control; no difference between preoperative or postoperative
Dahl et al (2000)[83]	Gynecologic	*N* = 89	RDBPCT	Preincision versus postincision ketamine versus placebo	Reduction of opioid consumption and pain score in postincision group only
Menigaux et al (2001)[84]	Orthopedic (laparoscopic)	*N* = 50	RDBPCT	Preincision ketamine versus placebo	Reduction of analgesic consumption and pain scores
Papaziogas et al (2001)[85]	Abdominal (laparoscopic)	*N* = 55	RDBPCT	Preincision ketamine versus placebo	Reduction of opioid consumption and pain scores
Lehmann et al (2001)[86]	Urologic (laparoscopic)	*N* = 80	RDBPCT	Preincision ketamine versus placebo	No difference in total opioid consumption or pain scores
Guignard et al (2002)[87]	Abdominal	*N* = 50	RDBPCT	Preincision + intraoperative ketamine versus placebo	Reduction of opioid consumption and pain scores
Gilabert Morell and Sanchez Perez (2002)[88]	Gynecologic	*N* = 69	RDBPCT	Preincision versus postoperative ketamine versus placebo	No difference in total opioid consumption or pain scores
Jaksch et al (2002)[89]	Orthopedic	*N* = 30	RDBPCT	Preincision + intraoperative ketamine versus placebo	No difference in total opioid consumption or pains scores
Guillou et al (2003)[15]	Abdominal	*N* = 101	RDBPCT	Preincision + intraoperative + postoperative ketamine versus placebo	Reduction of opioid consumption; no difference in pain scores
Van Elstraete et al (2004)[90]	Tonsillectomy	*N* = 40	RDBPCT	Preincision + intraoperative ketamine versus placebo	No difference in total opioid consumption or pain scores
Kwok et al (2004)[91]	Gynecologic (laparoscopic)	*N* = 135	RDBPCT	Preincision versus postoperative ketamine versus placebo	Reduction of opioid with preincision; no difference with postoperative
Lahtinen et al (2004)[92]	Cardiac	*N* = 90	RDBPCT	Preincision + intraoperative + postoperative ketamine versus placebo	Reduction of opioid consumption; no difference with pain scores
Katz et al (2004)[93]	Urologic	*N* = 143	RDBPCT	Preincision + intraoperative ketamine versus intraoperative versus placebo	No difference in total opioid consumption or pain scores
Kafali et al (2004)[94]	Abdominal	*N* = 60	RPCT	Preincision ketamine versus placebo	Reduction of opioid consumption and pain scores
Kapfer et al (2005)[95]	Abdominal	*N* = 77	RDBPCT	Postoperative ketamine versus placebo	Reduction of opioid consumption
Ganne et al (2005)[42]	ENT	*N* = 31	RDBPCT	Preincision + intraoperative ketamine versus placebo	No difference in total opioid consumption or pain scores
Karaman et al (2006)[96]	Gynecologic	*N* = 60	RPCT	Preincision ketamine versus placebo	No difference in total opioid consumption or pain scores
Pirim et al (2006)[97]	Gynecologic	*N* = 45	RPCT	Postoperative ketamine versus placebo	Reduction of opioid consumption and pain scores

TABLE 33-1 **Randomized Controlled Trials of Perioperative Intravenous Ketamine in Adults** (Continued)

Author	Procedure	Size	Design	Intervention	Outcome
Lebrun et al (2006)[98]	Oral	*N* = 84	RPCT	Preincision versus postoperative ketamine versus placebo	No difference in total opioid consumption or pain scores
Gillies et al (2007)[99]	Mixed	*N* = 41	RDBPCT	Postoperative ketamine versus opioid	No difference in total opioid consumption or pain scores
McKay and Donais (2007)[100]	Abdominal	*N* = 42	RDBPCT	Postoperative ketamine versus placebo	No difference in total opioid consumption or pain scores; more hallucinations
Yamauchi et al (2008)[101]	Spine	*N* = 202	RPCT	Preincision + intraoperative ketamine versus placebo	Reduction of opioid consumption and pain scores
Engelhardt et al (2008)[102]	Spine (pediatric)	*N* = 34	RPCT	Preincision + intraoperative ketamine versus placebo	No difference in total opioid consumption or pain scores
Aveline et al (2009)[103]	Orthopedic	*N* = 75	RDBPCT	Preincision + intraoperative + postoperative ketamine versus placebo	Reduction of opioid consumption and pain scores
Remerand et al (2009)[104]	Orthopedic	*N* = 150	RDBPCT	Preincision + intraoperative + postoperative ketamine versus placebo	Reduction of opioid consumption and pain scores
Sen et al (2009)[105]	Gynecologic	*N* = 60	RDBPCT	Preincision + intraoperative ketamine versus placebo	Reduction of opioid consumption and pain scores
Deng et al (2009)[106]	Orthopedic	*N* = 200	RDBPCT	Intraoperative + postoperative ketamine versus placebo	Reduction of opioid consumption and pain scores
Dullenkopf et al (2009)[107]	Mixed	*N* = 120	RDBPCT	Preincision ketamine versus placebo	No difference in total opioid consumption or pain scores
Reza et al (2010)[108]	Gynecologic	*N* = 60	RDBPCT	Preincision ketamine versus placebo	Reduction of opioid consumption only 0-2 hr postoperatively; no differences thereafter
Lak et al (2010)[109]	Abdominal	*N* = 50	RDBPCT	Postoperative ketamine versus placebo	Reduction of opioid consumption and pain scores
Hadi et al (2010)[110]	Spine	*N* = 30	RDBCT	Intraoperative ketamine versus standard	Reduction of opioid consumption and time to first analgesic
Loftus et al (2010)[111]	Spine	*N* = 102	RDBPCT	Preincision + intraoperative ketamine versus placebo	Reduction of opioid consumption and pain scores

ENT, ear, nose, and throat; *RDBPCT,* randomized double-blind placebo-controlled trial; *RPCT,* randomized placebo-controlled trial.

TABLE 33-2 **Meta-Analyses of Perioperative Ketamine**

Author	Subjects	Intervention	Outcome
Elia and Tramer (2005)[112]	Ketamine versus no ketamine (n = 2721) in adult and pediatric population	Perioperative ketamine (bolus/infusion/epidural/caudal/PCA) versus conventional analgesic	Reduction of total opioid consumption and decreased pain scores
Bell et al (2006)[113]	Ketamine versus placebo (n = 2240) in adult population	Intraoperative ketamine (bolus or infusion or epidural) versus placebo or conventional analgesic	Reduction of total opioid consumption and decreased pain scores
Bell et al (2006)[113]	Ketamine + opioid versus opioid only (n = 432) in adult population	Postoperative PCA with ketamine + opioid versus PCA with opioid	Reduction in opioid consumption in first 24 hr
Carstensen and Moller (2010)[114]	Ketamine + opioid versus opioid only (n = 887) in adult population	Postoperative PCA with ketamine + opioid versus PCA with opioid	No clear advantage of ketamine over opioid PCA except in thoracic surgery
Laskowski et al (2011)[115]	Ketamine versus placebo (n = 4701) in adult population	Intraoperative ketamine (bolus or infusion) versus placebo	Reduction in total opioid consumption and increased time to first opioid
Dahmani et al (2011)[116]	Ketamine versus no ketamine (n = 985) in pediatric population	Ketamine (systemic, local, and caudal) versus conventional analgesic	Decreased PACU pain scores and nonopioid analgesic, no opioid-sparing effect
Schnabel et al (2011)[117]	Ketamine + local versus local only (n = 584) in pediatric population	Intraoperative ketamine (caudal) + local versus local (caudal)	Reduction in rescue analgesic and increased time to first analgesic

PACU, postanesthesia care unit; *PCA,* patient-controlled analgesia.

children who received ketamine in the emergency department found no reduction in emergence delirium with benzodiazepine administration.[123-125] Compared with adults, children may tolerate ketamine better and have a low incidence of recovery reactions. In one small study, the addition of ketamine prevented emergence delirium in children who received sevoflurane anesthesia.[126]

Ketamine and Intracranial Pressure

Clinicians have avoided ketamine in patients at risk of elevated ICP. Some studies have shown, however, that ketamine does not increase cerebral blood flow or ICP if CO_2 levels are controlled.[127,128] In children with intracranial hypertension whose lungs are mechanically ventilated, ketamine decreased ICP and increased cerebral perfusion pressure.[129] In combination with benzodiazepines, ketamine prevented fluctuations in ICP.[40,130,131] Hemodynamic variables appear to be preserved in patients with brain or spinal cord injuries.[132] These results suggest that the adequacy of sedation is more important than the choice of sedative in the management of ICP.

Ketamine and Hemodynamic Changes

In normotensive patients, ketamine infusions do not significantly alter hemodynamic profiles.[37,132-134] Given the potential for direct negative inotropy with hemodynamic instability in a catecholamine-depleted state, avoiding ketamine as an induction agent in patients with decompensated ventricular failure or catecholamine depletion has been advised.[29,30,135] As an infusion, however, ketamine may improve hemodynamic profiles in tachycardic, hypotensive, or critically ill patients.[16,133,136,137] Although clinicians may not give ketamine to patients with coronary artery disease and hypertension, there is little evidence that increased coronary perfusion in a hyperdynamic state accompanies an increase in myocardial oxygen demand.[25,138,139]

Ketamine and Psychotropic Effects

Although ketamine use is associated with mind-altering effects such as hallucinations and delirium, psychotropic effects are unlikely with subanesthetic doses. The analgesic effects of ketamine occur at plasma concentrations lower than those associated with its psychotropic activity.[140-143] Effects are likely dose dependent and attenuated by simultaneous administration of hypnotics such as propofol or midazolam.[140,144-146] In a Cochrane database review of subanesthetic ketamine, 21 of 37 trials found no psychotropic effects.[113] In one study, neuropsychiatric effects increased in patients in whom ketamine was efficacious.[115] Another review of perioperative ketamine found 30 trials with reports of hallucinations. Almost all patients who experienced hallucinations were awake or sedated and had not been premedicated with benzodiazepines (odds ratio, 2.32; 95% confidence interval, 1.09 to 4.92).[112] Risk factors for psychotomimetic effects included male sex, old age, history of psychopathology, high ketamine dosage, and rapid IV infusion.

AREAS OF UNCERTAINTY

The lack of correlation among ketamine dosing, efficacy, and neuropsychiatric effects is problematic. The clinical advantage of the more potent S(+) isomer compared with the racemic mixture is not clear. It would be interesting to evaluate the potential dose-sparing effect of S(+) ketamine for reduction of undesirable side effects. There is a paucity of literature on the appropriate duration of postoperative ketamine for prevention of chronic postsurgical pain. Studies with long-term follow-up are necessary, especially in groups at risk of chronic postsurgical pain.

Although ketamine has been administered to humans for decades, it is not clear whether the neurotoxic effects of ketamine observed in animals are clinically relevant in humans.

GUIDELINES

After reviewing meta-analyses of randomized controlled trials, the American Society of Anesthesiologists suggests in their Practice Guidelines for Acute Pain Management in the Perioperative Setting that the combination of morphine and ketamine is equivalent to morphine alone in terms of pain or nausea scores and analgesia (level of evidence: C).

The 2010 German sedation guidelines recommend ketamine in burn patients for sparing of opioids and preventing secondary hyperalgesia, especially in children. These guidelines suggest that racemic ketamine with a gamma-aminobutyric acid receptor agonist can be used in patients with traumatic brain injury, intracranial hypertension, or both during controlled mechanical ventilation and that cerebral perfusion pressure can be maintained.[147]

AUTHORS' RECOMMENDATIONS

What is the role of ketamine in perioperative management? Based on the evidence presented, ketamine is a unique sedative analgesic that may spare opioid use and prevent postoperative pain and hyperalgesia. Ketamine may be used safely in brain-injured patients whose lungs are mechanically ventilated and who are receiving a gamma-aminobutyric acid antagonist. Although studies of ketamine for patients in the intensive care unit are sparse, subanesthetic ketamine should be considered for managing bronchoconstriction, ensuring hemodynamic stability in patients who are not catecholamine depleted, preventing hyperalgesia, and improving quality of life in a palliative care setting.

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CHAPTER 34

Should Hypothermia Be Used Routinely after Intraoperative Cardiac Arrest?

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INTRODUCTION

More than 400,000 people have cardiac arrests in the United States each year, and approximately half of these occur in the hospital.[1-3] Resuscitation attempts are unsuccessful in the majority of cardiac arrest victims, although as many as 30% to 45% of patients achieve the restoration of circulatory function (return of spontaneous circulation [ROSC]). Even among those who are successfully resuscitated, many still have a guarded prognosis secondary to neurologic injury that often results in crippling long-term disabilities for cardiac arrest survivors.[4] Neurologic outcomes from cardiac arrest have been greatly improved over the past decade by the use of therapeutic hypothermia (increasingly referred to by the more broad term *targeted temperature management* [TTM]), and protocols for this therapy have been implemented in a wide variety of hospital environments.[5] TTM after cardiac arrest involves three phases of care: induction, maintenance, and rewarming (Figure 34-1), and each phase requires commitment of time and resources as well as potential exposure to specific adverse effects. Therefore risks and benefits of TTM use have to be considered carefully in light of the published evidence.

In this chapter, we will review the therapeutic options and approach to TTM induction and maintenance, discuss the current evidence regarding the use of TTM in patients who have experienced cardiac arrests, and evaluate whether such evidence extends to the perioperative or intraoperative setting.

OPTIONS/THERAPIES

Hypothermia Induction: Pharmacology

Before TTM is induced, patients are typically sedated and paralyzed. Given that postarrest patients are typically intubated, sedation is usually already in place, but neuromuscular blockade is additionally required to prevent shivering. It is generally held that shivering can occur during TTM induction until a patient's core temperature falls below 33° C, when the brainstem shivering reflex appears to become attenuated.[6] Shivering has a number of deleterious effects, including increased metabolic rate, increased risk of rhabdomyolysis and secondary acute tubular necrosis, and heat generation, which, in turn, can slow the desired rate of therapeutic cooling.[7] A number of pharmacologic options exist for sedation and paralysis, and there are no convincing data that specific agents are preferred over others. An understanding of pharmacology during postarrest TTM is limited, but some data support that benzodiazepine metabolism may be altered with reduction of core body temperature, resulting in higher than expected drug levels in the cooled patient; this may result in more prolonged mechanical ventilation and a longer duration in the critical care environment.[8]

Hypothermia Induction: Cooling

Several cooling options exist, including intravascular and external modalities. Intravascular methods include the use of cooling catheters and the administration of chilled fluids (typically normal saline or lactated Ringer's solution). External options include the use of icepacks, cold air mattresses, and precooled or water-filled cooling pads that are applied to the skin. A combination of methods can be used; for example, chilled fluids are often used in TTM protocols as an initial "booster" to start the cooling process while either intravascular or external TTM devices are prepared and applied. Observational studies have confirmed that for the majority of postarrest patients (e.g., not including those with renal failure), the bolus administration of 1 to 2 L of chilled saline is safe and carries little risk of pulmonary edema, despite the concern for postarrest myocardial depression.[9] This is a useful approach for accelerating the cooling process because laboratory trials have shown that more rapid attainment of the goal temperature (32° C to 34° C) is associated with improved survival rates and neurologic outcomes.[10,11] However, chilled saline or ice packs alone have limited utility, except perhaps in the prehospital setting as a bridge to hospital care because temperature control during the required 12- to 24-hour maintenance is problematic.[12] Prior work has shown that overcooling and undercooling are common unless a thermostat-driven device is used to maintain 32° C to 34° C.[13] During induction and maintenance, continuous temperature measurement should be established via an esophageal, bladder, or rectal probe. Most commercially available TTM devices can receive temperature input from such

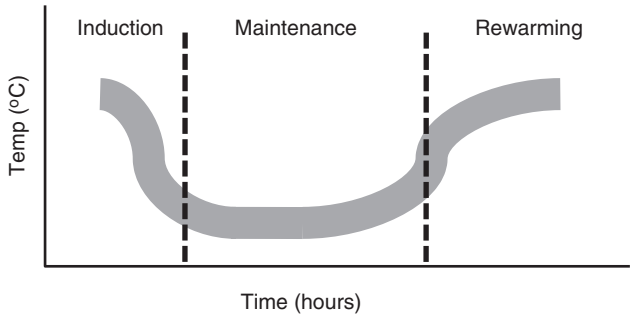

FIGURE 34-1 ■ Schematic of Postarrest Targeted Temperature Management (TTM) Treatment, Showing Temperature Curve with Three Phases of TTM Process: Induction, Maintenance and Rewarming.

TABLE 34-1 **Possible Adverse Effects during Postarrest Targeted Temperature Management Process**

Physiologic Category	Adverse Effect
Neuromuscular	Shivering Seizures
Electrolyte	Hypokalemia Hypomagnesemia
Hematologic	Coagulopathy
Cardiac	Bradycardia
Infectious	Increased pneumonia risk

This list is meant to highlight common potential findings and is not intended to include all possible adverse effects.

probes and control the rate of cooling or warming accordingly. Some evidence suggests that each of these measurement sites lags behind the core body temperature; whether this makes a practical difference during patient care has not been established and is likely to be, at most, of modest importance.[14]

Hypothermia Maintenance

Once the goal temperature is achieved, the maintenance phase of TTM begins. The landmark trials of postarrest TTM[15,16] established that hypothermia maintenance should last a minimum of 12 hours; most protocols use 24 hours of maintenance at the goal temperature, following the duration of TTM from the larger of the two randomized trials. A number of key variables require careful monitoring in the maintenance phase. During TTM maintenance, electrolytes should be checked frequently (every 4 to 6 hours) because hypomagnesemia and hypokalemia are common phenomena related to "cold diuresis." Hyperglycemia is also common. Bradycardia, often exhibited by a heart rate in the 40 to 50 beats-per-minute range, is frequent but well tolerated; specific treatments such as intravenous atropine or transcutaneous pacing are rarely required.[17] Bleeding is also a concern with hypothermia induction because a reduced core body temperature can lead to both platelet dysfunction and abnormal kinetics of the serologic clotting cascade, seen clinically as prolongation of the partial thromboplastin time (PTT). This is a key issue with respect to postoperative or intraoperative cooling and will be discussed later in this chapter. Key potential adverse effects of TTM are shown in Table 34-1.

After the goal temperature has been maintained for 12 to 24 hours, slow rewarming is initiated (0.2° C to 0.4° C per hour) until normothermia is once again attained (36.5° C to 37.5° C). This rewarming process can be accomplished with the use of the same commercial TTM devices used for cooling. After rewarming, hyperthermia (often termed *rebound pyrexia*) often occurs, and careful attention is required to treat such temperature elevations because neurologic recovery may be impaired.[18] After rewarming, paralytics and sedative medications can be weaned to assess patient responsiveness. The time during which a patient remains comatose after arrest and TTM treatment is highly variable, and the amount of time that a patient remains comatose does not necessarily correlate with the magnitude of neurologic recovery. Accordingly, the ability to accurately neuroprognosticate in this patient population remains elusive and is an area of intense research focus.[19,20]

EVIDENCE

Evidence from Randomized Trials

The modern use of TTM after cardiac arrest was established in two landmark randomized trials published in 2002. The Hypothermia after Cardiac Arrest (HACA) trial,[15] a European study coordinated in Vienna, evaluated external cooling after out-of-hospital ventricular fibrillation cardiac arrest, with randomization of patients to either a cooled group (32° C to 34° C for 24 hours) or a normothermic group, in which temperature was not actively managed. This investigation, which included more than 250 subjects, demonstrated significant survival and neurologic outcome benefits from hypothermia treatment: 59% of cooled patients were alive at 6 months compared with only 45% of patients in the normothermic group. The second crucial randomized trial, based in Melbourne, Australia, also evaluated hypothermia treatment in patients after out-of-hospital ventricular fibrillation cardiac arrest.[16] In this investigation, 49% of the patients in the cooled cohort survived to hospital discharge compared with only 26% of patients in the normothermia group.

These two randomized trials were not without key limitations. Although patients were randomly allocated in both studies, blinding was not possible, and therefore other confounders of care in the emergency department or subsequent intensive care unit stay may have theoretically affected outcomes. Another weakness ascribed to these investigations was that mild temperature elevations were common in the normothermic groups; therefore it is possible that aggressive avoidance of fever was the most important therapeutic benefit of the TTM protocols. Despite these concerns, the measured survival benefits were impressive and had a larger effect size than any other cardiac arrest treatment subjected to randomized

trials previously. For instance, no pharmacologic treatment in the Advanced Cardiovascular Life Support regimen (e.g., epinephrine, atropine, or amiodarone) has been shown to contribute to long-term survival with a magnitude comparable to that seen with hypothermia.[21]

Additional Evidence beyond Key Randomized Trials

The two landmark randomized trials in support of post-arrest hypothermia only enrolled patients who had had out-of-hospital cardiac arrest, which arguably has a number of pathophysiologic differences from in-hospital cardiac arrest (and therefore perioperative arrest). No randomized trials to date have evaluated TTM after in-hospital, intraoperative or perioperative arrest. It is also important to note that the two randomized trials only enrolled patients with initial arrest rhythms of ventricular fibrillation, one of the most common underlying rhythms of out-of-hospital cardiac arrest. Pulseless electrical activity (PEA) and/or asystole, rhythms that are more frequently seen during in-hospital cardiac arrest, have also not been the subject of TTM randomized trials. However, a number of single-center observational cohort investigations with historic control subjects have evaluated cooling after in-hospital arrest and from a variety of initial rhythms.[5] These single-center studies have generally shown a benefit to TTM, although effect sizes have varied and sample sizes are generally small. For example, Oddo and colleagues reported outcomes from a single hospital postarrest cohort and found that, among the patient subset with asystole or PEA, two of 12 patients receiving cooling had good neurologic outcomes, whereas zero of 11 patients who were not cooled had favorable outcomes.[22] A meta-analysis of such studies confirmed that TTM may be generally beneficial after cardiac arrest, regardless of initial rhythm or location of arrest, although the meta-analysis had a lower quality of data.[5] It is important to note that some investigations have provided data that conflict with this conclusion. For example, in a single-center study of 40 patients experiencing in-hospital cardiac arrest, Rittenberger and colleagues found no significant benefit from cooling patients after cardiac arrest.[23] Only one of 13 cooled patients achieved a good neurologic outcome, whereas two of 25 noncooled patients achieved good outcomes. Of note, no patients with an initial rhythm of ventricular fibrillation or ventricular tachycardia survived in either group of this study.

The rationale for applying TTM to perioperative or in-hospital arrest patients is largely based on extrapolation from the two randomized trials of cooling after out-of-hospital arrest, already described. However, there are important differences between out-of-hospital and in-hospital arrests that might make this extrapolation problematic. For example, the majority of out-of-hospital arrests have cardiac causes of arrest; that is, lethal arrhythmias occur secondary to myocardial ischemia or at the site of prior myocardial infarction. Related to this point, the most common initial arrest rhythms for these out-of-hospital events are either ventricular fibrillation or ventricular tachycardia.[2] In contrast, perioperative and in-hospital cardiac arrest has a broader set of causes, including medication reactions, fluid or electrolyte derangements, or primary respiratory failure. In these conditions, PEA is the most frequent initial arrest rhythm, and defibrillation is less commonly required. At the present time, there are no randomized trial data evaluating TTM for perioperative or in-hospital cardiac arrest or for PEA arrest in any location.

The notion that TTM can be safely used in concert with surgical interventions has largely been inferred from indirect evidence. For example, several case reports[24,25] have demonstrated successful use of TTM after postoperative arrest with good outcomes. Another case report[26] demonstrated the successful use of TTM after surgery complicated not by arrest but rather marked hypotension and cerebral ischemia, a situation frequently faced by surgeons and anesthesiologists. While not representing a perioperative arrest but rather perioperative cooling, another case report[27] described the successful use of TTM in a pregnant woman who was delivered of her infant via caesarean section with resulting good outcomes for both mother and infant.

A number of laboratory studies have used hypothermia techniques in the setting of massive pulmonary embolism and cardiopulmonary bypass[28] or traumatic exsanguination arrest with surgical repair.[29] Direct clinical evidence at the cohort level supporting TTM after perioperative arrest is, however, lacking. Case series of postoperative arrest with cooling would be a welcome addition to the growing literature on TTM. Randomized trials of perioperative arrest cooling would be difficult for a number of reasons, including the challenge of patient accrual for such an uncommon event. Illustrating this point, studies from two large tertiary care referral centers reporting on intraoperative cardiac arrests revealed a combined total of 246 events from 736,578 surgical procedures.[30,31] This equates to 3.3 arrests per 10,000 cases. Resuscitation was successful in approximately 40% of cases across both studies; thus less than two patients per 10,000 procedures would be available for postarrest care investigation. Neither of these studies examined functional or neurologic outcomes after the arrest.

Pathophysiologic Rationale for Targeted Temperature Management

After global ischemia and subsequent reperfusion, a number of pathophysiologic mechanisms become active and lead to clinical morbidity and mortality (Figure 34-2). This set of injuries is often termed *postreperfusion syndrome* or *postarrest syndrome* and has clinical features that resemble septic shock.[32] Patients often exhibit marked lowering of systemic vascular resistance, hypotension, and organ dysfunction (e.g., acute tubular necrosis, acute lung injury, and hepatic necrosis). Cerebral edema can also occur and may serve as a precursor to cerebral herniation, which serves as a common cause of postresuscitation death. A hallmark of postarrest syndrome, both in laboratory models and in the clinical environment, is the rapidity of onset, often within several hours of resuscitation.[33]

Despite its clinical characterization, the underlying mechanisms of postarrest syndrome remain to be fully

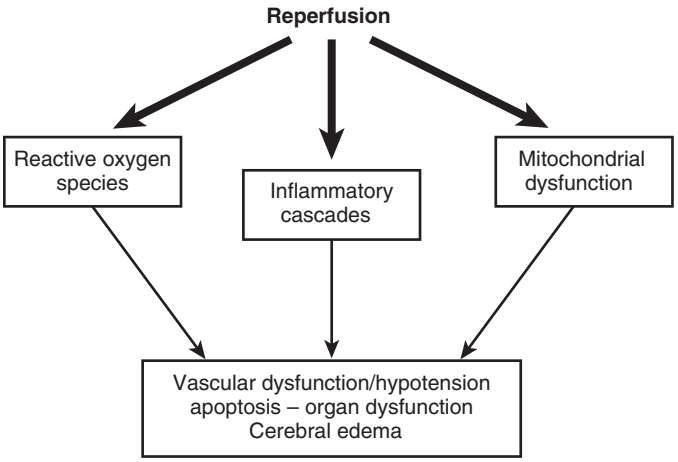

FIGURE 34-2 ■ Diagram Showing Mechanisms of Ischemia–Reperfusion Injury.

elucidated. Some investigations have found evidence of a "cytokine storm," with marked elevations of interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)-alpha.[32] It is unclear, however, whether this is a cause of injury or an epiphenomenon related to another underlying mechanism. Other laboratory work has described mitochondrial dysfunction after ischemia and reperfusion, including the release of cytochrome c and other molecular derangements.[34] Cellular studies have demonstrated apoptosis after reperfusion; oxygen toxicity has been proposed as a possible culprit.[33] Regardless of specific mechanisms, a number of laboratory investigations have shown that lowered temperature mitigates a number of these injury processes; indeed, it is likely that a number of mechanisms for hypothermic protection are active simultaneously in an overlapping fashion. For example, hypothermia has been associated with reduced inflammation and attenuated neuronal apoptosis. In addition, hypothermia has been shown to lessen the generation of oxygen free radicals, thereby minimizing oxidative injury.

It is these underlying mechanisms and the notions of ischemia–reperfusion injury that act as a key rationale for the use of TTM for patients resuscitated from arrest, regardless of the initial rhythm; that is, reperfusion injury is likely to be similar whether a patient had an arrest from ventricular fibrillation or PEA. Similarly, whether an arrest event occurs in the out-of-hospital setting or within the walls of the hospital should not affect subsequent reperfusion injury processes. Therefore it is plausible that TTM could be beneficial for any type of cardiac arrest.

CONTROVERSIES/AREAS OF UNCERTAINTY

Risk of Bleeding

It is generally held that induction of mild hypothermia may lead to coagulopathy and the risk of bleeding. Lowered temperature can induce platelet dysfunction and inhibit the serologic clotting cascade, the latter phenomenon being manifested by an increase in PTT. It is not clear how significant these effects of cooling are in actual clinical practice and whether the concern is great enough to dissuade use of TTM after surgical intervention. One retrospective registry study of 462 patients treated with postarrest hypothermia[35] revealed that 3% of the cohort experienced some degree of hemorrhage; only 1.5% required an intervention (e.g., a surgical procedure) for bleeding. Another registry study of 754 postarrest patients found a bleeding rate of 6%.[17] Given that the randomized trials of postarrest TTM found that the effect size of neurologic benefit was much larger than this magnitude of risk (e.g., a twofold survival improvement in one study), a risk of bleeding is probably tolerable. The central caveat of this conclusion, however, is that the populations under study were not surgical. Whether bleeding risk would be much higher in the postoperative patient remains to be studied.

Timing of Cooling

Another current question surrounding the use of postarrest TTM is when cooling should be initiated. The current consensus of critical care practitioners is to induce TTM as soon as possible after resuscitation because animal models suggest that the longer it takes to reach the goal temperature, the less benefit that is conferred by cooling.[10,11] As the logical extension of this notion, when cooling is begun during the intra-arrest period (during cardiopulmonary resuscitation) in laboratory experiments using whole animal models of arrest, initial survival rates are dramatically improved.[10] However, in the clinical setting, TTM has still been shown to be effective even when the initiation of therapy is delayed for up to 6 hours.[15,16] This unresolved question has great practical relevance for intraoperative arrest, as it might dictate whether patients could wait until transfer to the critical care environment before TTM initiation.

A recent Italian study[36] of 122 postarrest patients attempted to address this question. Unexpectedly, investigators found that postarrest patients who were cooled to the goal temperature within 2 hours of resuscitation exhibited a higher mortality (47%) compared with patients who had cooling initiated more than 2 hours

after the start of arrest (24%). Neurologic recovery in both cohorts was statistically indistinguishable. One possible explanation for the unexpected mortality in the early TTM group is one of retrospective bias from patient level confounding. That is, patients with increased morbidity and brain injury might cool more quickly and therefore enrich the "early cooling group" with patients who were more likely to die. This study illustrates a key challenge of studying cooling kinetics, in that two factors contribute to the cooling rate: iatrogenic factors (care processes) and patient factors (the state of neurologic injury and homeostatic dysfunction).

Cooling Methods

There are a number of methods currently available to induce TTM, and whether specific techniques and devices are preferred remains an open question. Options include intravenous delivery of chilled saline, commercial devices with external cooling wraps or pads, intravenous catheter cooling devices, or immersion ice bath equipment. Single-center studies have suggested that each of the commercial systems is able to provide adequate cooling to reach the goal temperature within 6 hours (depending on body habitus and other factors) and that each form of device may have a similar effect on patient survival. These data, however, are limited by small sample size; large device comparison trials to test clinical outcome differences have not been published at this time. As a practical matter, many practitioners administer chilled saline as an initial cooling "induction" agent while commercial cooling equipment is prepared and applied to the patient. This ensures that cooling is started promptly and can accelerate the times to the goal temperature.

GUIDELINES

In 2003 the International Liaison Committee on Resuscitation (ILCOR) formally recommended the use of therapeutic hypothermia after resuscitation from cardiac arrest.[37] After this, the American Heart Association and the European Resuscitation Council included therapeutic hypothermia in their respective guidelines for resuscitation.[7] These recommendations suggested that adult patients who had experienced out-of-hospital ventricular fibrillation cardiac arrest who were comatose after successful resuscitation should have their core body temperature lowered to 32° C to 34° C. Cooling should be started as soon as possible after the arrest and should be continued for at least 12 to 24 hours. The resuscitation guidelines also suggested that cooling could be considered for any postarrest patient unable to follow verbal commands after resuscitation, regardless of the initial rhythm (albeit with a lower class of recommendation given the paucity of direct evidence). Given the relative uncertainty of posttherapeutic hypothermia neurologic prognostication, current resuscitation guidelines recommend waiting at least 72 hours after resuscitation before making determinations regarding poor neurologic outcome and possible withdrawal of care.

AUTHORS' RECOMMENDATIONS

Patients resuscitated from cardiac arrest should be considered as candidates for postarrest targeted temperature management (TTM) so that mortality rates and neurologic injury can be reduced. Although evidence most strongly supports this approach to patients with out-of-hospital ventricular fibrillation arrest, practitioners should consider TTM for intraoperative or postoperative arrests on a case-by-case basis. Careful consideration should be given to bleeding risks inherent in a given operative procedure, and general attention should be given to electrolyte and fluid management during the postarrest TTM period of time.

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CHAPTER 35

Which Are the Best Techniques for Reducing the Incidence of Postoperative Deep Vein Thrombosis?

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INTRODUCTION

Venous thromboembolism (VTE) is a major public health issue. VTE is thus one of the main causes of mortality. It is also associated with considerable morbidity because nonfatal pulmonary embolism (PE) and deep vein thrombosis (DVT) induce short- and long-term complications.[1,2] In addition, anticoagulant treatment, although effective, may be a potential source of iatrogenic complications.

Nevertheless, the benefit–risk ratio of widespread postoperative prophylaxis is highly positive, at least in patients at moderate or high risk of DVT. Furthermore, the global VTE rate has been continuously decreasing since the early 1970s, as a result of prophylaxis, the development of day surgery, fast-track procedures and related improvements in the rehabilitation processes, and major progress in surgical and anesthetic techniques. Currently, less than 1.5% of patients undergoing major orthopedic surgery will develop a symptomatic VTE event. The PE rate is well below 0.5%, and the fatal PE rate is much lower than 0.1% in this setting.

Although the likelihood of a fatal PE episode in a patient with a hip fracture is now very low, this is not the case in other surgical settings such as thoracic or bariatric surgery. In addition, an increasing number of elderly patients with severe risk factors are undergoing major surgical procedures. Therefore many questions still need to be answered. New controversial data have recently been published on mechanical prophylaxis and are causing much debate. The new oral anticoagulants (OACs) are also an issue of interest in that their high efficacy rate may be offset by an increase in bleeding risk.

PATHOPHYSIOLOGY AND RISK

Postoperative thromboembolic risk comprises both patient-related risk and surgical risk.[2]

Patient-related risk increases linearly with age, becoming more marked after 40 years of age and even more so after 60 years.[3,4] Obesity is responsible for an increased risk of thrombosis as a result of longer immobilization and decreased fibrinolytic activity. Cancer, especially lung, pancreas, colon, or pelvic cancer, increases thromboembolic risk, although surprisingly metastases do not. Cancer-related risk is independent of age. Several other important factors increasing perioperative VTE risk have been reported (Box 35-1).[4]

The surgical risk is usually well-established and ranges from low or absent (e.g., hand surgery or osteosynthesis device removal) to high (e.g., surgery for hip fracture or pelvic surgery for cancer) (Table 35-1). However, the risk may also be uncertain in instances such as laparoscopy. Although the minimally invasive nature of laparoscopy might be thought to reduce risk,[5] other aspects—the reverse Trendelenburg position, gas insufflation (vena cava compression with impaired venous return), and a longer operative time—might increase the risk.

The overall risk, which combines patient-related risk and surgical risk, can be classified into three broad categories: low, moderate, and high; however, these categories have not been precisely quantified.[2] The level of risk should be a consideration in the choice of prophylaxis, but if three moderate risks are summed (e.g., prolonged immobilization, obesity, and age older than 60 years), the crucial question is whether the overall risk is significantly increased.

Prevention not only stops the formation of a thrombus but also controls its extension.[6] The new generation of antithrombotic agents, which interact with both free and clot-bound thrombin, should prove to be particularly useful in prevention.[7]

The bleeding risk should also be considered. The clinical development of new antithrombotic agents during the last 10 years has focused on several intrinsic and extrinsic criteria that could increase the perioperative bleeding risk in anticoagulant-treated patients. Renal insufficiency, age older than 75 years, and a low body weight (<50 kg) represent the three major bleeding risk factors that can be summarized by the use of the Cockroft-Gault formula for the calculation of creatinine clearance. A patient with a clearance less than 30 mL/min has a definite increased risk of bleeding. Other bleeding factors are shown in Box 35-2.[3]

BOX 35-1 Patient-Related Risk Factors for Thrombosis[2,9,48]

- Age older than 40 years
- Obesity (body mass index >30)
- Cancer and cancer treatment (hormones, chemotherapy, radiotherapy)

and

- History of venous thromboembolism
- Idiopathic or acquired thrombophilia
- Acute medical illness
- Active heart or respiratory failure
- Severe infection
- Estrogen-containing contraception or hormone replacement therapy
- Selective estrogen response modifiers
- Inflammatory bowel disease
- Immobilization, bed rest, limb paralysis
- Nephrotic syndrome
- Myeloproliferative syndrome
- Paroxysmal nocturnal hemoglobinuria
- Smoking
- Varicose veins
- Central venous catheter

TABLE 35-1 **Risk Categories for Venous Thromboembolism Surgery[2]**

Examples of Surgical Procedures	Risk Category
Varicose vein	Low
Minor abdominal surgery	Low
Knee arthroscopy	Low
Trauma to knee without fracture	Low
Endoscopic prostate surgery	Low
Percutaneous kidney surgery	Low
Diagnostic laparoscopy (<30 mm)	Low
Minor abdominal surgery with extensive and/or bloody dissection, very long operative time or emergency	Moderate
Fracture of lower extremity	Moderate
Laminectomy	Moderate
Vaginal hysterectomy	Moderate
Breast cancer surgery	Moderate
Major abdominal surgery (even in the absence of cancer)	High
Bariatric surgery	High
Total hip or knee replacement	High
Hip fracture	High
Open kidney surgery	High
Open prostate surgery	High
Prolapse surgery	High
Uterine and ovarian surgery for cancer	High
Lung resection by thoracotomy	High
Intracranial neurosurgery	High

OPTIONS

The first method of VTE prevention should be early mobilization and ambulation. However, this is not always possible, and other techniques are needed. Mechanical and pharmacologic prevention can be proposed either separately or concomitantly, even if chemical prophylaxis appears to be more effective than mechanical prophylaxis, which is usually the first-line approach.

BOX 35-2 Risk Factors for Bleeding

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalized ratio higher than 2)
- Lumbar puncture/epidural/spinal anesthesia expected within the next 12 hr
- Lumbar puncture/epidural/spinal anesthesia within the previous 4 hr
- Acute stroke
- Thrombocytopenia (platelets less than 75 × giga/L)
- Uncontrolled systolic hypertension (230/120 mm Hg or higher)
- Untreated inherited bleeding disorders (such as hemophilia and von Willebrand disease)

Data from Hill J, Treasure T, Group GD. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital: summary of the NICE guideline. Heart 2010;96(11):879–82.

EVIDENCE

Mechanical Prophylaxis

There are two main techniques for mechanical prophylaxis: (1) graduated elastic compression and (2) intermittent pneumatic compression of the leg or a venous foot pump.[8] Their aim is to increase venous flux and reduce stasis. Both techniques have proven efficacy, neither increases the risk of bleeding, and contraindications are few, mainly peripheral arterial occlusive disease and skin lesions. In both cases, the longer the compression is kept in place throughout a 24-hour period, the greater the efficacy.

In graduated elastic compression, the stocking exerts graded circumferential pressure on the lower limb (18 mm Hg at the ankle, 14 mm halfway up the calf, 8 mm at the knee, and, if the stocking goes to the thigh, 10 mm at the lower half of the thigh and 8 mm at the top of the thigh). Venous flux velocity is increased by 75% (Table 35-2). The 2010 guidelines published by the National Institute for Health and Clinical Excellence (NICE) recommend the systematic use of compression in all patients who have undergone surgery.[3]

In intermittent pneumatic compression, bags wrapped around the calf, thigh, or both are intermittently inflated and deflated for acceleration of venous return. The reduction in risk was found to be 56% for all thromboses and 44% for proximal thromboses.[9] However, the studies were not powerful enough to establish an effect on PE. The results for venous foot compression vary and depend on the indication. It seems to be more effective in surgery for hip replacements than for total knee prostheses but is recommended in hip replacement surgery only if

anticoagulants are contraindicated. An effect on proximal thromboses and PE has not been demonstrated.[10]

Pharmacologic Prophylaxis

Three types of anticoagulants—vitamin K antagonists, heparins (unfractionated heparin [UFH] and low-molecular-weight heparin [LMWH], and fondaparinux—and new oral antithrombotic agents (anti-IIa and anti-Xa) are currently being used or are under clinical development for VTE prophylaxis. Hirudins, danaparoid, and dextran are excluded here as they have been the subject of few studies, their efficacy is a matter of debate, and the benefit–risk ratio is lower than for the aforementioned agents.

Vitamin K Antagonists

The most frequently used vitamin K antagonist is warfarin, even though acenocoumarol and fluindione are still prescribed in Europe and Africa. Vitamin K antagonists inhibit a carboxylation step in the synthesis of factors II, VII, IX, and X by the liver and thus, by decreasing the levels of these factors, exert powerful anticoagulant activity.[11] They are still used postoperatively in North America but are gradually being replaced by injectable anticoagulants such as LMWH and fondaparinux[12]; they will probably finally disappear when the new oral antithrombotic agents become fully available in the near future.[13] In the 2007 NICE review,[9] an analysis of 11 pooled studies (1320 patients) found a reduction in risk of 51% for all thromboses, 58% for proximal thromboses, and 82% for PE as compared with no prophylaxis. The efficacy of OACs is somewhat counterbalanced by interactions with other drugs and food and by an increased risk of bleeding: OACs increased the risk of major bleeding by 58%.

Heparins: Fondaparinux

UFH is extracted from pig intestine. It is a mixture of medium-molecular-weight polysaccharides (15,000 daltons) with equivalent anti-thrombin (IIa) and anti-Xa activity. UFH interacts with antithrombin via a pentasaccharide moiety present in one third of its molecules. It is eliminated by the reticuloendothelial system. Two or three daily subcutaneous injections are usually given to prevent postoperative thromboembolic disease.[14,15]

Even though UFH has uncontested efficacy, it is being replaced by one or two daily subcutaneous injections of LMWHs. LMWHs have been marketed in Europe since 1985 and in the United States since 1993.[15] Their anti-Xa activity is two to six times higher than their antithrombin activity, and they are eliminated by the kidneys. They are more effective than UFH in terms of the overall risk of thrombosis and proximal thrombosis and better at preventing PE without increasing the risk of bleeding (Table 35-3).[9,16] In addition, the risk of heparin-induced thrombocytopenia is 5 to 10 times lower than with UFH.[17] LMWHs have become the gold standard for the prevention of perioperative VTE, and they are used as the comparator for all new anticoagulants in clinical trials of superiority or noninferiority.[18] However, because LMWHs and UFH are extracted from pig intestine (one pig for one syringe!), it is important to remember that these molecules are not synthetic and adverse events can occur. For example, an outbreak of adverse reactions associated with contaminated heparin occurred in 2008.[19] The contaminant was identified as oversulfated chondroitin sulfate, and the issue was resolved after a very impressive industrial reaction by Baxter, Pfizer, and Sanofi.

Fondaparinux, a short pentasaccharide moiety of the heparin molecule synthesized as a product of research on

TABLE 35-2 **Effect of Graduated Compression Stockings (GCS) Alone or with Additional Antithrombotic Measures (AAM) on Deep Vein Thrombosis (DVT) Prophylaxis**[8]

			Total DVTs		
Study, Year	**Number of Trials**	**Number of Subjects (Intervention/ No Intervention)**	**Intervention**	**Control**	**Odds Ratio (Confidence Interval)**
Cochrane database 2010	8 10	1279 (662/617) 1248 (621/627)	GCS alone 86 (13%) GCS + AAM 26 (4%)	Control 161 (26%) AAM 99 (16%)	0.35 (0.26-0.47) 0.25 (0.17-0.36)

TABLE 35-3 **Pooled Analysis of Randomized Controlled Trials (RCTs) of Low-Molecular-Weight Heparin versus Unfractionated Heparin**[9]

			Relative Risk			
Study, Year	**Number of RCTs**	**Number of Subjects**	**DVT**	**Proximal DVT**	**Pulmonary Embolism**	**Bleeding**
NICE, 2007	76	22,574	0.87	0.62	0.66	0.87

DVT, deep vein thrombosis.

LMWH, was put on the market at the end of 2002. It binds reversibly to antithrombin and inhibits factor Xa and the subsequent coagulation cascade.[20] Once released from antithrombin, it is recycled two or three times and becomes available for binding again. This attractive mechanism of action explains its high activity at low doses. Currently, it is the most potent injectable anti-Xa agent available. It was first tested in VTE prevention in orthopedics, then in abdominal surgery. It is effective in preventing asymptomatic DVT but has a significant tendency to increase bleeding complications and transfusion requirements.[15,18,21] Safety is of much less concern when it is administered late, that is, 6 to 8 hours (even 24 hours) after surgery. Fondaparinux does not seem to induce thrombocytopenia, unlike UFH and LMWH; however, a few case reports[22,23] have suggested a link between fondaparinux and thrombocytopenia, and confirmation is needed.

New Oral Anticoagulants

Several apparently safe, highly effective, oral drugs are in the final stages of development. They are either anti-IIa or anti-Xa agents and show no apparent superiority over each other.[24] These new drugs have long been awaited as options to the disadvantages that vitamin K antagonists and LMWHs present. Vitamin K antagonists, although oral drugs, have a delayed onset of action and a narrow therapeutic window. They also interact with many medications and are not powerful enough. LMWHs are safe and effective but injectable and nonsynthetic.

Dabigatran. Dabigatran (Pradaxa) is a direct thrombin inhibitor with the following properties: its bioavailability is 6% to 8%, peak plasma concentrations are reached within 2 hours, postoperative peak concentrations occur later and are lower, the terminal half-life is 14 to 17 hours, it is given once or twice daily, and it is excreted unchanged via the kidneys. Dabigatran was first developed for orthopedic surgery. Two large randomized double-blind studies of short- (10 to 14 days) and long-term prophylaxis (28 days) after total knee replacement (TKR) and total hip replacement (THR), respectively, found it to be noninferior to enoxaparin (40 mg once daily).[25,26] Dabigatran has been approved by the European Medicines Agency (EMA) and is now used in daily clinical practice for orthopedic patients. As compared with North American dosing of enoxaparin (30 mg twice daily) in TKR patients, dabigatran did not meet the noninferiority criteria[27]; therefore this agent is not yet registered in North America for VTE prophylaxis in orthopedic patients.

Rivaroxaban. Rivaroxaban (Xarelto) is an orally active oxazolidone derivative that acts as a potent direct anti-Xa agent. Its properties are as follows: its oral bioavailability is greater than 80%, it inhibits factor Xa with an inhibition constant (Ki) of 0.4 nM, it reaches peak concentrations after 2 to 4 hours, and its terminal half-life is close to 9 hours. Two thirds of it is cleared by the kidneys (but only half as an active form), and one third is cleared by the gut. Like other oral compounds, rivaroxaban was first developed for orthopedic surgery, where it has been found to be superior to enoxaparin (THR and TKR, the RECORD program).[28,29] For the first time in the long history of antithrombotic agents, a new compound has significantly decreased the rate of symptomatic venous thromboembolic events. However, if the surgical site is taken into account, the rate of major bleeding was increased as compared with enoxaparin.[30] Rivaroxaban has also been approved by the EMA and is currently used in Europe. No increase in the bleeding risk has been reported by the recent pharmacovigilance surveys for this potent agent.

Apixaban. Apixaban (Eliquis) is also a potent direct reversible anti-Xa inhibitor with the following properties: its oral bioavailability is 51% to 85%, it inhibits factor Xa with a Ki of 0.08 nM, and its terminal half-life is about 10 to 15 hours. Renal elimination accounts for 25%, whereas the other 75% is accounted for by hepatic metabolism and biliary and intestinal excretion. Phase 3 studies (the ADVANCE program[31,32]) are now completed in orthopedic surgery and show that oral apixaban (2.5 mg twice daily) starting 12 to 24 hours postoperatively is as safe and more effective than 40-mg once-daily subcutaneous injections of enoxaparin in TKR and THR patients with no differences in the bleeding rate. However, when compared with the North American enoxaparin dosing (30 mg twice daily) in TKR patients, apixaban (similar to dabigatran) did not meet the noninferiority criteria.[33] Apixaban has obtained European approval for VTE prophylaxis in scheduled orthopedic surgery.

In December 2010, the European Society of Anaesthesiology published new guidelines on regional anesthesia and antithrombotic agents.[34] Several recommendations have been made regarding the delay between the last dose of oral anticoagulants and the start of a neuraxial anesthesia procedure and the minimal delay before catheter removal (Table 35-4).

The new oral anticoagulant agents should be used with caution after an initial period of observation, as there are no specific antidotes.[35,36] Biologic monitoring is now available, even if the interpretation of the tests remains controversial.[37,38] Two tests are ready for use: a diluted thrombin time (Haemoclot for dabigatran) and a calibrated anti-Xa activity (for anti-Xa agents). One can only regret that these tests were not developed concomitantly with the phase 3 studies and that clinicians have had to wait for requirements to be issued from regulatory agencies in this regard. These three agents and some anti-Xa agents still under development have shown promising results as compared with warfarin for patients with atrial fibrillation[39] and for the treatment of VTE.[40]

No doubt these new agents will challenge the well-known LMWHs in the near future. New prophylactic indications will be added, and the use of these agents in one clinical setting in particular, that of the patient with a hip fracture, should be investigated. Unfortunately, given the median age (80 years), low body weight, and existence of numerous comorbidities such as impaired renal function in these patients with hip fractures, it appears that companies are hesitant and no studies have been planned. Another surgical setting of

TABLE 35-4 **Recommended Time Intervals before and after Neuraxial Puncture or Catheter Removal**[34]

	Time before Puncture/Catheter Manipulation or Removal	Time after Puncture/Catheter Manipulation or Removal	Laboratory Tests
Unfractionated heparins (for prophylaxis, ≤15,000 IU/day)	4-6 hr	1 hr	Platelets during treatment for more than 5 days
Unfractionated heparins (for treatment)	IV 4-6 hr	1 hr	aPTT, ACT, platelets
	SC 8-12 hr	1 hr	
Low-molecular-weight heparins (for prophylaxis)	12 hr	4 hr	Platelets during treatment for more than 5 days
Low-molecular-weight heparins (for treatment)	24 hr	4 hr	Platelets during treatment for more than 5 days
Fondaparinux (for prophylaxis, 2.5 mg/day)	36-42 hr	6-12 hr	anti-Xa, standardized for specific agent
Rivaroxaban (prophylaxis, 10 mg q.d.)	22-26 hr	4-6 hr	antiXa, standardized for specific agent
Apixaban (prophylaxis, 2.5 mg b.i.d)	26-30 hr	4-6 hr	antiXa, standardized for specific agent
Dabigatran (prophylaxis, 150-220 mg)	34 hr	6 hr	Diluted thrombin time
Coumarins	INR ≤ 1.4	After catheter removal	INR

ACT, activated clotting time; *aPTT,* activated partial thromboplastin time; *b.i.d.,* twice daily; *INR,* international normalized ratio; *IU,* international unit; *IV,* intravenously; *q.d.,* daily; *SC,* subcutaneously.

interest is long-term prophylaxis in patients undergoing major abdominal surgery for cancer.

INTERPRETATION OF DATA AND CONTROVERSIES

Clearly, effective prevention is available, but several points are still a matter of debate.

Mechanical prophylaxis with graduated compression stockings (GCS) is the first-line approach recommended by recent NICE guidelines,[3] but the 8th and 9th Guidelines of the American College of Chest Physicians (ACCP) are not quite as positive.[1,10] There is no proof of the efficacy of GCS on fatal or nonfatal PE. Available studies date back several years and often lack power. Most are not double-blind and are difficult to interpret because of the wide variety of compression modalities used. In 2009[41] and more recently,[42] the CLOTS studies shed a negative light on the use of GCS in the medical setting. In the first randomized controlled trial, 2518 patients who were admitted to the hospital within 1 week of an acute stroke and who were immobile were enrolled. Patients were allocated to routine care plus thigh-length GCS (n = 1256) or to routine care plus avoidance of GCS (n = 1262).[41] A technician who was unaware of treatment allocation undertook compression Doppler ultrasound of both legs at 7 to 10 days and, when practical, again at 25 to 30 days after enrollment. No difference was observed in the primary outcome (symptomatic or asymptomatic DVT in the popliteal or femoral veins) between the two groups. Skin breaks, ulcers, blisters, and skin necrosis were significantly more common in patients allocated to GCS. The second study[42] was performed in a different subset of immobile hospitalized patients with stroke, and it aimed to compare the effectiveness of thigh-length stockings with that of below-knee stockings for preventing proximal DVT. A total of 3114 immobile patients were included. The primary outcome occurred in 98 patients (6.3%) who received thigh-length stockings and in 138 (8.8%) who received below-knee stockings ($p < 0.008$), which was an odds reduction of 31% (confidence interval [CI], 9% to 47%). These results could be interesting. However, because the first study did not find any effectiveness of thigh-length stockings, this could be understood to mean that calf-length stockings have potential thrombogenicity. As stated by the authors when pooling the two studies and assuming that below-knee stockings were equivalent to no stockings, the pooled estimate of effect of thigh-length versus no stockings or ineffective below-knee stockings was 0.82 (CI, 0.68 to 0.99). In summary, the efficacy of GCS is very weak in immobile medical patients.

Should these data be extrapolated to surgical patients? This is a question best answered by large randomized studies assessing the efficacy of GCS in surgical patients.

Indeed, data are much more reassuring for pneumatic compression devices. The 9th ACCP Guidelines, especially in their nonorthopedic prophylaxis chapter,[10] are much more in favor of intermittent pneumatic compression (IPC) than the former 8th ACCP Guidelines. However, many questions are still unanswered. Are all compression devices comparable? For how long should compression be applied after surgery?

In practice, mechanical methods may be sufficient for patients at moderate risk but are insufficient for patients at high risk.

The clinical studies of pharmacologic agents (i.e., UFH, LMWH, fondaparinux, and anti-Xa and anti-IIa agents) have used asymptomatic DVTs assessed by bilateral ascending venography as a surrogate endpoint. The high rate of events observed with this method has meant

that the numbers of patients included in phase 2 and phase 3 studies have been relatively small. However, although there may be a relationship between venographic and symptomatic thrombosis, it ranges from a factor of 5 for THR to a factor of 21 for TKR.[43] In addition, the relevance of distal thromboses diagnosed by venography is debatable. The 2008 guidance from European regulators on outcomes in trials of prophylaxis for VTE therefore suggest the use of a combination of three criteria, namely, symptomatic or asymptomatic proximal DVT assessed by ultrasound (or venography), PE, and VTE-related death.[44] If these criteria are used in the development of future molecules, the results will probably better reflect the real-life situation, even if it is necessary to significantly increase the number of patients entered into trials.

The overall safety of the drugs used in prophylaxis is good, but most of the antithrombotic agents used are eliminated via the kidneys. Thus there is a genuine risk of drug accumulation and increased bleeding in patients with renal insufficiency. Furthermore, several cases of severe bleeding have been encountered. Starting the administration of drugs less than 6 hours before or after surgery to obtain better results on venographic asymptomatic distal DVTs has also led to an increase in perioperative bleeding and transfusion requirements (e.g., as found in the fondaparinux and ximelagatran studies). The ACCP guidelines do not see any benefit to the preoperative injection of LMWHs. The development of all new agents is now based on systematic administration after surgery, sometimes even on the day after surgery. Because efficacy is guaranteed (the rate of thromboembolic events is 1.5% at 3 months), the current emphasis is naturally on safety. In the ESCORTE survey[45] published in 2006 of nearly 7000 hip fractures with prolonged postoperative LMWH prophylaxis, the overall rate of thromboembolic events was 1.34% at 3 months, the rate of severe bleeding was 1.2% at 6 months, the rate of fatal bleeding and the rate of PE were both 0.2%, and the rate of fatal PE was 0.04%. Fatal bleeding was assessed at 6 months, and PE and fatal PE were assessed at 3 months.

GUIDELINES

There are many well-conducted studies and several meta-analyses on the prevention of thromboembolic disease. Several recent guidelines are available. The ACCP guidelines are updated every 4 years, and the 9th version was published in February 2012.[10,46,47] NICE published very detailed guidelines in 2010.[3]

AUTHOR'S RECOMMENDATIONS

- Overall thromboembolic risk is the result of patient-related risk and surgical risk. Surgical risk is decreasing, especially with the introduction of new procedures such as fast-track surgery.
- The value of prophylaxis has been firmly established.
- Mechanical prophylaxis is to be used as first-line treatment when there is a risk of bleeding. Combining mechanical prophylaxis with drugs increases antithrombotic efficacy. Intermittent pneumatic compression devices are more effective than graduated elastic stockings. However, the effectiveness of both these techniques on pulmonary embolism and mortality has not been demonstrated.
- Renal function needs to be evaluated when low-molecular-weight heparin, fondaparinux, dabigatran, apixaban, or rivaroxaban are prescribed. Age older than 75 years and low body weight (<50 kg) have to be taken into account.
- There is a risk of spinal or epidural hematoma in patients receiving anticoagulants. Caution should be exercised, especially when the newer agents are administered. Follow guidelines.
- Patients undergoing surgery that involves a moderate or high overall risk should receive prophylaxis until full mobilization. Patients who have undergone a total hip replacement, surgery for hip fractures, or major abdominal surgery should receive prophylaxis for approximately 5 weeks longer.[47]
- The relevance of distal vein thromboses is still being debated. Surrogate venographic endpoints should be gradually replaced by a combination of ultrasound and clinical criteria.
- The new antithrombotic agents will probably modify prevention in the years to come; however, currently, very few long-term data exist for these products, and, importantly, no antagonists are available.

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CHAPTER 36

Are There Special Techniques in Obese Patients?

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INTRODUCTION

The obesity epidemic affects a very significant proportion of the adult population in the United States and throughout developed nations.[1] The body mass index (BMI) is the most widely accepted classification used to assess weight status. The BMI is defined as the individual's weight, measured in kilograms, divided by the square of the individual's height, measured in meters. With this system, patients are considered overweight with a BMI between 25 and 29.9 kg/m^2 and obese with a BMI between 30 and 49.9 kg/m^2. Obese classification is further subdivided into Class 1 (BMI range, 30-34.9 kg/m^2), Class 2 (35-39.9 kg/m^2), and Class 3 (40-49.9 kg/m^2), based on increasing risk of developing health problems. Patients with a BMI of 50 kg/m^2 or greater are considered superobese and have an extreme risk of developing health problems.

Over 100,000,000 residents of the United States, or 65% of the country's adult population, are overweight or obese. Obesity is often accompanied by multiple comorbid states, including insulin resistance, type 2 diabetes mellitus, obstructive sleep apnea, hypoventilation, cardiovascular disease, hypertension, certain malignancies, and osteoarthritis. The clustering of a group of defined metabolic and physical abnormalities is known as the "metabolic syndrome."[2] Patients having metabolic syndrome are subject to abdominal obesity, reduced levels of high-density lipoprotein (HDL), hyperinsulinemia, glucose intolerance, hypertension, and additional characteristic features (Box 36-1).[2] Clinical criteria for diagnosing metabolic syndrome require that at least three of the five specific diagnostic criteria appearing in Table 36-1 be present. In the United States, some 50 million people have metabolic syndrome; thus its age-adjusted prevalence is nearly 24%, and more than 40% of the population is affected by the age of 60 years.[2] Patients with metabolic syndrome are at increased risk of cardiovascular disease events and are at increased risk for all-cause mortality.[2,3] Metabolic syndrome is also associated with many other health abnormalities including polycystic ovary syndrome, nonalcoholic fatty liver disease, gallstones, sleep disturbances, sexual impotence, and various cancers, giving it significant overlap with obesity for comorbid states.

Obesity is associated with early death. The rapid rate of increase in the prevalence of both morbid obesity and superobesity, taken together with the increased risk of early demise within the obese population and complicated by the presence of metabolic syndrome, has significantly increased the number of bariatric surgical procedures performed annually to enable patients to undergo weight loss. It is estimated that more than 200,000 bariatric surgeries were performed in 2010 and probable that more than 250,000 will be performed in 2014 and beyond. Care of obese patients is not limited to obesity surgery, however, because these patients are seen for all types of operations.

Obese patients present special challenges for the anesthesiologist in airway management, maintenance of lung volume, positioning, monitoring, choice of anesthetic technique and anesthetic agents, pain control, and postoperative care. The most significant and best studied of these are in the areas of endotracheal intubation after careful patient positioning and pulmonary physiology and maintenance of oxygenation and lung volume. Evidence continues to accumulate that specific interventions, techniques, and approaches used in caring for obese patients alter outcomes.

PATIENT POSITIONING AND AIRWAY MANAGEMENT

Laryngoscopy and endotracheal intubation have historically been considered more difficult to perform in obese patients than in those with a normal BMI. This is usually thought to result from the obese patient having a short and thick neck, a large tongue, and significant redundant pharyngeal soft tissue. The correlation between morbid obesity and difficulty with laryngoscopy and intubation is not, however, the universally observed clinical experience. In fact, it is also frequently reported that there is no difference between laryngoscopy and intubation in thin and obese individuals. This may be the result of simple but important differences in clinical practice. Careful attention to patient positioning before induction of general anesthesia plays an important role in providing optimal conditions for successful placement of the endotracheal tube under direct vision.

PULMONARY PHYSIOLOGY AND MAINTENANCE OF OXYGENATION AND LUNG VOLUME

Obese patients have multiple pulmonary abnormalities, including decreased vital capacity, inspiratory capacity,

BOX 36-1 Features Associated with Metabolic Syndrome

Abdominal obesity
Atherogenic dyslipidemia (↑ TGs, ↓ HDL-C, ↑ ApoB, ↑ small LDL particles)
Elevated blood pressure
Insulin resistance ± glucose intolerance
Proinflammatory state (↑ hsCRP)
Prothombotic state (↑ PAI-1, ↓ FIB)
Other (endothelial dysfunction, microalbuminuria, polycystic ovary syndrome, hypoandrogenism, nonalcoholic fatty liver disease, hyperuricemia)

ApoB, apolipoprotein-B; *FIB*, fibrinogen; *HDL-C*, high-density lipoprotein cholesterol; *hsCRP*, high-sensitivity C-reactive protein; *LDL*, low-density lipoprotein; *PAI*, plasminogen activator inhibitor; *TGs*, triglycerides.

TABLE 36-1 **Clinical Criteria for Diagnosing Metabolic Syndrome***

Criteria	Defining Value
Abdominal obesity	Waist circumference > 102 (88) cm in men (women)
Triglycerides	≥150 mg/dL
HDL cholesterol	<40 (50) mg/dL in men (women)
Blood pressure	≥130/85 mm Hg
Fasting glucose	≥110 mg/dL

HDL, high-density lipoprotein.
*Three of 5 criteria must be met.

expiratory reserve volume, and functional residual capacity. Closing capacity in obese individuals is close to, or may fall within, tidal breathing, particularly with patients in a supine or recumbent position. The obese patient therefore is likely to undergo rapid oxygen desaturation, particularly during periods of apnea such as those that occur during induction of general anesthesia. Derecruitment of gas exchange units may occur throughout the anesthetic course.[4] A variety of maneuvers have been studied as measures to preserve oxygenation and maintain lung volume, specifically in the obese population.

EVIDENCE

Many studies have been conducted to determine the incidence of difficult laryngoscopy or intubation in the obese population. Although many of these studies have demonstrated a significant increase in the incidence of difficult laryngoscopy or intubation in comparison with the general population, several studies have shown no difference whatsoever. One study attempting to associate oropharyngeal Mallampati classification along with BMI as predictors of difficult laryngoscopy found a significantly higher positive predictive value of difficult laryngoscopy using both indices (BMI and Mallampati classification).[5] During laryngoscopy, patients' heads were maintained in optimum sniffing position, regardless of BMI. In a study conducted exclusively with obese patients, BMI was not found to be associated with intubation difficulties.[6] A high Mallampati score was identified as a predictor of "potential intubation problems," but intubation by direct laryngoscopy was successful in 99 of 100 patients studied. All patients were positioned with pillows or towels under their shoulders, with the head elevated and neck extended. Another group studied both lean and obese patients and found a Mallampati score of III or IV to be the only independent risk factor for difficult intubation in the obese study group.[7] The authors determined the Mallampati score to have low specificity and positive predictive values (62% and 29%, respectively) for difficult intubation. They concluded that intubation was more difficult in the obese patients. During intubation, patients in this study were placed in a semirecumbent position (30 degrees) with the head in the sniffing position. Another group of authors used ultrasound to quantify the amount of soft tissue between the skin and the anterior aspect of the trachea at the level of vocal cords.[8] They also used classic assessment of difficult intubation including measurement of thyromental distance, mouth opening, degree of neck mobility, Mallampati score, neck circumference, and presence of sleep apnea. Only the abundance of pretracheal soft tissue measured ultrasonically and neck circumference were positive predictors of difficult intubation. Laryngoscopy was carried out with patients in the sniffing position. A meta-analysis of 35 studies, including the four studies just described, was conducted to determine the diagnostic accuracy of preinduction tests for predicting difficult intubation in patients having no airway pathology.[9] A major finding was that the incidence of difficult intubation in obese patients was three times the incidence determined in the nonobese population. This may have resulted from suboptimal patient positioning, which was not clearly described in any of the preceding studies to include ramped positioning or elevation of the upper body and head of morbidly obese patients to align the ear with the sternum horizontally, as has been shown to improve laryngoscopic views.[10] In that study of morbidly obese patients, patients were assigned to be in either sniffing position or ramped position for the laryngoscopy and intubation. The study results showed a statistically significant difference in laryngeal view, in that the ramped position provided the superior view.

Research has also been conducted to examine the rate of development of hypoxemia in patients during apnea. In one study patients received 100% oxygen by face mask for denitrogenation before induction of general anesthesia.[4] Apnea was permitted until the SpO_2 fell to 90%. Obese patients reached the endpoint in less than 3 minutes, whereas it took 6 minutes in patients having a normal BMI. Efforts to prevent atelectasis formation and desaturation during induction of general anesthesia in the obese population have included application of continuous positive airway pressure (CPAP) during preoxygenation,[11-13] along with the addition of positive end-expiratory pressure (PEEP) and mechanical ventilation by mask after induction.[13] Application of 10 cm H_2O CPAP during preoxygenation in the supine position resulted in a higher PaO_2 after intubation and decreased

the amount of atelectasis that developed.[11] The combination of CPAP during preoxygenation and PEEP/mechanical ventilation after induction significantly prolonged the nonhypoxemic apnea duration to 3 minutes from 2 minutes found in control subjects not receiving CPAP or PEEP. The use of 7.5 cm H_2O CPAP during 3 minutes of preoxygenation while supine, however, did not alter the time required for obese patients to show desaturation to an SpO_2 of 90%.[12] Preoxygenation using 25 degrees head-up (i.e., back inclined), as opposed to supine, positioning without positive airway pressure did prolong the time required for anesthetized, apneic, obese individuals to show desaturation to an SpO_2 of 92%.[14] The patients in head-up position had a significantly higher PaO_2 after preoxygenation, just before induction. The obesity-associated gas exchange defect was shown to depend on the waist-to-hip ratio, an index of the distribution of adipose tissue surrounding the thorax.[15] This study also demonstrated that morbidly obese men are more likely to have poorer pulmonary gas exchange than morbidly obese women. In another study conducted to assess effects of patient positioning on development of hypoxemia in superobese patients during apnea after anesthetic induction and intubation, patients received ventilation with 50% oxygen/50% air mixture for 5 minutes before the ventilator circuit was disconnected.[16] Apnea persisted until the SpO_2 fell to 92% before ventilation resumed. Patients in the supine position reached the endpoint in 2 minutes, whereas it took 30 seconds longer for those in a supine position with the back elevated 30 degrees, and 1 minute longer for patients in a 30-degree reverse Trendelenberg position. The use of 30-degree reverse Trendelenberg position in obese patients undergoing bariatric surgery was also shown to reduce the alveolar-to-arterial oxygen difference, as well as increase total ventilatory compliance and reduce peak and plateau airway pressures when compared with the supine position.[17] Vital capacity has also been shown to decrease to a greater extent under general anesthesia in obese patients compared with normal-weight patients.[18]

Perioperative maneuvers to maintain lung volume and oxygenation have also been studied. Increasing tidal volume incrementally from 13 to 22 mL/kg in obese patients receiving ventilation under general anesthesia did not improve the gas exchange defect but did increase airway pressures.[19] The use of 10 cm H_2O PEEP in obese patients compared with normal-weight subjects has been demonstrated to have a greater effect on improving ventilatory mechanics, increasing PaO_2, and decreasing the alveolar-to-arterial oxygen difference during general anesthesia with neuromuscular blockade.[20] It is especially important to consider obese patients undergoing laparoscopic procedures because pneumoperitoneum negatively effects pulmonary mechanics by increasing pulmonary resistance and decreasing dynamic lung compliance.[21] During pneumoperitoneum, alterations in body position, tidal volume, and respiratory rate did not alter the alveolar-to-arterial oxygen difference in obese patients.[22] During pneumoperitoneum for laparoscopic bariatric surgery, alveolar recruitment by repeated sustained lung inflation to 50 cm H_2O followed by mechanical ventilation with 12 cm H_2O PEEP was shown to increase PaO_2 intraoperatively while causing hypotension that required vasopressor use.[23] An attempt to optimize PEEP in obese patients undergoing laparoscopic gastric bypass surgery showed that a normal functional residual capacity was maintained with 15 ± 1 cm H_2O PEEP, but intravascular volume expanders had to be infused to prevent PEEP-induced hemodynamic embarrassment.[24] Regarding postextubation care, in a study of morbidly obese patients proven to have obstructive sleep apnea who underwent laparoscopic bariatric surgery, patients received either CPAP via the face mask–oxygen tank Boussignac system or supplemental oxygen by face mask immediately after extubation.[25] All patients then received CPAP by traditional noninvasive ventilation during subsequent recovery and postoperative care. Spirometric lung function was significantly better preserved 24 hours after surgery in those patients who immediately received CPAP than in those who received supplemental oxygen before CPAP was applied in the postanesthesia care unit.

AREAS OF UNCERTAINTY

There is no ideal preinduction examination or test that clearly identifies patients at risk of difficult laryngoscopy and difficult intubation. Although some evidence indicates that difficult laryngoscopy and difficult intubation are more frequently encountered in the obese population, studies conducted with obese patients positioned in the ramped state clearly indicate a superior laryngoscopic view is observed compared with that found in obese patients placed in the sniffing position. No studies have been conducted to determine the ideal position for proper alignment of the airway to optimize the likelihood of success of laryngoscopy and intubation of obese patients.

The optimal patient position and the use of PEEP during preoxygenation, induction of anesthesia, and intraoperatively have not been clearly defined in the care of the obese patient. The use of noninvasive modes of ventilation, including pressure support and bilevel pressure support delivered by mask for preoxygenation, induction, and maintenance of anesthesia to maintain oxygenation and ventilatory mechanics in obese patients, has not been explored sufficiently. Ideal patient positioning, the use of PEEP, and special modes of ventilation just before emergence and extubation for maintenance of pulmonary function and gas exchange after extubation have not been clearly identified.

GUIDELINES

There are currently no established guidelines published by national societies to address the issue of airway management in obese patients. As in any anesthetic induction, practitioners should be prepared to encounter difficulty. Therefore emergency methods of establishing and maintaining an airway should be readily available, as set forth in the American Society of Anesthesiologists algorithm for difficult airway management. Careful patient positioning in the ramped position should be accomplished before induction of general anesthesia. With regard to

maintenance of oxygenation and ventilatory mechanics in obese patients undergoing general anesthesia, no guidelines have been published by national societies to address the issues. Considering both the airway management issues already detailed and the oxygenation, lung volume, and ventilatory mechanics issues also described for obese individuals, practitioners must aim to position patients to achieve the combined goals of providing a superior laryngoscopic view for ease of endotracheal intubation while establishing optimal conditions for oxygenation and preservation of pulmonary mechanical function.

AUTHOR'S RECOMMENDATIONS

Airway Management, Oxygenation, and Intraoperative Management

- Based on the evidence from randomized controlled trials and the body of literature for airway management of obese patients, patients should be readily intubated by direct laryngoscopy if placed carefully in a ramped position.
- Obese patients should be thoroughly examined for the usual objective signs of potential difficult intubation such as small mouth opening, large protuberant teeth, limited neck mobility, and retrognathia.
- Techniques such as awake, topicalized direct laryngoscopy with modest sedation can be used to assess the laryngoscopic view and decide whether to proceed with induction of general anesthesia or awake, sedated fiberoptic intubation.
- Equipment for emergency airway management including laryngeal masks and a fiberoptic bronchoscope or video laryngoscope apparatus should be kept available.
- Put patients in the ramped position and then use the reverse Trendelenberg position, if needed, to achieve a 25- to 30-degree incline of the thorax before preoxygenation.
- Preoxygenate patients for 3 to 5 minutes with 100% oxygen using positive pressure. For a patient accustomed to continuous positive airway pressure (CPAP) for obstructive sleep apnea, use CPAP or pressure support ventilation by mask identical to the patient's home CPAP setting. Otherwise CPAP of 10 cm H_2O should be used.
- Maintain 10 to 12 cm H_2O positive end-expiratory pressure intraoperatively, but make sure to treat hypotension that may occur.
- If a patient's position changes intraoperatively, return the patient to the head-up position before emergence and extubation.
- Supplemental oxygen should be applied immediately on extubation and noninvasive ventilation established soon thereafter in patients known to have obstructive sleep apnea.

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CHAPTER 37

Is There an Ideal Approach to the Patient Susceptible to Malignant Hyperthermia?

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INTRODUCTION

Malignant hyperthermia crisis (MHC) is a potentially lethal inherited syndrome triggered by exposure to anesthetic agents. The anesthesia community is best prepared to deal with MHC and patients who have a diagnosis of malignant hyperthermia susceptibility (MHS). Most often, MH is triggered by anesthesia and stress. Identification and treatment of MHC is most common in the perioperative setting.[1] The outcome of MHC has improved, and alternative methods of identifying other family members at risk[2] have supplemented the expensive in vivo caffeine halothane contracture test (CHCT) and positive family history as a basis for establishing risk. There is an increasing population of MHS individuals who may require elective or emergent surgery. Anesthesia for MHS patients is high risk because anesthetic drugs or stress may induce an MHC with resultant death or major morbidity.

Malignant Hyperthermia Update

The incidence of unexpected MHC reported in surgical populations ranges from 1:5000 to 1:50,000 patients.[3] MHC can follow anesthetic exposure to succinylcholine and all of the potent volatile anesthetic agents. It is characterized by hypermetabolism, a mounting fever, and evolving multiple organ failure. Clinical signs of MHC are progressive and nonspecific: tachydysrhythmias, tachypnea with hypercapnia, unstable blood pressure, and fever. The setting almost always involves anesthesia exposure. Laboratory findings of progressive mixed metabolic and respiratory acidosis, hyperkalemia, and rising creatine phosphokinase levels presage arrhythmias, rhabdomyolysis, disseminated intravascular coagulation, hepatic injury, renal dysfunction, encephalopathy, and death unless recognized promptly and treated. Treatment requires withdrawal of inhalational agents, hyperventilation, treatment of acidosis and hyperkalemia, control of fever, administration of dantrolene sodium, and preventive critical care.[1,4,5] MHS is genetically determined.[6]

Before the introduction of early recognition and treatment protocols, MHC was largely fatal. After widespread educational efforts in the 1970s that highlighted early suspicion of MHC and expectant management, the fatality rate decreased to 60% to 80%. With the introduction of dantrolene sodium and increased awareness of the syndrome in the late 1970s and 1980s, mortality rates fell to very low levels[3,7,8]; however, perioperative deaths continue to be attributed to MHC.[9,10] Since the 1990s, genetics has been an important focus of MH research.[11] A number of genetic variations have been identified in patients who have exhibited MHC in response to anesthetic triggers or demonstrated a phenotypic, positive reaction to the CHCT. Most genotypes are associated with abnormalities in the skeletal muscle ryanodine receptor. Although genetic testing offered the hope for a simple means of establishing which patients have MHS, the genetic background of individuals with phenotypic MH is increasingly complex.[12-17] Indeed, genetic variability, together with the development of isolated mutations, may account for the observed variation in clinical presentations and severity of MHC.[18]

Who Is Susceptible to Malignant Hyperthermia?

MHC has been observed in very young and elderly patients of both sexes. It is common in patients who have no indication in their histories and who have uneventful anesthetic procedures.[19] In one report, only 35% to 50% of patients who had MHS developed MHC when exposed to triggering anesthetic agents.[20] Anesthetic agents that trigger MHC are widely used because they are convenient and effective. Unfortunately, there is no simple means of establishing MH risk. MHC is relatively uncommon. Consequently, clinicians must assume that all patients may have MHS. MHC and other hypermetabolic perioperative crises provide a strong rationale for monitoring all anesthesia patients for signs of unexpected hypermetabolism, rigidity, and fever.

Although MH is associated with several neuromuscular syndromes,[21-23] there are no physical findings that identify MHS patients.[24] Individuals who have had family members die in the perioperative period of MHC or who, themselves, have had MH-like events often give a suggestive history or identify a family relationship with an MHS patient. When patients report an obvious, well-documented MHC, positive genetic screening, or a strong family history of the MHC, the clinician must be alert to a heightened risk of MHC in the

perioperative period and must treat the patient as having MHS. When a patient provides a history of a suggestive perianesthetic episode without having had a CHCT, most clinicians would assume that the patient has MHS. Some recommend that any patient with an unknown neuromuscular disease be treated as having MHS because of a high correlation between CHCT MH and specific neuromuscular diseases such as central core and multimini central core disease.[25] Both retrospective and prospective data show that the outcome will be optimal for patients who are thought to have MHS if they have anesthesia that is designed to prevent triggering the MHC.

TREATMENT OPTIONS FOR PATIENTS SUSCEPTIBLE TO MALIGNANT HYPERTHERMIA

Anesthesia plans for patients with MHS should avoid known triggering agents. These include all the potent, volatile, inhalational anesthetics and the nondepolarizing muscle relaxant succinylcholine. General anesthesia with a "balanced" technique that uses nitrous oxide and intravenous (IV) agents and total intravenous anesthesia (TIVA) with or without nondepolarizing muscle relaxants is considered safe. Regional anesthesia with any technique and any local anesthetic agent is safe. Nitrous oxide analgesia, regional analgesia, and all levels of sedation with any narcotic/sedative/hypnotic combination are acceptable. Nontriggering anesthetics are less likely to evoke MHC, but close monitoring is required because the anesthetic and procedural experience may trigger MHC even when specific triggering agents are not used.

Pretreatment of patients with MHS with oral or IV dantrolene may prevent or abort the MHC but is no longer recommended.

The ideal anesthetic approach should meet the needs of the patient, surgeon, and anesthesiologist. Unusual techniques that involve rarely used drugs, skills, or equipment are ill advised. Whatever the specific anesthetic chosen, MHC treatment protocols, equipment, and drugs must be available for management of the patient who develops MHC or MH-like reactions during anesthesia and surgery. Procedural facilities or offices that provide anesthesia but do not employ known triggering agents should carefully screen individuals with MHS. Rarely, patients with MHS may develop MH when stressed, even though triggering agents are not used.[26-28] Evidence for the idea that MHC is a "stress syndrome" is tenuous, and the issue is controversial. If a patient presents with a history of unstable myopathic syndromes and has MHS, anesthesia care should not be undertaken without preparation because of phenotypic variability and an unknown risk of MH-like symptoms. If the anesthesia provider at an institution does not have access to MH support protocols, trained staff, rapidly available laboratory tests, and resuscitation equipment, the patient with MHS should be referred to another institution (Table 37-1).

TABLE 37-1 **Safe Anesthesia for the Malignant Hyperthermia Susceptible (MHS) Patient**

Safe Anesthesia for the MHS Patient	Drug Choices
Local anesthesia with or without sedation	All local anesthetics All sedative/narcotic drugs
General "balanced" anesthesia	Nitrous oxide, nondepolarizing muscle relaxants, opiates, all induction agents, sedatives, total intravenous anesthesia
Regional anesthesia and analgesia with or without sedation	All local anesthetic agents All IV/IM sedatives, opiates, hypnotic agents

EVIDENCE

Both experiential and prospective data support these approaches to the patient with MHS. Data regarding management of MHS are most often evidentiary or experiential. Important ethical questions limit prospective exposure of individuals to experimental anesthetic protocols if they are thought to be at risk of life-threatening MHC.

Experiential data demonstrate improved outcomes after MHC over the past four decades. The decrease in death and other morbidity after MHC is likely multifactorial. Improved outcomes are attributed to earlier recognition, withdrawal of triggering agents, early use of dantrolene, and supportive care designed to minimize secondary insults associated with MHC, together with attempts to identify patients with MHS for receipt of trigger-free anesthetics.[21,29] One retrospective review of outcomes from New Zealand reported no deaths associated with MHC over two decades from 1981 to 2001.[8]

In contrast with recent findings reported by Pollock and colleagues,[8] sporadic case reports, court cases, and deaths reported in the press[10] or known to volunteer physician MH Hotline Consultants (MHHLCs) in the United States (https://about.mhaus.org/index.cfm/FUSEACTION/Hotline.Home.cfm, Malignant Hyperthermia Association of the United States [MHAUS], Sherbourne, NY) and abroad,[30] confirm the impression of continued perioperative mortality from catastrophic MHC. Legal issues likely prevent or delay scientific reporting of MH deaths. Secondary complications of MHC also may be underreported as demonstrated by sporadic case publications[31] and MHHLC reports.

In the era before dantrolene, clinicians were unwilling to provide elective anesthesia for patients with MHS, judging the risk of MHC to be too great. No one would undertake a comparison of management approaches involving triggering agents in humans known to have MHS for ethical reasons. Experience with animal models of MHC showed that anesthesia performed without triggering agents was safe. A specific in vivo test for MHS that required a muscle biopsy, the CHCT, was developed. A muscle biopsy could be performed in adults with local anesthesia or nerve block. In small children in whom a muscle biopsy for CHCT is not feasible without

anesthesia, prospective controlled studies of the best elective anesthetic for the patient with MHS were undertaken as the only recourse. An experience with children in which nontriggering agents were used for CHCT muscle biopsy was reported to be safe.[32] These experiences, together with sporadic case reports of successful avoidance of MHC in patients with MHS who required urgent anesthesia, provided evidence for a cautious approach to elective surgery for the patient with MHS.[26,33,34] Consequently, anesthesia and surgical staff are more willing to undertake both emergency and elective surgery for patients with MHS.[35-38]

Additional experiential evidence includes the content of approximately 650 phone calls a year[39] made to volunteer advisory physicians serving as MHHLCs, sponsored by the MHAUS, a lay advocacy organization established in 1981. This experience is summarized and published quarterly in *The Communicator*, published by MHAUS. MHAUS also provides information on its website and produces a "case of the month" that discusses management of MHC or MH-like events. MHC and MH-like experiences collected as voluntary "Adverse Metabolic Reaction to Anesthesia" reports form the basis of a privacy-protected database, the MH Registry, established in 1987 (www.mhreg.org). These growing databases provide retrospective information but no denominator of MHC and MH-like events experienced by the general population, nor is there information establishing the frequency of MHS in the general population. Retrospective data provide invaluable insight into MHC management and MH-like episodes that take place in the anesthesia setting.[9,40,41] They have also highlighted key aspects of MHC management. For example, although the average effective dose of dantrolene is approximately 2.5 mg/kg, MH registry reports of patients requiring as much as 10 mg/kg for control of MHC and occasional case reports illustrate the value of increasing dantrolene doses beyond the typical ceiling dose of 10 mg/kg.[30] Similarly, case reports of delayed-onset MHC[42] and recurrent MHC have led to evidence-based recommendations by MHHLCs for continued therapy for the MHC and at least an hour's observation postoperatively.

Only a small number of prospective studies of management of MHS/MHC patients have been published. These, together with subsequent experience, add a higher level of evidence-based support for current management strategies. The multicenter U.S. Food and Drug Administration (FDA)-approved dantrolene trial, published in 1982,[43,44] demonstrated that dantrolene sodium was effective in treating MHC, provided it was recognized and treated before sudden death or outcome-limiting organ system injury. In fact, the FDA approved the drug for this purpose in 1979, before formal peer-reviewed publication of outcome data. Subsequent experience with dantrolene after its acceptance as a treatment for MHC[45] allowed prospective studies of patients undergoing muscle biopsies with sedation, as well as studies of "trigger-free" general and regional anesthetics, of which the majority were general anesthetics.[19,32]

This prospective evidence, together with published case reports[46,47] and accumulated reporting of encounters to the MH Registry and voluntary physician MHHLCs, has changed the anesthetic approach to patients with MHS by demonstrating that trigger-free anesthetics are safe. Not only is the frequency of MHC low when patients are given anesthetics that avoid triggering agents but also, when MHC occurs and is managed in a prepared setting, its outcome in this population is better than that after unexpected MHC in other environments.

AREAS OF UNCERTAINTY

Dantrolene Pretreatment

Initial recommendations included preoperative pretreatment with dantrolene.[26] Subsequently, clinical experience with patients with MHS,[32] side effects of dantrolene,[48] a small number of complications after oral dantrolene therapy,[49] and the ability to measure serum dantrolene levels[50] after Flewellen and colleagues[51] demonstrated that effective serum dantrolene levels can be achieved with short-term IV loading supported a rationale for eliminating routine pretreatment of patients with MHS with oral dantrolene loading before anesthesia.[52] IV dantrolene treatment was extended to children after demonstration of dantrolene pharmacokinetics in that population.[53] Also, intermittent IV dantrolene injections, maintenance IV infusions, or both for continuing MH suppression after the crisis have been based on necessity during case experience. Evolving practice has been tested by experience, although not in controlled, prospectively blinded trials. Dantrolene pretreatment is no longer recommended for patients with MHS having elective surgery with trigger-free anesthetics.

There are unusual patients whose underlying muscle disease is so symptomatic that they take oral dantrolene when stressed in daily life outside the anesthesia setting.[27,54] This, together with a pathologic similarity between MHC and heat stroke fatality, has raised the question of whether heat stroke is a variant, or more common, in MHS.[55-58] Stress-induced MHC may be associated with unknown myopathy or may occur only in a unique genetic subset of patients with MHS. Data repositories are inadequate to guide the practitioner, but it would seem prudent to give dantrolene preoperatively and for some time postoperatively to very symptomatic patients who have myopathic, MH-like symptoms with stress and exercise.

Is Masseter Muscle Rigidity a Malignant Hyperthermia Crisis until Proved Otherwise?

Masseter muscle spasm or rigidity (MMR) in response to depolarizing muscle relaxants[59] or MH triggering agents has been identified as an early clinical sign of MHC[60,61] or as a myotonic reaction[62,63] commonly followed by elevated muscle enzymes, hyperkalemia, dysrhythmias, and metabolic acidosis. The relationship between MMR and both acute myopathic response and MHC argues for a conservative approach to MMR.[64] It is recommended that triggering agents and anesthesia be discontinued after observation of MMR while possible causes for MMR

are evaluated.[65] CHCT in adults who had various myopathies subsequently demonstrated a high incidence of MH-positive and MH-equivocal contracture responses.[66] The extent to which the myopathic response to anesthetic agents resembles MHC is further confused by the fact that MH CHCT is probably less specific in these patients.[25] This supported a clinical impression that various myopathies, in addition to MH, may manifest with MMR or muscle injury after anesthetic induction with MH-triggering agents.

The recognition of sudden cardiac arrest and rhabdomyolysis after succinylcholine administration to male infants and children amplified recognition of the risk, regardless of whether the etiology was the same.[67] After administration of triggering agents, cardiac arrest and dysrhythmias that are seen during myotonic reactions are caused by acute hyperkalemia, myopathic muscle responses, or both.[68] Subsequently, case reports[69] and retrospective reviews[70,71] of MMR after succinylcholine administration in children without either severe myotonic reactions or MHC generated controversy. Is MMR observed during anesthesia in children or adults a normal variant of the succinylcholine response or is it a high-probability sign of significant muscle injury associated with potentially lethal MHC or myotonic crisis?

It has long been known that adults and children who receive succinylcholine develop creatine phosphokinase elevation and myoglobinuria.[72,73] One prospective study of 500 children[74] has shown a low incidence of MMR and, more commonly, incomplete jaw relaxation after halothane anesthesia and succinylcholine. In a prospective study of more than 5000 children[75] who had succinylcholine or a nondepolarizing relaxant after an induction and intubation technique with or without inhalational halothane, it was evident that the inhalational agent was associated with MMR. Of note, although MHC did not occur, three of 600 patients (0.5%) developed MMR after paralysis for intubation after a technique that used halothane before intubation. Two of these had MMR with highly increased CK enzyme levels after receiving halothane and thiopental with nondepolarizing relaxants. Therefore MMR is not simply a normal variant of the succinylcholine response in children and is also seen during administration of inhalational agents and nondepolarizing muscle relaxants.

The incidence of MH and sudden death after MMR is not as high as initially thought, but the implications of MMR are clear: a significant percentage of those who demonstrate MMR have rhabdomyolysis associated with an unknown myopathy that should be evaluated. Young boys with unrecognized muscular dystrophy, in particular, are at risk of hyperkalemia that could cause death or significantly complicate anesthesia and surgical care. Regardless of whether unrecognized myopathy or dystrophinopathy is the cause, MMR is often associated with significant muscle injury and the risk of secondary insults associated with rhabdomyolysis, for example, hyperkalemic dysrhythmia, myalgias, peripheral compartment syndrome and limb compromise, renal failure, and sudden death.

Although the subsequent anesthetic course may appear benign, MMR may be associated with rhabdomyolysis and the aforementioned associated insults. The incidence may vary with the population, but MMR is abnormal. MMR signals a need for careful monitoring of cardiorespiratory and metabolic parameters, urine testing for myoglobin, blood testing for electrolytes, CK measurement, and, possibly, arterial blood gas measurement. MMR associated with MHC or a severe myopathic response may require withdrawal of triggering anesthetic agents together with aggressive critical care management. It may be necessary to abort surgery. Clinical MMR should be investigated whenever it is observed.

The Pregnant Patient Susceptible to Malignant Hyperthermia

Aside from the recommendation that pregnant patients who have MHS should have a trigger-free anesthetic, whether it be regional or general, no specific data exist on the risk to the fetus. In addition, there is no evidence regarding safe maternal anesthesia when the infant in utero has MHS but the mother does not. The topic of infant exposure to maternally administered dantrolene has been raised,[76] but withholding dantrolene treatment for MHC during cesarean section or other maternal surgery has not been recommended.[77] No dantrolene side effect other than uterine atony after cesarean section has been reported.[78,79] Collected case reports and inferential reasoning provide our only source of guidance.[77,80-83] Newborn MHC has been suspected but not definitively confirmed,[84] although MH has been sporadically reported in infants from 7 days to 6 months old.[85-89]

The parturient with MHS should be given appropriate regional analgesia when needed. She should have operative procedures under trigger-free anesthetic techniques. Dantrolene prophylaxis is not indicated, but dantrolene should not be withheld in acute MHC for fear of fetal compromise or maternal complications.

AUTHOR'S RECOMMENDATIONS

- Elicit a patient history of neuromuscular disease, malignant hyperthermia susceptibility (MHS), malignant hyperthermia (MH)-like family or personal events, or hyperthermic demise associated with anesthesia.
- Assume that patients with a suggestive history have MHS.
- Inform the patient of MHS concerns.
- Plan anesthesia with nontriggering agents.
- Preoperative dantrolene prophylaxis is generally not necessary.
- Avoid unfamiliar drugs or techniques.
- Have a recommended supply of dantrolene and an MH kit available.
- Ensure that facility and clinical support is sufficient to treat malignant hyperthermia crisis (MHC).
- Monitor patients with MHS or those suspected of having MHS more closely for signs of MHC.
- Treat episodes suggestive of MHS promptly with dantrolene and supportive care.
- Assume that masseter muscle spasm or rigidity (MMR) is associated with MH, dystrophinopathy, or other causes of critical rhabdomyolysis and monitor patients who demonstrate MMR carefully.

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CHAPTER 38

What Is the Best Strategy for Prevention of Postoperative Nausea and Vomiting?

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INTRODUCTION

Postoperative nausea and vomiting (PONV) are among the most common side effects associated with anesthesia and surgery. Currently, the overall incidence of PONV for all surgeries and patient populations is estimated to be 25% to 30%.[1] Furthermore, it is estimated that approximately 0.18% of all patients may experience intractable PONV, leading to a delay in postanesthesia care unit (PACU) discharge, unanticipated hospital admission, or both, thereby increasing medical costs.[2] Symptoms of PONV are also among the most unpleasant experiences associated with surgery and one of the most common reasons for poor patient satisfaction ratings in the postoperative period.[3] In one survey, surgical patients were willing to pay up to $100 to avoid PONV.[4]

Because only 25% to 30% of the surgical patient population overall will experience PONV, not all patients will require antiemetic prophylaxis. Identification of patients at high risk for PONV is therefore important. Anesthesia-, patient-, and surgery-related risk factors have been identified (Table 38-1). Apfel et al[5] developed a simplified risk score consisting of four predictors: female gender, history of motion sickness or PONV, nonsmoking status, and the use of opioids for postoperative analgesia. If none, one, two, three, or four of these risk factors were present, the incidences of PONV were 10%, 21%, 39%, 61%, and 79%, respectively.

THERAPIES

Pharmacologic Agents

Pharmacologic agents available for the prevention of PONV can be summarized as follows:

- Conventional antiemetics
  - Dopamine (D_2) receptor antagonists: phenothiazines (e.g., promethazine, prochlorperazine), butyrophenones (e.g., droperidol, haloperidol), benzamides (e.g., metoclopramide)
  - Antihistamines (e.g., dimenhydrinate, cyclizine)
  - Anticholinergics (e.g., scopolamine)
  - Serotonin receptor antagonists (e.g., ondansetron, dolasetron, granisetron)
  - Neurokinin-1 receptor antagonists (e.g., aprepitant)
- Nonconventional antiemetics
  - Steroids, propofol
- Other therapies shown to be of benefit
  - Benzodiazepines,[6] ephedrine,[7] aggressive intravenous hydration[8]

Nonpharmacologic Techniques

Nonpharmacologic techniques include P6 stimulation[9] with the use of acupuncture, acupressure, electroacupuncture, transcutaneous acupoint electrical stimulation, or laser, as well as hypnosis.[10]

EVIDENCE

There are hundreds of published randomized controlled trials (RCTs) investigating the efficacy of different antiemetic interventions. This plethora of data has resulted in a number of systematic reviews being published in this area. Although systematic reviews are a powerful tool to further our understanding of the efficacy of interventions and likelihood of harm when there are data from many small trials, they are not a substitute for a well-conducted large prospective RCT. In this chapter, the evidence reported is based on the results of RCTs and systematic reviews. Four issues will be addressed in providing evidence for the best strategy for prevention of PONV:

1. Evidence for selecting a single antiemetic.
2. Is combination antiemetic therapy better than monotherapy?
3. What is the best available combination of antiemetics?
4. Evidence for the use of a multimodal approach to prevent PONV.

Evidence for Selecting a Single Antiemetic

There are at least five major receptor systems involved in the etiology of PONV: dopaminergic (D_2), cholinergic (muscarinic), histaminergic (H_1), serotonergic (5-HT_3), and the neurokinin-1 (NK-1) receptors. Traditionally,

TABLE 38-1 **Risk Factors for Postoperative Nausea and Vomiting (PONV)**

Anesthetic Factors	Patient Factors	Surgical Factors
1. Volatile agents 2. Nitrous oxide 3. Opioids 4. High doses of neostigmine	1. Female gender 2. History of PONV or motion sickness 3. Pain 4. High levels of anxiety	1. Long surgical procedures 2. Certain types of surgery: intra-abdominal; major gynecologic; laparoscopic; breast; ear, nose, and throat; strabismus; intracranial

antagonists at these receptors have been the mainstay of PONV management. Metoclopramide and droperidol are the most commonly studied dopamine receptor antagonists. Although metoclopramide has prokinetic effects, its antiemetic efficacy when used in a dose of 10 mg is uncertain.[11] Two studies, however, suggested that higher doses of metoclopramide (20 to 50 mg) might be efficacious.[12,13] Droperidol, on the other hand, has been shown to be an effective antiemetic and has been widely used. In a meta-analysis of RCTs involving droperidol, the number needed to treat (NNT) was found to be five to seven.[14] However, after the U.S. Food and Drug Administration (FDA) black box warning on droperidol, a significant decline has been seen in the use of this cost-effective agent.[15] Some studies suggested that 1 to 2 mg intravenous (IV) haloperidol might be a suitable alternative,[16] but large well-conducted studies investigating its use for this purpose are lacking.

The 5-HT_3 receptor antagonists are highly specific and selective for nausea and vomiting. Their antivomiting efficacy is better than their antinausea efficacy.[17] Members of this group exert their effects by binding to the 5-HT_3 receptor in the chemoreceptor trigger zone and vagal afferents in the gastrointestinal tract. Their favorable side effect profile and, in particular, the lack of sedation make them particularly popular and suitable for ambulatory surgery. Currently available first-generation 5-HT_3 receptor antagonists include ondansetron, granisetron, and dolasetron. There is no evidence that the efficacy or side effect profiles of the various 5-HT_3 receptor antagonists differ when appropriate doses are used for the management of PONV. Therefore acquisition cost is the main factor that differentiates the 5-HT_3 compounds from one another.[11] It is of note that ondansetron, the most commonly studied agent in this group, has become generic. The NNT for the prevention of PONV with ondansetron is five to six.[17] Palonosetron is a more recent 5-HT_3 receptor antagonist. It has a unique pharmacokinetic profile with a duration of action of up to 72 hours. In two placebo-controlled multicenter studies, a dose of 0.075 mg IV reduced the incidence of nausea and vomiting for up to 3 days after surgery.[18,19] Two recent studies suggested that palonosetron might be more effective than 8 mg ondansetron and 3 mg granisetron for PONV prophylaxis.[20,21] Ramosetron is another recent 5-HT_3 receptor antagonist, available mainly in Japan and Korea, with a more potent and longer antagonistic effect at the 5-HT_3 receptor compared with the first-generation members of this group. Some studies have suggested that 0.3 mg IV ramosetron might provide better antiemetic prophylaxis compared with ondansetron.[22]

Dexamethasone has also proved to be an effective antiemetic. In a meta-analysis of 17 studies (1946 patients),[23] dexamethasone was reported to be especially effective against late PONV. When 8 or 10 mg IV was used in adults or 1 to 1.5 mg/kg IV was used in children, the NNT to prevent early and late vomiting compared with placebo was 7.1 and 3.8, respectively. In adults, the NNT to prevent late nausea was 4.3. There were no reports of dexamethasone-related side effects when it was used in a single dose for PONV prophylaxis. However, more recent studies have suggested that antiemetic doses can cause elevations in blood sugar levels, particularly in obese and diabetic patients.[24-26] Smaller doses (4 mg) of dexamethasone also proved to be effective for PONV prophylaxis.[27]

In a large multicenter study involving patients having at least a 40 % risk of PONV, 4 mg ondansetron, 1.25 mg droperidol, and 4 mg dexamethasone were reported to produce a similar reduction in the incidence of PONV of approximately 26%.[27] Any of these antiemetics could therefore be recommended for use as a first-line agent.

Scopolamine (hyoscine) is an anticholinergic agent with antiemetic properties. A 1.5-mg transdermal patch can be applied for up to 72 hours. Its efficacy is similar to that of 4 mg ondansetron and 1.25 mg droperidol.[28] A recent systematic review confirmed the efficacy of transdermal scopolamine for the prophylaxis of PONV for 24 hours after surgery, regardless of whether it was applied the night before or on the morning of surgery. The incidence of anticholinergic adverse events (e.g., dry mouth, sedation, and urinary retention) was no different from placebo. However, the incidence of visual disturbances was significantly higher with scopolamine at 24 to 48 hours postoperatively compared with placebo (relative risk, 3.35; 95% confidence interval, 1.78 to 6.32).[29]

The antihistamines include the ethanolamines (i.e., dimenhydrinate and diphenhydramine) and the piperazines (i.e., cyclizine, hydroxyzine, and meclizine). Their major disadvantages are sedation, dry mouth, blurred vision, urinary retention, and delayed recovery room discharge.[30] Promethazine is an effective antiemetic with a long duration of action. In a dose of 12.5 to 25 mg given toward the end of surgery, it has been shown to be effective for PONV management.[31] Its use, however, is limited by sedation and prolonged recovery from anesthesia. One study did not show increased awakening time or duration of PACU stay when compared with ondansetron and placebo in patients undergoing middle ear surgery.[31] The use of low-dose promethazine (6.25 mg) was shown to be as effective as higher doses and might be associated with less sedation.[32,33] Another antihistamine, dimenhydrinate, appears also to be effective for PONV prophylaxis.[34]

The NK-1 receptor antagonists belong to a new class of antiemetics that may act on the final common pathway to the emetic center. This group of compounds has a long half-life, is not associated with sedation, and appears to be particularly effective against vomiting. In females undergoing abdominal surgery, the incidence of no

vomiting (0 to 24 hours) was significantly higher with 40 mg aprepitant (84% to 90%) and 125 mg aprepitant (86% to 95%) versus ondansetron (71% to 74%) ($p < 0.001$ for both comparisons). Both aprepitant doses also had higher incidences of no vomiting over 0 to 48 hours ($p < 0.001$).[35,36] The 40 mg dose of aprepitant was approved for the prophylaxis of PONV. Similar results were also reported in patients undergoing craniotomy when the antiemetics were used in combination with dexamethasone.[37] More recently rolapitant, another NK-1 antagonist with a very long half-life of up to 180 hours, was effective for PONV prophylaxis compared with placebo and at doses of 70 and 200 mg was associated with a higher incidence of no vomiting compared with ondansetron at 72 and 120 hours postoperatively.[38]

Total intravenous anesthesia (TIVA) with the use of propofol has also been shown to reduce the incidence of PONV and to be as efficacious as 4 mg ondansetron in reducing postoperative nausea.[39] The protective effect of propofol against PONV was not evident when it was used as an induction agent only.[40] A dose-response relationship of propofol for improvement of nausea has also been established.[41]

A recent meta-analysis[9] concluded that P6 stimulation with 10 different acupuncture modalities reduced nausea, vomiting, and the need for rescue antiemetics compared with sham stimulation. The efficacy of P6 stimulation was similar to that of prophylactic antiemetics, such as ondansetron, droperidol, metoclopramide, cyclizine, and prochlorperazine. In subgroup analysis, there was no difference in effectiveness in adults compared with children or invasive versus noninvasive modalities for P6 stimulation.

Some studies suggested that this modality was particularly effective for prophylaxis against nausea.[42] The benefits and side effects of the main classes of agents used for the prophylaxis of PONV are summarized in Table 38-2.

Is Combination Antiemetic Therapy Better Than Monotherapy?

Because PONV is multifactorial and a number of receptors are involved in the pathogenesis of PONV, interest in using a combination of antiemetics targeting different receptors in the emetic pathway has been growing. The combinations of one of the 5-HT_3 receptor antagonists with droperidol, dexamethasone, or metoclopramide were the most commonly studied. With the exception of combinations involving metoclopramide, the majority of these studies have reported improved antiemetic prophylaxis with combination therapy compared with monotherapy.[43] Meta-analyses and a large multicenter study involving more than 5000 patients confirmed the superiority of combination antiemetic prophylaxis compared with monotherapy.[23,27,44] The combination of

TABLE 38-2 **Benefits and Side Effects of the Main Classes of Agents Used for Postoperative Nausea and Vomiting (PONV) Prophylaxis**

Class of Antiemetics	Benefits	Side Effects
Dopamine receptor antagonists:		
Phenothiazines (e.g., promethazine, prochlorperazine)	Long duration of action	Sedation, extrapyramidal side effects, hypotension, restlessness, anticholinergic syndrome
Butyrophenones (e.g., droperidol, haloperidol)	Improved prophylaxis against nausea	Sedation with high doses, hypotension, extrapyramidal side effects, neuroleptic malignant syndrome, droperidol has an FDA black box warning regarding prolongation of QTc, although the risk is considered minimal with antiemetic doses
Benzamides (e.g., metoclopramide)	Have prokinetic effects	Sedation, restlessness, extrapyramidal side effects
Anticholinergics (e.g., scopolamine)	Effective against motion sickness Transdermal preparation with a long duration of action available	Sedation, blurred vision, dry mouth, restlessness, central cholinergic syndrome
Antihistamines (e.g., dimenhydrinate, cyclizine)	Effective against motion sickness Effective for PONV after middle ear surgery	Sedation, dry mouth, restlessness
5-HT_3 receptor antagonists (e.g., ondansetron, dolasetron, granisetron)	Specific for PONV Do not have sedative side effects	Headache, constipation, elevated liver enzymes
NK-1 receptor antagonists (e.g. aprepitant)	Long duration of action Improved efficacy against vomiting Do not have sedative side effects	Headache, constipation
Corticosteroids (e.g., dexamethasone)	Do not have sedative side effects Long duration of action	Few data available regarding side effects after single dose for PONV prophylaxis; may cause hyperglycemia in diabetic and obese patients
Acupuncture (P6 stimulation)	Improved efficacy against nausea	None reported when used for PONV prophylaxis

5-HT_3, 5-hydroxytryptamine 3; *FDA,* U.S. Food and Drug Administration; *NK-1,* neurokinin-1.

casopitant, an NK1 receptor antagonist, with ondansetron and that of scopolamine with ondansetron were also more effective than ondansetron alone, and no increase in side effects was seen.[45,46] Because the efficacy of antiemetics depends on the patients' underlying baseline risk, patients with moderate to high risk for PONV derive the most benefit from receiving a combination of antiemetics.[27]

What Is the Best Available Antiemetic Combination?

Data directly comparing the efficacy of different antiemetic combinations are sparse. A meta-analysis suggested that there was no difference in antiemetic efficacy or side effect profiles between the combination of the 5-HT_3 receptor antagonists with droperidol and the combination of the 5-HT_3 receptor antagonists with dexamethasone.[44] These findings were subsequently confirmed in a large multicenter study that reported no differences in antiemetic efficacy between the combination of ondansetron with droperidol, ondansetron with dexamethasone, and droperidol with dexamethasone.[27]

Evidence for Using a Multimodal Approach to Prevent Postoperative Nausea and Vomiting

Because the etiology of PONV is multifactorial, a multimodal approach may be the best strategy for successfully reducing its incidence, particularly in high-risk patients. Scuderi and colleagues[47] investigated a multimodal approach to the management of PONV in female patients undergoing outpatient laparoscopy. Their multimodal algorithm consisted of TIVA with propofol and remifentanil, no nitrous oxide, no neuromuscular blockade, aggressive IV hydration, triple prophylactic antiemetics (1 mg ondansetron, 0.625 mg droperidol, and 10 mg dexamethasone), and 30 mg ketorolac. Control groups included standard balanced outpatient anesthetic with inhaled agents with or without 4 mg ondansetron prophylaxis. Multimodal management resulted in a 98% complete response rate (no vomiting and no antiemetic rescue) in the PACU. No patient in the multimodal group vomited before discharge compared with 7% of patients in the ondansetron group ($p = 0.07$) and 22% of patients in the placebo group ($p = 0.0003$).

Habib and colleagues[48] also found that a triple antiemetic combination with ondansetron and droperidol in the presence of propofol-maintained anesthesia was associated with a lower incidence of PONV and greater patient satisfaction compared with a similar antiemetic combination with an isoflurane-based anesthetic.

In a large prospective study, Apfel and colleagues[27] evaluated three antiemetic interventions (4 mg ondansetron, 1.25 mg droperidol, and 4 mg dexamethasone) and three anesthetic interventions (TIVA with propofol, omitting nitrous oxide, and substituting remifentanil for fentanyl) for the prophylaxis of PONV. The authors employed a multifactorial design allowing them to evaluate the effectiveness of each of the interventions plus all possible combinations of two or three interventions. The resulting data suggest that antiemetics with different mechanisms of action have additive rather than synergistic effects on the incidence of PONV. Each antiemetic reduced the risk of PONV by about 26%. Using TIVA with propofol rather than a volatile-based anesthetic reduced the risk of PONV by about 19%, whereas avoiding nitrous oxide reduced the risk by about 12%. Substituting remifentanil for fentanyl was of no benefit. When combinations of interventions were used, the benefit of each subsequent intervention was always less than that of the first intervention. The authors also reported that the efficacy of the interventions depends on the patient's baseline risk; the greatest absolute risk reduction from the antiemetic interventions was achieved in patients with a high risk of PONV.

AREAS OF UNCERTAINTY

Droperidol has been used for the management of PONV for more than 30 years with an acceptable side effect profile. In December 2001, the FDA issued a new "black box" warning on droperidol, noting that its use had been associated with QTc segment prolongation, torsades de pointes, or both and, in some cases, had resulted in fatal cardiac arrhythmias. Although the package insert of droperidol included a warning about cases of sudden death at high doses (greater than 25 mg) in patients at risk of cardiac arrhythmias, the FDA noted there had been cases of serious cardiac arrhythmias and death when droperidol was given at or below the currently labeled dose range and cautioned that droperidol should only be used when other "first line" drugs failed. The FDA also recommended that *all* surgical patients should undergo a 12-lead electrocardiogram (ECG) before administration of droperidol so that the presence of a prolonged QTc interval could be determined and that ECG monitoring should be continued for 3 hours after administration of droperidol.[49] A review of the cases on which the FDA based its warning revealed 10 cases in which 1.25 mg droperidol or less was used. It was difficult to draw any definitive evidence of a cause–effect relationship because of the presence of several confounding factors.[15] Experts in the field, as well as practicing anesthesiologists, believe that this warning is not justified.[50] Studies have shown that QT prolongation with droperidol is not different than that caused by ondansetron.[51] Interestingly, the FDA has recently issued a warning concerning ongoing safety review and labeling changes for ondansetron, for similar reasons related to QT prolongation. Dolasetron has also recently been withdrawn from the market because of continued concerns about its QT prolongation effect.

No serious side effects related to the use of a single dose of dexamethasone for PONV prophylaxis have been reported. There are, however, some potential concerns.

Avascular necrosis (AVN) of the femoral head is a recognized complication of glucocorticoid therapy.[52] Case reports[53,54] have been published in which AVN developed after relatively brief courses (7 days) of orally administered steroids. AVN has also been described when dexamethasone was used for antiemetic prophylaxis in

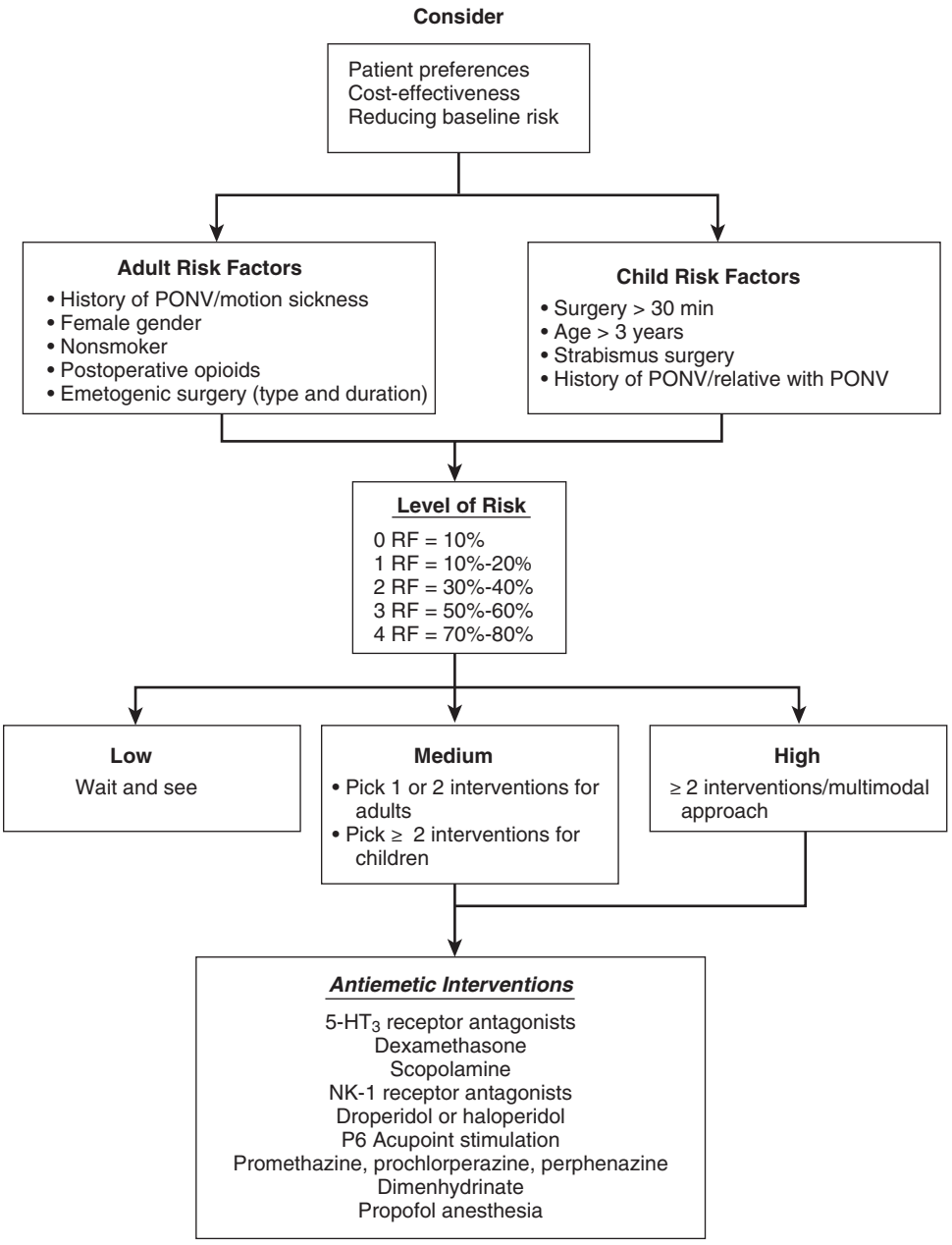

FIGURE 38–1 ■ Risk Factors *(RF)* for Postoperative Nausea and Vomiting *(PONV)* and Guidelines for Prophylactic Antiemetic Therapy. *5-HT$_3$,* 5-hydroxytryptamine 3; *NK-1,* neurokinin-1.

chemotherapy.[55] It is not known whether a single dose of dexamethasone given for PONV prophylaxis might lead to AVN in a high-risk patient. Other potential side effects of steroids such as immunosuppression and dysfunction of the hypothalamic–pituitary–adrenal axis were not tested or reported when steroids were used for PONV management. The impact of dexamethasone administration on wound healing and infections remains unclear. Although one retrospective study[56] suggested an increased infection rate, others[57,58] did not confirm this finding.

GUIDELINES

The Society for Ambulatory Anesthesia (SAMBA) has published consensus guidelines for the management of PONV.[11] Those guidelines can be summarized as follows (Figure 38-1):

BOX 38-1 Recommended Strategies for Reducing the Baseline Risk of Postoperative Nausea and Vomiting

Consider regional anesthesia
Avoid emetogenic stimuli
- Etomidate
- Nitrous oxide/inhalational agents
- Opioids (optimal analgesia should, however, be achieved by incorporating local anesthetics, nonsteroidal antiinflammatory drugs, and opioids, as required)

Consider the following:
- Total intravenous anesthesia with propofol
- Adequate hydration
- Effective analgesia
- Anxiolytics (e.g., benzodiazepines)

1. Evaluate the patient's risk factors for PONV (see Table 38-1).
2. Take steps to reduce the baseline risk (Box 38-1).
3. Use PONV prophylaxis with one or two interventions in adults at moderate risk of PONV.
4. Use combination therapy or a multimodal approach in adult patients at high risk of PONV.
5. Use PONV prophylaxis in children at higher risk of PONV. Combination therapy is more effective than monotherapy.

AUTHORS' RECOMMENDATIONS

A risk-adapted strategy for the management of postoperative nausea and vomiting (PONV) should be adopted as outlined in the Society for Ambulatory Anesthesia guidelines. Because the etiology of PONV is multifactorial and there is evidence that combination antiemetic therapy appears to be more effective than single agents, a multimodal approach for the management of PONV should be adopted in patients at high risk of PONV, including the use of a combination of antiemetic interventions coupled with strategies to reduce the baseline risk of PONV (see Figure 38-1).

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CHAPTER 39

How Should Beta-Blockers Be Used Perioperatively?

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INTRODUCTION

Perioperative beta-blockade (PBB) has been advocated for the reduction of cardiac risk for noncardiac surgery. The initial interest was based on nearly 50 years of research in the cardiology literature documenting the cardioprotective effects of beta-blockers.[1]

The primary role for beta-blockers in the perioperative setting is for the prevention of major adverse cardiac events (MACE). These adverse cardiac events account for up to 40% of all perioperative mortality.[2] Additionally, perioperative myocardial infarction (PMI) has been associated with a significant increased risk of nonfatal myocardial infarction (MI), as well as cardiovascular death for up to 6 months after surgery.[3]

To understand the role of PBBs in preventing MACE, it is important to understand the etiology of PMI. PMI is often preceded by prolonged tachycardia with ST depression–type ischemia and generally develops into non–Q-wave infarction with the resting electrocardiogram subsequently returning to baseline.[4] Thus PMI has traditionally been ascribed mostly to prolonged stress-induced ischemia in the setting of fixed coronary stenosis; only a small percentage has related to acute plaque rupture.[5-7] Given these assumptions, the natural role of beta-blockers in preventing PMI has been seen as improving myocardial oxygen balance by slowing the heart rate, reducing contractility, and improving diastolic coronary filling, thereby decreasing myocardial oxygen consumption.

Simply improving the balance of oxygen supply and demand is not the only benefit to PBBs, as the attenuation of perioperative hemodynamic stress can help prevent rupture or fissuring on the intimal surface of a vulnerable plaque.[8] There are several other pathologic effects of perioperative stress and inflammation that PBBs cannot readily modify. The perioperative milieu can promote thrombosis by increasing platelet activity and decreasing fibrinolysis, as well as cause endothelial coronary vasoconstriction and further plaque destabilization.[9] This more complex nature of PMI provides a rationale for why perioperative ischemia does not consistently lead to PMI[10] and why beta-blockers may not affect the incidence of PMI or perioperative mortality in some patients, despite reduction of perioperative ischemia.[11]

OPTIONS

Beta-adrenergic receptor antagonists have been the best studied medical therapy during the perioperative period. Beta-blockers can be both short- and long-acting (12- or 24-hour dosage scheduling), can be nonselective or $beta_1$ selective, and can be administered intravenously or orally. The potency of the agents varies greatly, and some demonstrate weak stimulatory properties.

There are several paradigms with respect to modes of delivery of these agents perioperatively. Patients may be taking beta-blockers on a long-term basis. Alternatively, beta-blocker therapy could be initiated several days to weeks before surgery with titration of effect, administered the day of surgery, or begun intraoperatively.

EVIDENCE

Early Studies

The first randomized trial of perioperative beta-blockers came from the Multicenter Study of Perioperative Ischemia (McSPI) study group.[12] The study consisted of 200 Veterans Affairs patients with or at risk of coronary artery disease (CAD) undergoing noncardiac surgery. (Table 39-1) Patients were randomly assigned to receive either placebo or atenolol (50 or 100 mg) 30 minutes before surgery and continued for 7 days. A 50% reduction in postoperative ischemia (from 34% to 17% in days 0 to 2, $p = 0.008$) based on Holter monitoring was detected.[11] Although beta-blockers did not affect perioperative MACE, during follow-up, the incidence of postoperative cardiac events and overall mortality were both shown to be significantly lower in the atenolol group at 6 months (0% versus 8%; $p < 0.001$) and remained significant throughout the 2-year study period (10% versus 21%; $p = 0.019$).

There were several important limitations to this trial. Patients were not excluded if they were already taking a beta-blocker; thus some patients randomly assigned into the placebo arm could have had effects from abrupt cessation of therapy. Beta-blocker withdrawal can lead to increases in heart rate and myocardial oxygen demand and predispose to myocardial ischemia.[13] Additionally, only patients who survived to hospital discharge were

TABLE 39-1 Cardiac Risk Stratification for Noncardiac Surgical Procedures (Risk of Cardiac Death and Nonfatal Myocardial Infarction)

Risk Stratification	Procedure Type
Major vascular surgery (reported cardiac risk generally >5%)	Aortic and other major vascular surgery
Intermediate-risk surgery (reported cardiac risk generally 1%-5%)	Intraperitoneal and intrathoracic surgery Carotid endarterectomy Head and neck surgery Orthopedic surgery Prostate surgery
Low-risk surgery (reported risk generally <1%)	Endoscopic procedures Superficial procedures Cataract surgery Breast surgery Ambulatory surgery

Adapted from Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2009;120(21):e169–276 [Table 4].

BOX 39-1 Preoperative Clinical Risk Factors Predictive of Perioperative Cardiovascular Complications

History of ischemic heart disease
History of compensated or prior heart failure
History of cerebrovascular disease
Diabetes mellitus
Renal insufficiency (serum creatinine, >2 mg/dL)

Adapted from Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100(10):1043–9.

examined because it was not an intention-to-treat analysis. If all in-hospital mortalities were included, the actual 2-year mortality rate would not have been significantly different ($p = 0.1$).

In contrast to the McSPI study in which patients just at "risk" of CAD were included, the first DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography) trial enrolled only patients with positive results on preoperative dobutamine stress echocardiography before major vascular surgery.[14] Patients were randomly assigned to either titrated bisoprolol therapy or standard perioperative care. Patients taking preoperative beta-blockers or those with extensive wall motion abnormalities were excluded. Bisoprolol (5 to 10 mg) was started at least 1 week before surgery (average, 37 days prior) and then continued for 30 days postoperatively; the target heart rate was 51 to 79 beats/min.

The results showed a significant reduction in the primary endpoint of composite death from cardiac causes or nonfatal MI within 30 days postoperatively (34% versus 3.4%, $p < 0.001$). The trial was stopped early despite only enrolling 112 patients (20 cardiac events). This study was not double-blind, the degree of risk reduction was larger than many authors deemed reasonable, and the event rate in the placebo arm was also greater than expected.[15,16]

The Perioperative Beta-Blockade (POBBLE) study found no difference in cardiovascular outcome in 97 vascular surgical patients randomly assigned to perioperative metoprolol versus placebo who underwent screening to ensure that CAD was not present.[17] Similarly, both the Diabetic Postoperative Mortality and Morbidity (DIPOM; 921 patients) and Metoprolol after Vascular Surgery (MaVS; 496 patients) studies found no benefit in short- and long-term (6- to 18-month) cardiac outcomes with the administration of perioperative metoprolol initiated immediately prior or very close to surgery.[18,19] A statistically significant increase in perioperative bradycardia and hypotension in the treatment arm was also shown.

It is important to note that the study populations in POBBLE, DIPOM, and MaVS represented a lower risk cohort than the DECREASE I trial did. Although DIPOM studied diabetic patients undergoing major surgery, *major* was defined as any procedure lasting greater than 1 hour and had somewhat vague exclusion criteria for patients with significant cardiac disease. The MaVS study specifically studied major vascular surgical patients but also had a low incidence of patients with known CAD and excluded those with significant comorbidities.

A large retrospective database cohort study of PBB by Lindenauer and colleagues[20] used propensity score matching to adjust for differences in patients. They found that the administration of any beta-blocker perioperatively to patients not already taking them was associated with no benefit and possible harm in patients with a Revised Cardiac Risk Index (RCRI) of 0 to 1 (1 point each for the following: high-risk surgery, serum creatinine >2 mg/dL, with diabetes and taking insulin, or history of CAD, congestive heart failure [CHF], or cerebrovascular disease)[21] (Box 39-1). However, in patients with an RCRI of 2 or greater, perioperative beta-blockade was associated with a decreased risk of death.

Although the results of the POBBLE, DIPOM, and MaVS studies question the utility of PBB in mostly intermediate risk patients, the DECREASE IV study showed more positive results for a similar cohort. The study enrolled 1066 patients considered to have a 1% to 6% perioperative cardiovascular risk who were randomly assigned to receive bisoprolol or placebo as well as fluvastatin or placebo. The study design for bisoprolol administration was identical to that of the DECREASE I trial. A significant reduction in MACE within 30 days was shown for the 533 patients who received bisoprolol (2.1% versus 6.0%, $p = 0.002$). Similar to the original DECREASE trial, this trial also was not double-blind and was terminated early.

Perioperative Ischemic Evaluation Trial and Subsequent Studies

The Perioperative Ischemic Evaluation (POISE) trial included 8351 patients with or at risk of atherosclerotic

disease who were randomly assigned to placebo or controlled release (CR) metoprolol. Initial therapy consisted of 100 mg orally 2 to 4 hours before surgery. Dosing was increased to 200 mg a day postoperatively and continued for 30 days. For those unable to take oral medications, 15 mg of intravenous metoprolol every 6 hours was given until oral therapy could be restarted. The study drug was held if heart rates were less than 50 beats/min or if systolic blood pressure (SBP) was less than 100 mm Hg; adjustments were then made in subsequent dosing.

Metoprolol CR therapy reduced the incidence of the primary endpoint of composite cardiovascular death, nonfatal MI, and nonfatal cardiac arrest within 30 days postoperatively (5.8% versus 6.9%, $p = 0.04$), and the reduction was driven by a decrease in PMI (4.2% versus 5.7%, $p = 0.0017$). Despite this decrease in MACE, there was a significant increase in the overall mortality in the study group (3.1% versus 2.3%, $p = 0.0317$) as well as a doubling in the stroke incidence (1% versus 0.5%, $p = 0.0053$). The increase in the all-cause mortality rate occurred mostly because of an increase in what was described as mortality related to infectious complications.

As stated by the POISE authors, for every 1000 patients treated with PBB, metoprolol CR would prevent 15 PMIs and seven cases of new onset atrial fibrillation while resulting in an excess of eight deaths and five strokes. The negative effect of stroke becomes even more significant when one considers that in the POISE cohort, most of those who sustained PMI had limited continued symptoms and only 6% to 9% required revascularization. In contrast, only 15% to 21% of the nonfatal stroke patients had complete recovery, whereas a significant number required functional support for daily activities.

Evaluation of the cause of this increase in morbidity and mortality showed the dominant factor to be perioperative hypotension. Significant hypotension (SBP <90 mm HG requiring intervention) was common in POISE, developing in 15% of the study group. The risk of death increased by fivefold, and the incidence of stroke associated with hypotension doubled. In addition to hypotension, intraoperative bleeding was also a predictor of stroke.

Subsequent to the release of POISE, the 2008 meta-analysis of Bengalore and colleagues[22] demonstrated a 116% increase in stroke risk with PBB, which significantly offset their cardiovascular benefit (35% reduction in nonfatal PMI). A similar relationship with beta-blockers in the cardiology literature has recently been shown. Although beta-blockers still remain one of the mainstays of pharmacologic management for ischemic heart disease,[23-25] this is not necessarily true for beta-blocker use in primary prevention, management of hypertension, and, now, even stable angina without prior MI in contemporary practice.[26] In a study of 19,257 hypertensive patients with three or more coronary risk factors but without overt CAD, there was a 14% higher incidence of coronary events and a 23% higher incidence of stroke when an atenolol-based regimen was used compared with an amlodipine regimen.[27]

Recent meta-analysis of beta-blocker use in the management of chronic hypertension has shown no benefit in all-cause mortality, cardiovascular mortality, and MI rates when they were compared with other antihypertensive agents.[28] These results were seen even when beta-blockers were compared with placebo.[28] To make matters worse, the incidence of stroke has consistently been shown to be higher with beta-blockers when compared with other therapies, ranging from 16% to 30% higher.[28,29-31] Inferior control of blood pressure was also found with beta-blockers.[28] This inefficiency in lowering pressure was even greater in the more important control of central aortic pressure.[32]

Conclusions regarding the association of PBB with sepsis or other infectious causes of death are less clear. Perioperative hypotension was likely a marker for varying degrees of shock in many patients, potentially affecting the maintenance of gut integrity. The early use of intravenous beta-blockade after MI was studied in the Clopidogrel and Metoprolol in Myocardial Infarction (COMMIT) trial and was associated with a 30% increase in cardiogenic shock.[33] The prevention of responsive tachycardia with the use of PBB in POISE could also have potentially delayed the recognition and treatment of sepsis. The effect of increased insulin resistance with PBB has not been studied in perioperative patients.

However, not all the recent evidence has been negative. In a large cohort study, Wallace and colleagues[34] reported on the experience at the San Francisco Veterans Administration Medical Center implementing a perioperative cardiac risk reduction protocol. The addition of beta-blockade was associated with a reduction in 30-day (odds ratio [OR], 0.52; 95% confidence interval [CI], 0.33 to 0.83; $p = 0.006$) and 1-year mortality (OR, 0.64; 95% CI, 0.51 to 0.79; $p < 0.0001$). Flu and colleagues[35] questioned the association of PBB use and stroke risk by demonstrating that beta-blocker treatment initiated more than 1 week before surgery was associated with improved outcomes compared with treatment initiated less than 1 week preoperatively, which was associated with an increased risk of stroke.

Continuation of Long-Term Therapy

Only a few studies and some nonsurgical data have implicated the withdrawal of beta-blockers in cardiac morbidity and mortality after surgery.[36,37] Shammash and colleagues[38] showed a significant increase in mortality (from 1.5% to 50%) and MI (from 5.3% to 50%) in those undergoing vascular surgery who had beta-blockers discontinued. It is important to note that this study was retrospective, only eight patients had beta-blockers discontinued, and the 50% mortality rate seems excessive for withdrawal. In a prospective survey study by Hoeks and colleagues,[39] those receiving beta-blockers the day of surgery who then had them discontinued after vascular surgery had a significant increase in mortality rate compared with those who either were never given a beta-blocker, those who newly started them, or those who continued their beta-blocker perioperatively. The group who had beta-blockers stopped comprised only 21 of the 711 patients, and no information was available about why the drug was discontinued. The increased short-term and 1-year mortality rates were, however, significant.

Wallace and colleagues[34] also studied perioperative beta-blocker withdrawal as part of their perioperative cardiac risk reduction protocol. A significant increase in 30-day and 1-year mortality rates were found with withdrawal and were more predictive of mortality than the presence of CAD or peripheral vascular disease (PVD). Similar to groups in previous studies, the withdrawal group represented only a small percentage of patients (4.6%), and no information was provided about why beta-blockers were discontinued. Because the University of California San Francisco has long employed an aggressive protocol for prophylactic PBB, the early withdrawal of beta-blockers in some patients was likely in response to other perioperative complications, potentially skewing their evidence.

AREAS OF UNCERTAINTY

Although the findings of the POISE trial should cause clinicians to proceed with significant caution regarding PBB, one must consider several important issues before making conclusions based on this trial. First, would the cardiovascular benefits of PBB have been fully offset by increases in stroke and overall mortality rates if the cohort from POISE had had more baseline cardiovascular disease? In contrast to the DECEASE cohort in which provocative ischemia in vascular surgical patients was the inclusion criteria, only approximately 40% of patients in the POISE trial had either known CAD or underwent vascular surgery. The incidence of previous CHF was just 6%.

The outcome of PBB in the patients with higher cardiovascular risk from the POISE cohort is not known. The POISE authors merely state that this relationship did not reach statistical significance.[15] It is not unreasonable to expect that the cardiovascular benefits would have been better in the higher risk patients compared with the only modest benefit (5.8% versus 6.9%) for MACE shown for the POISE trial cohort overall. It is unclear what degree of MACE risk reduction would have been needed to offset the complications recorded.

The second big issue regarding the POISE trial rests with the dosage of metoprolol used. As already discussed, therapy was initiated at 100 mg of metoprolol CR daily with a target daily dosing of 200 mg a day (the target dose could be reached as early as postoperative day 0). A potential starting dose of 200 mg/day is twice the maximum recommended starting dose. It is also 50% of the maximum recommended daily dose. In addition to the aggressive metoprolol dosage used in POISE, the threshold for allowing hypotension before withholding metoprolol (SBP >100) was also considered quite high. The POISE study also did not account for relative hypotension based on the percentage drop from baseline, although neither did any other study.

Despite the higher incidence of hypotension in study patients (15% versus 9.7% in control patients) and the significant association between hypotension and the risk of death and stroke, the POISE authors have taken issue with the notion that their negative results were related to excessive metoprolol dosing.[15] They state that the dosing was not significantly different than in the DECREASE trial, where the starting 5-mg dose of bisoprolol was at 100% of the maximum recommended starting dose and that the target dose of 5 to 10 mg daily was up to 50% of the maximum recommended dose. Additionally, the target dosing of atenolol in the McSPI trial was also 50% of the maximum recommended dose.

One potential explanation is that metoprolol may have led to worse outcomes with POISE. Wallace and colleagues[40] have published a comparison of outcomes depending on the choice of beta-blocker used for prophylaxis in surgical patients from the San Francisco Veterans Administration Medical Center. Thirty-day and 1-year mortality rates were significantly lower in the 1011 patients who received atenolol versus the 2776 patients who were given metoprolol. Possible mechanisms for this finding include the longer action of atenolol, which may allow for greater cardioprotection[41] and improved cardioselectivity with atenolol over metoprolol. Additionally, there may be greater variability in the metabolism of metoprolol.[41] A similar discrepancy has also recently been shown in the cardiology literature regarding outcomes after long-term use of atenolol versus metoprolol.[42]

Although the choice of beta-blocker prophylaxis may be relevant, the most important difference between DECREASE and POISE is probably not the drug or its starting dose but rather the timing of the initiation of therapy in relation to the surgery. It certainly seems plausible that titration with bisoprolol therapy (average, 37 days) in the DECREASE I and IV trials could have allowed for a greater safety margin in the avoidance of hypotension and, potentially, subsequent related complications. This schedule may also allow for the early recognition of variability in drug response, given the relatively recent acknowledgment of significant interpatient genetic differences in both the clinical response to beta-blockers and metabolism of the drug.[43-45] Some hypotension seen in the POISE trial may have been related to undiagnosed latent left ventricular dysfunction, which could also potentially be recognized with early initiation. Additionally, the pleotropic effects of beta-blockers on plaque stability and inflammation will take days to develop.[46,47]

The Erasmus group published the pooled results of DECREASE I, II, and IV trials in terms of stroke risk in patients receiving titrated bisoprolol therapy greater than 30 days before major noncardiac surgery.[47] The incidence of stroke was only 0.46% in the 3884 studied patients. A similar but even lower risk of stroke was also shown by the same group in patients undergoing noncardiac surgery who were receiving long-term beta-blocker therapy. In the more than 186,000 patients examined, only 34 suffered from a stroke (0.02%).

In contrast to the titration schedule in the DECREASE trials (average, 30 days) or to patients receiving long-term therapy, there was no preoperative titration in POISE, and maximum dosing occurred as early as day 0. The recommended titration schedule for metoprolol CR is on a weekly basis. The POISE authors have refuted the importance of the lack of titration[15] by noting that 10% of the patients receiving placebo in the POISE study also developed perioperative hypotension.

An important question is which patients should avoid PBB. Several of the major randomized trials have excluded patients with asthma,[14,48] whereas others have generally been more liberal in their inclusion. Fortunately, the use of beta$_1$ selective beta-blockers has been shown to have minimal effect on bronchial tone in cardiovascular patients.[49,50] A depressed left ventricular ejection fraction or a previous history of CHF has rarely been an exclusion criterion in most of the major trials, but only a small percentage of patients enrolled have actually had this history. The incidences of CHF or previous CHF in the McSPI, DECREASE, CARP (Coronary Artery Revascularization Prophylaxis), and POISE trials were only 8%, 12.5%, 10%, and 6%, respectively. Given the association of presumed hypoperfusion and increased mortality rate from the POISE trial, short-term beta-blockade, particularly large fixed doses, in those with depressed myocardial function should be used with great caution until better safety data are available.

An additional group of patients in whom initiation of PBBs should be carefully considered is those with known cerebrovascular disease. In the POISE cohort, a history of stroke or transient ischemic attack was a significantly better predictor of postoperative stroke (population attributable risk [PAR], 30.5%) than either perioperative hypotension (PAR, 14.6%), atrial fibrillation (PAR, 6.9%), or intraoperative bleeding (PAR, 10.1%).[51] Limburg and colleagues[52] also showed a profound relationship: in their study, previous cerebrovascular disease led to a more than twelvefold increase in the risk of postoperative stroke. These findings highlight the risk associated with beta-blocker–induced hypotension or hypoperfusion in those with a compromised cerebrovascular tree. This risk may be exacerbated in patients with concomitant ventricular dysfunction or anemia.[53,54]

GUIDELINES

American College of Cardiology Foundation/American Heart Association

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) updated their recommendations for prophylactic beta-blocker use in 2009.[55] In this document, the only Class I indication for the use of perioperative beta-blockers was that they be continued during the perioperative period in patients taking long-term beta-blockers preoperatively for Class I outpatient indications. Their use in patients undergoing vascular surgery with ischemia identified on preoperative testing was considered a Class IIa indication. Perioperative beta-blockade was also defined as *reasonable* (IIa recommendation) in those patients with CAD or in those with more than one major clinical risk factor undergoing vascular or intermediate-risk surgery. In those patients with defined IIa indications, it was recommended that some form of perioperative titration occur. Finally, in those with one or fewer clinical risk factors undergoing vascular or intermediate-risk surgery, the benefits of perioperative beta-blockade were considered uncertain. In their summary, the ACCF/AHA stated: "In light of the POISE results, routine administration of perioperative beta blockers, particularly in higher fixed-dose regimens begun on the day of surgery, cannot be advocated" (Table 39-2).

European Society of Cardiology

The European Society of Cardiology (ESC) also produced guidelines for perioperative beta-blockade in 2009.[56] This guideline was also endorsed by the European Society of Anesthesiology. In contrast to the ACCF/AHA document, Class I indications per the ESC included not only ongoing long-term beta-blockade use but also the presence of known ischemic heart disease or positive ischemia during provocative testing in all patients, as well as any high-risk surgery. Additionally, patients

TABLE 39-2 **2009 ACCF/AHA Guidelines for Perioperative Beta-Blocker Therapy**

Class I	Beta-blockers should be continued in patients undergoing surgery who are receiving beta-blockers for treatment of conditions with ACCF/AHA Class I guideline indications for the drugs (Level of Evidence: C)
Class IIa	Beta-blockers titrated to heart rate and blood pressure are probably recommended for patients undergoing vascular surgery who are at high cardiac risk due to CAD (Level of evidence: B), inducible ischemia on preoperative testing (Level of evidence: B), or perioperative assessment identifies more than one clinical risk factor (Level of Evidence: C) Titrated beta-blockers are reasonable in those undergoing intermediate-risk surgery in whom preoperative assessment identifies CAD or the presence of more than one clinical risk factor (Level of Evidence: B)
Class IIb	The usefulness of beta-blockers is uncertain for patients undergoing intermediate-risk or vascular surgery who have only a single clinical risk factor in the absence of CAD (Level of Evidence: C) or those undergoing vascular surgery with no clinical risk factors (Level of Evidence: B)
Class III	Beta-blockers should not be given to patients undergoing surgery who have absolute contraindications to beta-blockade (Level of Evidence: C) Routine administration of high-dose beta-blockers in the absence of dose titration is not useful and may be harmful to patients not currently taking beta-blockers (Level of Evidence: B)

ACCF/AHA, American College of Cardiology Foundation/American Heart Association; *CAD,* coronary artery disease.

Adapted from Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2009;120(21):e169–276.

undergoing intermediate-risk surgery, even those without clinical risk factors, were considered to have IIa indications for prophylactic beta-blockers. Essentially mirroring the DECREASE trial design, the authors further stated that therapy should ideally be started at least 7 to 30 days before surgery (Table 39-3).

Performance Measurements

As part of a collaborative effort under the direction of the Centers for Medicare and Medicaid Services and the Centers for Disease Control and Prevention, the prevention of adverse cardiac events during surgery was identified as one of the goals of the Surgical Care Improvement Project (SCIP). The SCIP-Card 2 measure seeks to prevent cardiac complications related to inappropriate perioperative discontinuation of beta-blockers that had been used on a long-term basis. The measure states that surgical patients taking beta-blockers must receive a beta-blocker within 24 hours of the perioperative period, and this period is defined as from the point of surgical incision to up to the first 6 hours of recovery. This recommendation mirrors the 2009 ACC/AHA focused update, which defines continuation of beta-blockers perioperatively as a Class I indication.[55] The SCIP-Card 2 measure has now been modified to mandate the continued administration of beta-blocker on postoperative days 1 and 2 in these patients.

TABLE 39-3 **2009 European Society of Cardiology Guideline Recommendations for Perioperative Beta-Blockers***

Class I	Beta-blockers are recommended in patients who have known CAD, myocardial ischemia on preoperative testing, or are scheduled for high-risk surgery (Level of Evidence: B) Continuation of beta-blockers is recommended in patients previously treated with beta-blockers because of CAD, arrhythmia, or hypertension (Level of Evidence: C)
Class IIa	Beta-blockers may be considered in patients scheduled for intermediate-risk surgery (Level of Evidence: B) Continuation in patients previously treated with beta-blockers because of chronic heart failure with systolic dysfunction should be considered (Level of Evidence: C)
Class IIb	Beta-blockers may be considered in patients scheduled for low-risk surgery with risk factor(s) (Level of Evidence: B)
Class III	Perioperative high-dose beta-blockers without titration are not recommended (Level of Evidence: A) Beta-blockers are not recommended in patients scheduled for low-risk surgery without risk factors (Level of Evidence: B)

CAD, coronary artery disease.
*Beta-blocker treatment should be initiated optimally between 30 days and at least 1 week before surgery. Target heart rate, 60-70 beats/min; systolic blood pressure >100 mm Hg.
Adapted from Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery; European Society of Cardiology (ESC), Poldermans D, Bax JJ, Boersma E, De Hert S, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. Eur Heart J 2009;30(22):2769–812.

AUTHORS' RECOMMENDATIONS

Despite almost 20 years of research in the field of prophylactic perioperative beta-blockade (PBB), no clear consensus exists about their best use or even their overall safety and efficacy. To make matters worse, the two most important studies in the field, the DECREASE and POISE trials, both have significant limitations.

When recommendations are formulated, the two most recent societal guidelines from 2009 should be considered. The European Society of Cardiology (ESC) guidelines advocate for the expansive use of PBBs, despite the concerns highlighted from POISE. It seems the authors believe that the use of early initiation protocols are protective enough to minimize the complications associated with PBBs. It is important to note that the task force chairman for the ESC guidelines was also the lead author of the DECREASE trial. We therefore advocate the approach of the American College of Cardiology Foundation/American Heart Association. In patients with known coronary artery disease who have not been taking beta-blockers, PBB may be considered as part of an overall perioperative risk reduction strategy in an intermediate-risk or vascular surgery setting. The agents should be started at least 1 week in advance and titrated to effect. Acute perioperative administration by protocol begun the day of surgery should be used with great caution. It is important to monitor for the effects associated with beta-blocker–induced hypotension. Large fixed dosages should be avoided, and perioperative titration should be used with stringent hold parameters. Longer acting drugs are preferred, and pharmacogenetic and pharmacodynamic disadvantages may occur with metoprolol.

Authors' Recommendations For Perioperative Beta-Blocker Therapy

- Prophylactic beta-blockers should be considered as part of an overall cardiovascular risk reduction strategy in patients undergoing intermediate or high-risk surgery with more than one clinical risk factor or evidence of ischemic heart disease.
- Patients with inducible ischemia may receive greater cardiovascular protection.
- Early initiation of preoperative drug titration is likely beneficial and ideally should occur 7 to 30 days before surgery. Initiation of beta-blockers the morning of surgery by protocol may be harmful.
- Longer-acting agents such as bisoprolol or atenolol may have advantages over metoprolol.
- Caution should be employed when using perioperative beta-blockers in patients with depressed ventricular function or those with cerebrovascular disease.
- The risks of perioperative beta-blockers may outweigh the benefits in patients with one or fewer clinical risk factors, even in those undergoing high-risk surgery. Early preoperative titration may decrease the risk, however.
- Patients receiving outpatient beta-blockers should have them continued during the perioperative period.

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CHAPTER 40

How Can We Prevent Postoperative Cognitive Dysfunction?

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INTRODUCTION

In 1955 Bedford published an article in *The Lancet* suggesting that patients older than 50 years should exercise discretion when choosing to undergo elective surgery because they are at high risk of adverse cognitive effects of surgery and anesthesia.[1] Unlike delirium and dementia, postoperative cognitive decline or dysfunction (POCD) is not a recognized disease or syndrome according to the current American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) and the World Health Organization's International Classification of Diseases (ICD-10) categorization systems. Currently, no definition exists for POCD outside a research context, and even within the research setting, there are no consensus diagnostic criteria and opinion is divided regarding the existence of POCD as a clinically meaningful entity. Researchers in this area suggest that POCD is a subtle deterioration in cognition that can only be diagnosed with sensitive neuropsychological tests, which detect minor perturbations in specific domains, such as attention, executive function, and memory.[2] Furthermore, for POCD to be detected, at least two test batteries are required, one before surgery and one after surgery.[2] Most studies that have observed patients over time suggest that POCD, with decline directly attributable to the surgery, is frequently reversible and appears to resolve in the majority of patients.[3-8]

Diagnosis of Postoperative Cognitive Decline

POCD has been diagnosed with several different approaches, all of which rely on arbitrary statistical thresholds rather than reproducible clinical diagnostic criteria.[9] The most stringent criterion for the diagnosis of POCD that is commonly used is a decline of at least two standard deviations (2 SD) in two cognitive domains or a decline of at least 2 SD in a composite cognitive score.[10] A liberal criterion that has been proposed for POCD diagnosis and has been used in several prominent studies is a decline in at least 1 SD in any cognitive domain or in a composite cognitive score.[11,12] This "1-SD" technique has been criticized as failing to account for factors that may confound interpretation of serially acquired cognitive test scores, including regression to the mean, measurement error caused by poor test–retest reliability, and practice effects.[13] With this liberal 1-SD diagnostic approach, the probability of detecting POCD purely by chance in just one of four domains, which is the diagnostic criterion used in one prominent study,[12] would be about 33%.[14]

To take into account the learning that occurs with repeated psychometric testing, a correction factor (based on the mean learning divided by the standard deviation of learning in a control population) was subtracted from the follow-up score in the relevant cognitive domain or in the composite cognitive score in several studies.[9,15,16] This approach to adjust for learning based on (average) improvement in a control group is termed *the reliable change index* and is based on several assumptions: (1) that control subjects who are not undergoing surgery learn no more efficiently than patients facing the prospect of surgery, (2) that the control subjects are well-matched with those undergoing surgery, and (3) that it is appropriate to correct for an individual's learning based on the average learning of a group. A study by Evered and colleagues[17] suggests that these assumptions might not be valid. This study included four groups, two surgical (cardiac and orthopedic surgery) groups and two nonsurgical control groups. One of the control groups was undergoing coronary angiography and the other control group was not undergoing any procedure. Learning in the nonprocedural control group was measured so that a reliable change index could be calculated and applied to the other three groups. When the three procedural groups were evaluated for cognitive decline at 3 months, the group that underwent coronary angiography (with no surgery and no general anesthesia) had the highest incidence of cognitive decline, after learning was corrected for with the nonprocedural control group's reliable change index. Perhaps it is not surprising that patients who are undergoing either surgical or nonsurgical procedures do not learn as efficiently as control subjects who are not distracted by the prospect of a procedure. Alternative statistical approaches, like mixed effects models, have been used in studies of POCD and are probably more robust than methods that rely on correction for learning based on a nonprocedural control group.[8,18,19]

Interestingly, most studies that have followed up postoperative cognition have ignored the fact that there are patients who appear to improve cognitively, just as there are patients who appear to decline.[20] This apparent cognitive improvement might represent artifact,

or it might reflect a genuine phenomenon.[21,22] It has been demonstrated that neuroplasticity occurs throughout life.[23] Pain and inflammation carry a cognitive burden, and successful elective surgery might result in alleviation of pain and resolution of inflammation. Functional recovery is also possible, with resultant enhancement in quality of life and physical fitness.[24-26] Taken together, these factors could be associated with cognitive improvement.

Delirium

Delirium is a well-recognized state of acute confusion in the elderly; it is described in the DSM-IV classification and has been assigned an ICD-10 code.[27] Delirium is an acute and fluctuating disorder of arousal, attention, and logical thinking.[28,29] In the nonsurgical setting delirium has been found to occur more commonly in patients with mild cognitive impairment or early dementia and is associated with clinical deterioration and an increased mortality rate.[30] Postoperative delirium is common (10% to 70% incidence) among elderly patients older than 65 years in the early postsurgical period[29] and typically resolves within the first 1 to 2 postoperative weeks. Risk factors for delirium include baseline cognitive impairment and age. An association between postoperative delirium and increased mortality rates has been shown,[31,32] but a link between postoperative delirium, POCD, and incident dementia has not been definitively established, although the evidence is mounting.[32-34] A study published in the *New England Journal of Medicine* found that patients who had delirium after cardiac surgery were more likely than those who did not have delirium to have lower mini-mental status evaluation scores (compared with their baseline scores) 1 year postoperatively.[35] Whether prevention of postoperative delirium is possible and could prevent this cognitive decline is currently unknown.

Dementia

Unlike delirium and POCD, dementia is thought to be an irreversible, degenerative loss of brain function that occurs with various disorders (e.g., Alzheimer disease, vascular dementia, Lewy body disease, and Huntington disease). The symptoms of dementia include impairments in cognition, especially memory, personality changes, depression, impaired judgment, sleep disturbances, decreased ability to perform daily activities, and, ultimately, inability to recognize loved ones and to function even at a basic level.[36] No conclusive association has been found between POCD and incident dementia. However, epidemiologic research has shown that patients with repeated hospital admissions are more likely to become demented.[37] There is also a suspicion that specific general anesthetic agents, such as isoflurane, might initiate pathologic processes (e.g., the generation in the brain of beta amyloid proteins or phosphorylated tau), which could initiate or accelerate the development of dementia.[38] Surgery might promote neuroinflammation, which could also theoretically increase susceptibility to dementia.[39-41] However, a potential causal association between surgery or anesthesia and subsequent incident dementia is purely speculative. Although it has been reported that surgery increases the risk of subsequent dementia,[42] the majority of studies that have explored this hypothesized link have been negative.[43,44]

THERAPEUTIC OPTIONS

Because no consensus exists regarding the definition of POCD and given that no definite causal factors have been identified, general principles should govern preventive and therapeutic options. Physiologic derangements should be assiduously prevented, including hypotension, hypoxia, hypoglycemia, and metabolic abnormalities. Efforts should be taken to ensure that adequate cerebral perfusion is maintained in the perioperative period. Patients who require admission to intensive care units might be at higher risk of persistent cognitive decline, especially if they have dysfunction of one or more organ systems. It is likely that brain dysfunction occurs as part of systemic inflammatory response syndrome (SIRS) and multiorgan dysfunction syndrome (MODS).[39,41,45,46] Therefore preventing other organ dysfunctions, such as acute renal insufficiency, probably provides indirect protection to the brain. Similarly, the avoidance of surgical complications, such as hemorrhaging and wound infection, is also likely to facilitate improved postoperative outcomes in general and cognitive outcomes specifically. Other general strategies that are probably beneficial for cognition include aggressive multimodal treatment of pain and inflammation, minimization of perioperative sleep disruption, and active promotion of physical and mental fitness through perioperative physical therapy and training programs.[47]

EVIDENCE

Uncontrolled Studies

Uncontrolled observational trials have suggested that approximately half of patients undergoing cardiac surgery or major noncardiac surgery have persistent cognitive decline. One of these studies focused on cardiac surgery patients and was published in the *New England Journal of Medicine* in 2001. This study showed that 41% of patients who underwent cardiac surgery had persistent cognitive decline 5 years postoperatively.[11] This study had a major impact in the medical community and on public opinion and reinforced the perspective that cognitive decline is a major complication of cardiac surgery, potentially attributable to cardiopulmonary bypass. The concern about brain damage associated with cardiopulmonary bypass was a major stimulus for the advent of off-pump cardiac surgery. Another influential study published in *Anesthesiology* showed that 46% of older patients had persistent POCD 1 year after major noncardiac surgery.[12] The main limitations of these studies have been the lack of appropriate controls and the use of the liberal approach to diagnose POCD (a decline by more than 1 SD in any cognitive domain), which, purely by statistical

chance, would be likely to detect a high incidence rate of POCD.[14]

Serial Assessments

Even with a more rigorous diagnostic approach, the methodologic obstacle to reliably diagnosing POCD is reflected in studies that have assessed patients at serial time points. These studies have generally reported poor intrapatient reproducibility in the diagnosis of POCD.[20] For example, in one study, the patients given diagnoses of POCD at 3 months postoperatively had very poor overlap with the patients who were given diagnoses of POCD at 2 years postoperatively.[5]

Control Subjects

Studies that have included control subjects, including the seminal and influential International Study of POCD (ISPOCD), have generally found that POCD appears to resolve with time.[3-8,43,48] The ISPOCD was established as an international research consortium in 1994. This group was founded on the basis that POCD occurred commonly in elderly patients and frequently persisted. Members of the ISPOCD group suggested that POCD after cardiac surgery was a recognized complication, which was probably attributable to cardiopulmonary bypass. Their major purpose was to characterize POCD after noncardiac surgery (www.sps.ele.tue.nl/ispocd/sub0/main.html). The main goals of ISPOCD-1 were to determine whether POCD occurred after noncardiac surgery with general anesthesia and to test the hypothesis that intraoperative hypotension and hypoxemia contributed to POCD. The resulting study was published by the ISPOCD group in 1998 in *The Lancet* and showed that 26% of patients older than 60 years had POCD at 1 week and 10% had POCD at 3 months postoperatively.[10] While age and educational level were found to be risk factors for POCD, counter to the investigators' hypothesis, hypotension and hypoxemia did not appear to be associated with POCD.[10] A relationship was noted between POCD and impaired functionality as reflected by decrements in Instrumental Activities of Daily Living scores.[10] Two studies that have included control groups have found that POCD might persist up to 1 year postoperatively.[6] One of these studies was hard to interpret; there appeared to be persistent cognitive decline in the visuospatial domain but lasting improvement in language.[6] A study by Ballard and colleagues,[49] in which 256 subjects were assessed at 1 year (roughly balanced between surgical patients and nonsurgical community age-matched control subjects), found that, according to a global composite cognitive score, 11.8% of mostly orthopedic surgical patients experienced cognitive decline 1 year postoperatively compared with only 3.8% of the nonsurgical control patients. In this study, impairments in attention and executive function were particularly noticeable. These are striking results, but their validity rests on the assumption that the control subjects were appropriately matched for the surgical patients and that both groups would learn (or improve on the cognitive test battery) as efficiently.

Cardiac Surgery

Recent evidence from cardiac surgery studies has challenged the broadly accepted perspective that persistent and severe POCD is common, especially when there is a period of cardiopulmonary bypass. Using an elegant research design, Selnes and colleagues[7,8] followed up four age- and education-matched cohorts. The first had coronary artery disease and underwent cardiac surgery, the second had coronary artery disease and had percutaneous coronary intervention, the third had coronary artery disease and was treated medically, and the fourth did not have heart disease. Their findings were surprising. The three cohorts with coronary artery disease all declined cognitively over 6 years, whereas the cohort without heart disease did not decline. This study suggested that specific comorbidities, like vascular disease, are likely to be much more potent drivers of cognitive decline than cardiac surgery or general anesthesia. In an article published in the *New England Journal of Medicine*, Selnes and colleagues[19] commented, "it is now increasingly apparent that the incidence of both short- and long-term cognitive decline after CABG has been greatly overestimated, owing to the lack of a uniform definition of what constitutes cognitive decline, the use of inappropriate statistical methods, and a lack of control groups." They also proposed that "Most patients in whom new cognitive symptoms develop during the immediate postoperative period can be reassured that these symptoms generally resolve within 1 to 3 months."[19]

Randomized Trials

In the last 15 years, major studies have randomly assigned patients with coronary artery disease to receive either surgery or percutaneous coronary intervention.[22,24,50] These trials have provided an important opportunity to judge whether cardiac surgery and general anesthesia are really potent independent agents of cognitive decline and decrements in quality of life. The trials have not demonstrated that patients randomly assigned to surgery had worse cognitive outcomes, and generally, quality of life was improved whether patients underwent surgical treatment or percutaneous coronary intervention. Taken together, the evidence suggests that persistent POCD is not a common phenomenon, and surgery and anesthesia are, at worst, very minor culprits in relation to lasting cognitive decline.

CONTROVERSIES

Subsequent to the ISPOCD-1 findings, ISPOCD-2 was established to elaborate and refine the findings of ISPOCD-1 and to address outstanding controversies. The ISPOCD-2 study made important contributions and was generally not able to identify causal factors for POCD. Other investigators have similarly not been able to reliably demonstrate persistent POCD attributable to a surgical event or to discover pathologic mechanisms responsible for POCD. Many studies have identified advanced age, depression, low educational level, and

preoperative cognitive impairment as risk factors of POCD.[51] However, these are known risk factors for cognitive decline in general and do not point to a potential mechanism for an added insult triggered by surgery or general anesthesia.

General Anesthesia

One approach to teasing out the relative contribution of general anesthesia to POCD is to randomly assign surgical patients to general or regional anesthesia and track postoperative cognition in both groups. Randomized trials that have followed this approach have usually not found that regional anesthesia was associated with a decrease in persistent POCD. A meta-analysis of 21 trials published in the *Journal of Alzheimer's Disease* showed that general anesthesia was marginally but nonsignificantly associated with POCD (odds ratio, 1.34; 95% confidence interval, 0.93 to 1.95).[52] If, despite the current negative evidence, general anesthesia does independently contribute to POCD, it is likely that its contribution is minor.

Cardiopulmonary Bypass

Recent rigorously conducted randomized controlled trials have been instrumental in dispelling the popular myth that cardiopulmonary bypass is a major independent cause of cognitive decline. The Octopus trial randomly assigned 281 patients to cardiac surgery with or without the use of cardiopulmonary bypass. Both 1-year and 5-year cognitive outcomes have been published for this trial in the *Journal of the American Medical Association*.[53,54] At 5 years, the investigators found that about one third of patients in both the on-pump and the off-pump groups had cognitive decline.[54] The 2200-patient ROOBY trial, published in the *New England Journal of Medicine*, also randomly assigned largely male patients to cardiac surgery with or without cardiopulmonary bypass.[21] Patients underwent baseline and follow-up neuropsychological tests that were designed to evaluate dysfunction in attention, memory, and visuospatial skills. Similar to the Octopus trial and against prevailing views, no difference in cognitive outcomes was found between groups. Perhaps even more intriguing was that, with comprehensive follow-up of about 1150 patients at 1 year postoperatively, the long-term postoperative changes in individual neuropsychological test scores were similar to or improved from baseline for both treatment groups.[21]

Genetic Risk Factors

It has been hypothesized that genetic risk factors for POCD would probably overlap with those for neurodegenerative disorders, such as Alzheimer disease. The epsilon4 allele of the apolipoprotein E gene is a known risk factor for Alzheimer disease, poor outcome after cerebral injury, and accelerated cognitive decline with normal aging.[55] No association has been demonstrated between the apolipoprotein E genotype and POCD.[12,55,56] It remains possible that some people have a genetic predisposition for POCD. Because no agreed-on diagnostic criteria exist for POCD, detecting an association between candidate genotypes and the phenotype (i.e., POCD) is a major challenge.[14]

AREAS OF UNCERTAINTY

There remain several important unanswered questions in relation to POCD that warrant further study. Although it now seems clear that persistent POCD is not as common as had previously been thought, specific patients populations may be more likely to experience POCD. For example, a study in collaboration with the Alzheimer's Disease Neuroimaging Initiative (ADNI) found that patients with early dementia might be more susceptible to early POCD and a decrease in volume of specific brain regions.[57] Interestingly, these changes appeared to be reversible in some patients, reflecting neuroplasticity even in elderly patients, as well as the potential for both cognitive decline and cognitive improvement.

Most studies to date have focused on POCD and have tended to dismiss postoperative cognitive improvement as a statistical artifact. This dismissal might be inappropriate; it is actually conceivable that certain patients might improve cognitively after successful surgery that alleviates pain, improves functionality, and decreases inflammation. As noted previously, several rigorous studies have suggested that quality of life and, perhaps, even cognition might be improved after cardiac surgery.[22,24] Studies that have combined neuroimaging, pain, and functional assessments have shown that when back surgery or hip replacement surgery is successful, cognition improves and gray matter increases in areas such as the dorsolateral prefrontal cortex, the anterior cingulate cortex, and the amygdala.[58,59] The possibility of postoperative cognitive improvement would be of tremendous relevance and comfort to surgical patients and could be an important objective for perioperative clinicians.

It is unknown whether some anesthetic agents are safer than others and even whether some drugs might confer protection against POCD. For example, one small study by Zhang and colleagues[60] compared desflurane with isoflurane for noncardiac surgery and found that isoflurane was associated with early POCD but that desflurane was not. Hudetz and colleagues[61,62] have found in small studies that supplementary low-dose ketamine decreased delirium, inflammation, and early POCD after heart surgery. Whether and to what extent anesthetic techniques, specific anesthetic agents, types of surgery, inflammatory responses, postoperative complications, and surgical outcomes contribute to cognitive trajectories remains obscure. These are important areas for future investigation.

GUIDELINES

Currently, no established clinical practice guidelines exist for the prevention of POCD. Experts in the field are recommending that routine preoperative cognitive assessment should be implemented, considering that

patients with baseline impairment are at increased risk of postoperative delirium and POCD. Similarly, there is a strong motivation to incorporate postoperative delirium assessment into standard practice, as delirium is associated with increased morbidity and mortality rates and might predict persistent POCD.

AUTHOR'S RECOMMENDATIONS

It has been established that the incidence of persistent postoperative cognitive decline or dysfunction (POCD) has been greatly overestimated. Patients should be reassured that even if they experience early cognitive decline, this usually resolves within a few months of surgery. Although there is no specific evidence for practices to decrease POCD, counseling patients, avoiding perioperative physiologic derangements, promoting sleep hygiene, limiting sedative and anesthetic agents, incorporating regional anesthetic techniques, using nonopioid analgesics, minimizing the extent of surgery, mobilizing patients early, reinstituting feeding early, and preventing perioperative complications are all plausible candidate interventions for preventing POCD. Perioperative physical and mental training (i.e., general health promotion) might confer protection against POCD. It is important to acknowledge patients' possible concerns about POCD and to mention what steps can be taken to promote postoperative physical and cognitive health. If surgery goes well and results in decreased pain and inflammation and increased functionality, postoperative improvements in quality of life and cognition are realistic and desirable outcomes.

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CHAPTER 41

Do Intensive Care Specialists Improve Patient Outcomes?

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INTRODUCTION

Intensive (critical) care units (ICUs) first appeared in the 1950s as specialized wards to care for patients with acute respiratory failure. Subsequent technical and pharmacologic advances led to the provision of life-sustaining care for a medley of medical and surgical problems. Admission to an ICU is determined by a requirement for ventilatory or cardiovascular support, invasive monitoring or correction of life-threatening fluid and electrolyte abnormalities, or the expectation that severe, life-threatening abnormalities may arise without warning. Although ICUs are characterized by a high ratio of nurses to patients (usually 1:2 or less), physician staffing is variable. Based on the size of the hospital, ICUs may be generalized ("mixed") or specialized. Subtypes include coronary care units (CCUs), burn units, medical ICUs (MICUs), surgical and trauma ICUs (SICUs), and cardiac surgical and neurosurgical units.

The use and availability of critical care beds have increased dramatically over the past 50 years. There are more than 6000 ICUs and 59,162 ICU beds providing a variety of services covering surgical, neurosurgical, medical, and cardiovascular specialties in the United States.[1-3] The number of critical care beds in hospitals is increasing, while the number of non–critical care beds is diminishing.[4] Consequently, the cost of providing critical care services will continue to escalate. Inevitably, rationing of resources will result.[5] Since its inception, intensive care has cost the United States approximately $1 trillion.[6] Overall health care costs in the United States now amount to $2.6 trillion annually. This amount constitutes 17.9% of the gross domestic product (GDP), and despite the fact that U.S. health spending in 2010 is estimated to have grown at a historic low of 3.9%, the number is rising.[7,8] Indeed, with the institution of the Affordable Care Act of 2010, the expenditures are expected to escalate by 8.3% in the year 2014.[9] From 2000 to 2005, the cost of providing critical care increased from $55.5 billion to $81.7 billion, representing 13.4% of hospital costs and 4.1% of national health expenditures, respectively.[10] The cost of those patients using critical care services while in the hospital, as well as costs accrued after ICU discharge, resulted in estimates ranging from $121 billion to $263 billion, representing 5.2% to 11.2% of total U.S. health care spending.[11] Given the cost of critical care and the need to contain health care expenditures, the utility of critical care must be rigorously validated. This chapter reviews the data addressing this issue.

OPTIONS: THE ARGUMENT FOR INTEGRATED CRITICAL CARE SERVICES

Historically, significant diversity has existed in the operation and organization of ICUs. An early consultant-based model is now being supplanted by one featuring an intensive care specialist ("intensivist"). In the consultant model, one physician typically manages mechanical ventilation while dysfunction of other organs is directed by a combination of the primary care team and a series of specialist consultants. Responsibility for orders, consultations, and decision making may lie with the primary physician, but this often is unclear. Faults with this system include diffusion of responsibility, expertise imbalance between the decision maker and consultant, high cost, competing and conflicting orders, duplication of services, lack of cohesive planning, inconsistent coverage (particularly nights and weekends), and potentially worse patient outcomes.[12]

Specialized critical care training has been introduced over the past 30 years to deal with the shortcomings of the consultant system. This change has led to an integrated model whereby the intensivist coordinates the care of the patient, taking primary responsibility while the patient is in the ICU, and requests consultations only when necessary. Still, implementation of this approach may vary. The approach most diametrically opposed to the consultant system is a "closed" model in which care is transferred to a full-time intensive care physician who assumes "ownership." This individual controls all admissions, discharges, orders, clinical management, and consultations for all patients admitted to the ICU. Advantages of this system include consistency of care, cost control, communication, availability, a clear hierarchy of responsibility, facilitation of standards, and improved nurse–physician relations. Faults with this system include the capacity to "lock out" the primary physician, loss of continuity of care, and the potential for conflict. In practice, the most common change has been the adoption of a "high-intensity" approach, encompassing all the features of the closed system apart from the actual transfer of ownership.

Unfortunately, the value of having critical care medicine delivered by specifically trained specialists has not been accepted universally. In several countries, specific

vocational training is available.[13] In the United States, critical care is a subspecialty of anesthesiology, surgery, internal medicine, pediatrics, and, more recently, emergency medicine, neurology, and neurosurgery. Wide variation in the educational process exists.[13] A recent position paper[14] has advocated for a hospitalist pathway to critical care because of the rapid growth of this subspecialty and the role of these providers both in medicine, increasing from 2000 to 34,000 practitioners in 15 years, and in the care of the critically ill.[15] It is hoped that choosing to offer a rigorous pathway to certification in critical care for hospitalists will increase the number of available intensivists.[16]

It has been necessary for intensivists to justify their existence using the evidence-based platform. This situation is what distinguishes critical care from specialties such as cardiology, trauma surgery, and emergency medicine, with which it shares features. At its core, critical care requires an integrationist approach: the 1970s and 1980s were characterized by the hyperspecialization of the medical profession along system lines—the cardiovascular system, the renal system, the gastrointestinal tract—and even systems within systems. Intensive care specialists provide general holistic medical care according to severity of illness. Conceptually, critical care may be both horizontally and vertically integrated, with its own specialists, its own team, and its own management structure. This includes an intensive care director and a multidisciplinary critical care team.

Thus evaluation of outcomes relating to the appointment of an intensive care specialist mandates appraisal of all literature relating to critical care organization. Three questions are asked: (1) Do intensive care specialists improve outcomes, specifically, mortality and morbidity rates, cost reduction, and length of stay (LOS)? (2) What impact does the appointment of a critical care director have on ICU performance and outcomes? and (3) Does the adoption of a high-intensity model, with concomitant introduction of an intensive care team, confer additional benefit?

EVIDENCE

The Intensive Care Specialist

Physician staffing in intensive care has not been rigorously studied. The literature is largely anecdotal or observational, usually detailing changes in costs and outcomes after planned changes in critical care staffing or configuration. Changes in physician staffing were usually accompanied by other alterations, for example, the introduction of a critical care team or an ICU director. Simultaneous changes in case mix or severity of illness require adjustment in statistical results. The definition of physician staffing varies from an intensivist doing daily rounds (often in collaboration with the primary care team) to a closed 24-hour critical care service (Table 41-1). Both the American College of Critical Care and the Society of Critical Care Medicine recommend intensivist coverage 24 hours per day 7 days per week. However, with increasing numbers of ICU beds and decreasing numbers of trainees selecting the field of critical care, achieving 24-hour coverage has proven to be challenging. Although the idea of a 24-hour intensivist is appealing, the necessity for this approach may be questionable. Recently, Wallace and colleagues[17] found that night-time intensivist staffing in low-intensity daytime-staffed ICUs was associated with a reduced mortality rate. However, this benefit was not seen in those units with a high-intensity daytime staffing model. A low-intensity model was one in which consultation with an intensivist was optional.[17]

Different styles of critical care service that involve the intensivist may or may not use external physician consultants, may envelop consultation services such as nutrition or pharmacy, and may operate quite differently but carry the same "intensivist" label.[18-20] Attention should also be paid to specialist nurse training, nurse-to-patient ratios, and the presence or absence of certified nurse practitioners.[21]

Li and colleagues[22] looked at outcomes and interventions in a community hospital ICU before (n = 463) and after (n = 491) the introduction of an ICU physician. There was a significant reduction in adjusted hospital mortality rate (adjusted for reason for admission, age, and mental status) after the change, with a concomitant increase in the use of invasive monitors.

Pollack and colleagues[19] studied ICU mortality rates, the use of monitoring and therapeutic modalities, and efficiency of ICU bed utilization in the 3 months before (n = 149) and after (n = 113) the appointment of a pediatric intensivist and daytime ICU team. There was a clear improvement in the efficiency of bed utilization after the arrival of the intensivist. There was a reduction in the number of admissions for monitoring and for patients with low severity of illness and a parallel increase in therapeutic and monitoring interventions in the postintensivist period. Mortality rate, adjusted for case mix, was reduced in the intensivist period by 5.3% (number needed to treat to prevent one death [NNT], 19; odds ratio [OR], 0.51; 95% confidence interval [CI], 0.16 to 1.67).

Reynolds and colleagues[23] studied outcomes in patients with septic shock in the year before (n = 100) and after (n = 112) the introduction of a critical care service, staffed by intensivists. A significant reduction was seen in the hospital mortality rate from 74% to 64% (absolute risk reduction [ARR], 10%; NNT, 10; OR, 0.46; 95% CI, 0.26 to 0.83), after introduction of the critical care service. The use of invasive monitors also significantly increased, but the number of external consultations did not change.

Brown and Sullivan[24] performed a cohort analysis of patients admitted to the ICU before (n = 223) and after (n = 216) the introduction of an intensivist operating in an open model. The intensive care mortality rate decreased from 28% to 13% (ARR, 15%; NNT, 6.6; OR, 0.40; 95% CI, 0.25 to 0.66). The hospital mortality rate decreased from 36% to 25% (ARR, 11%; NNT, 9; OR, 0.59; 95% CI, 0.39 to 0.90). This effect was consistent irrespective of the severity of illness.

Hanson and colleagues[25] undertook a cohort study comparing two parallel models of critical care. One group of patients was looked after by an on-site critical care team, supervised by an intensivist. The other cohort was

TABLE 41-1 **Summary of Published Studies on Intensive Care Specialists**

Study	Intervention	Design	Unit Type	Number Study Group	Number Control Group	Survival Benefit (OR)	Hospital LOS Reduced	Cost Benefit	Survival Benefit
Li[22]	Intensivist	Cohort retrospective observational	Mixed	463	491	0.91* Hosp	—	Yes	—
Pollack[19]	Intensivist plus daytime ICU team	Cohort prospective observational	Pediatric	149	113	0.51*	—	—	—
Reynolds[23]	Intensivist plus team	Cohort prospective HC	MICU	100	112	0.46	—	—	—
Brown[24]	Intensivist	Cohort prospective HC	Mixed	223	216	0.40 ICU 0.59 Hosp	—	—	—
Hanson[25]	Intensivist plus team	Cohort retrospective concurrent	SICU	100	100	—	Yes	Yes	Yes
Blunt[27]	Intensivist	Cohort HC	MICU	393	328	0.59*	—	—	—
Dimick[28]	Intensivist; daily rounds	Cross-sectional	SICU	182	169	—	Yes	Yes	Yes
Pronovost[29]	Intensivist; daily rounds	Cross-sectional	SICU	2036	472	0.56	Yes	Yes	Yes
Baldock[45]	Intensivist; closed	Cohort HC	Mixed	330	395	0.61 ICU 0.54 Hosp	—	—	—
Carson[46]	Intensivist; closed	Cohort HC	MICU	121	124	0.89† predicted	No	Yes	—
Ghorra[47]	Intensivist; closed	Cohort HC	SICU	125	149	0.36* ICU	—	Yes	Yes
Multz[49]	Intensivist; closed	Cohort HC	MICU	154	152	—	Yes	Yes	Yes
Multz[49]	Intensivist; closed	Prospective cohort HC	MICU	185	95	—	Yes	Yes	Yes
Tai[56]	Intensivist; during day	Cohort HC	MICU	127	112	—	—	Yes	—
Manthous[57]	ICU director	Cohort HC	MICU	930	459	0.63 ICU 0.66 Hosp	Yes	Yes	—
Nathens[52]	Intensivist; intensive care team	Prospective cohort	Trauma SICU			0.78 ICU 0.64 trauma centers	—	—	—
Treggiari[50]	Intensive care team; closed	Cohort	MICU (ARDS)	684	391	0.68 Hosp	—	—	—
Levy[35]	Intensivist	Cohort	All types	18,618	22,870	1.40‡ Hosp	—	—	—
Wallace[17]	Night-time; intensivist coverage	Retrospective	All types	14,424	51,328	1.02 overall; 0.62 in low-intensity ICU staffing	—	—	—

ARDS, acute respiratory distress syndrome*; HC*, historical control; *ICU,* intensive care unit; *LOS,* length of stay; *MICU*, medical intensive care unit; *SICU*, surgical intensive care unit.
*Adjusted for severity of illness.
†Adjusted for standardized mortality ratios.
‡Indicates unfavorable outcome with intensive care specialist.

managed by a surgical team, supervised by a general surgeon, that had commitments outside the ICU. Despite having higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores, patients cared for by the critical care team spent less time in the SICU, had fewer complications, used fewer resources, and had lower total hospital charges. No significant difference was found in hospital or ICU mortality rates. Selection bias may have been an issue with this study.

Samuels and colleagues[26] examined the impact of the implementation of a neurointensivist-led neurocritical care team on the discharge disposition of those patients (n = 703) retrospectively found to have subarachnoid hemorrhage. Patients cared for after the change (n = 386) were significantly more likely to be discharged home (25.2% versus 36.5%; $p < 0.001$) and less likely to be discharged to a rehabilitation facility (42.5% versus 32.4%, $p < 0.01$) than those admitted before (n = 317) the

service was installed. Shortcomings included the retrospective nature of the study and the prolonged (7-year) period of data collection, making it likely that many things other than the institution of a critical care team changed.

Blunt and Burchett[27] compared outcomes in ICUs covered by intensivist versus nonspecialist consultants (anesthesiologists) covering multiple sites using standardized mortality ratios. The case mix–adjusted hospital mortality rate of intensive care patients improved significantly in the intensivist group compared with the nonspecialist group (standardized mortality ratios, 0.81 versus 1.11; OR, 0.73; 95% CI, 0.55 to 0.97).

Dimick and colleagues[28] and Pronovost and colleagues,[29] using similar methodology, studied outcomes after high-risk surgery in the state of Maryland via a large database.[30] After esophageal resection, lack of daily rounds by an ICU physician was associated with longer lengths of stay (7 days; 95% CI, 1 to 15; $p = 0.012$), higher hospital costs (61% increase or $8839; 95% CI, $1674 to $19,192; $p = 0.013$), and increased frequency of postoperative complications.[28] After aortic repair surgery, not having daily rounds by an ICU physician was associated with a threefold increase in the in-hospital mortality rate (OR, 3.0; 95% CI, 1.9 to 4.9) and in major postoperative complications, such as cardiac arrest (OR, 2.9; 95% CI, 1.2 to 7.0), acute renal failure (OR, 2.2; 95% CI, 1.3 to 3.9), and sepsis (OR, 1.8; 95% CI, 1.2 to 2.6). Thus daily rounds by an intensive care physician are efficient, effective, and economical.

Reriani and colleagues[31] examined the impact of mandatory versus on-demand intensivist care on long-term patient mortality rates and quality of life. Baseline quality of life surveys were reviewed on discharge and again at 6 months. The baseline characteristics between the two groups did not vary greatly according to their respective APACHE III scores. After the institution of a 24-hour intensivist, no difference was seen in long-term survival rates of medical ICU patients. However, this same group had previously demonstrated that the change in staffing was associated with improved processes of care and staff satisfaction, as well as decreased ICU complication rates, hospital LOS, and hospital cost. In these two previous studies,[32,33] there was no change in ICU or hospital mortality rates.

Numerous other studies have haphazardly appeared in the literature in abstract form. Pronovost and colleagues[34] have completed a systematic review to include these data. ICU physician staffing was divided into low intensity (no intensivist or elective intensivist consultation) or high intensity (mandatory intensivist consultation). High-intensity staffing reduced the risk of ICU mortality (pooled relative risk [RR], 0.61; 95% CI, 0.50 to 0.75), hospital mortality (RR, 0.71; 95% CI, 0.62 to 0.82), and ICU and hospital LOS, regardless of whether it was adjusted for case mix.

Levy and colleagues[35] studied the impact of intensive care specialists on hospital mortality rate using a large database (Project IMPACT) that had been designed to address resource use in 123 ICUs across the United States. The study was performed by intensivists using a database constructed by intensivists. Patients who were managed by intensive care specialists had greater severity of illness than those managed by the primary physician and they underwent more procedures. When outcomes were adjusted for illness severity and a propensity score was used, patients cared for by intensive care specialists had greater in-hospital mortality rates than those who were not. Critical care predicted the hospital mortality rate with a crude OR of 2.13 ($p < 0.001$). The addition of SAPS II (a severity of illness scoring system) to this model reduced this OR to 1.42 ($p < 0.001$). Further inclusion of the propensity score decreased the OR to 1.40 ($p < 0.001$). Several potential limitations to this study should be noted. The study tests two different hypotheses. The first looked at outcomes, depending on whether an intensivist was chosen by the primary physician. This likely resulted in selection bias because chosen patients were likely to be less severely ill and intensivists were presumably consulted because of clinical concerns. The second study involved more robust groups: critical care for the entire stay (18,618 patients, critical care medicine [CCM] group) versus no critical care (22,870 patients, no CCM group), presumably because of lack of availability. The CCM group was more likely to be at academic medical centers in urban locations, indicating that selection bias, which included racial background, chronic health problems, and socioeconomic status, may have had an impact. Another form of selection bias may have been evident—that of the units themselves.[36] It is likely that there is a cohort of nursing-led ICUs that may function at a very high level of care. This may result from strict adherence to protocols and guidelines, with meticulous attention to infection control and involvement in, and submission to, national benchmarking databases (such as Project IMPACT).[37] Thus this study may illuminate the effectiveness of an elite group of ICUs, absent an intensive care specialist, that through tight organizational controls may have better outcomes.

In conclusion, the majority of studies have demonstrated that availability of an intensive care specialist may reduce mortality rate, LOS, and costs in intensive care. Interestingly, impressive epidemiologic data show that intensive care outcomes for many diagnoses are improving.[26,38-43] This may reflect the overall increase in awareness of critical illness; improved vertical integration between emergency medicine, medicine, surgery, and anesthesia; and a problem-oriented, systems-based approach to medical education and practice.

Young and Birkmeyer[44] have estimated that full implementation of intensivist-model ICUs would save approximately 53,850 lives each year in the United States. Conversely, Levy and colleagues[35] have suggested that management of patients in "choice" ICUs by intensivists and in units with full critical care management of patients, compared with a no-intensivists model, may be associated with worse outcomes. No clear explanation for the adverse outcomes in this patient subgroup has emerged. However, it is worth noting that the presence of an intensive care specialist alone is not a "critical care service" and that improved outcomes may result from an integrated model of specialist and multidisciplinary team care, strategic management, and tight organizational structure.

Intensive Care Organization

As previously noted, the introduction of intensive care specialists is one part of a system, usually referred to as a critical care service. A critical care team, led by an intensivist and including residents, fellows, nurse practitioners, respiratory therapists, and a pharmacist, provide 24-hour care to the patient. This may be in full collaboration with the primary care team (the open model) or may replace that team as primary caregivers (the closed model).

Baldock and colleagues[45] prospectively studied 1140 patients admitted into a mixed medical–surgical ICU over a 3-year period, during which time resident medical staff and a closed configuration were introduced. The ICU mortality rate was reduced from 28% to 19% (ARR, 9%; NNT, 11; OR, 0.61; 95% CI, 0.42 to 0.89). The hospital mortality rate was reduced from 36% to 24% (ARR, 12%; NNT, 8; OR, 0.54; 95% CI, 0.38 to 0.77).

Carson and colleagues[46] studied change from an open ($n = 121$) to a closed ($n = 124$) format in a medical ICU. APACHE II scores indicated that patients admitted after closure of the unit were significantly sicker. Mortality rates increased after unit closure. However, the ratio of the actual mortality rate to the predicted mortality rate was lower in this system. Resource utilization remained similar, which is surprising in view of the increase in the severity of illness. Consequently, this article suggests the cost-effectiveness and probable clinical effectiveness of the closed unit format.

Ghorra and colleagues[47] retrospectively studied the conversion of an SICU from an open ($n = 125$) to a closed ($n = 149$) format. Again, primary care was provided by an intensive care team. There was a significant reduction in mortality rate, from 14% to 6% (ARR, 8; NNT, 12; OR, 0.38; 95% CI, 0.17 to 0.88,), and in complications from 56% to 44% (ARR, 12; NNT, 8). This was accompanied by a reduction in the number of consultations (from 0.6 to 0.4 per patient). The incidence of renal failure and the use of low-dose dopamine were higher in the open format, reflecting outdated approaches to critical illness.[48]

Multz and colleagues[49] retrospectively looked at outcomes in a community hospital before and after conversion to a closed ICU model and prospectively compared outcomes with a nearby hospital's open ICU. Although no significant differences in mortality rate were found in either arm of this underpowered study, there was a significant reduction in ICU LOS (retrospective, 6.1 versus 9.3 days; $p < 0.05$; prospective, 6.1 versus 12.6 days, $p < 0.0001$), hospital LOS (retrospective, 22.2 versus 31.2 days; $p < 0.02$; prospective, 19.2 versus 33.2 days; $p < 0.008$) and days of mechanical ventilation (retrospective, 3.3 versus 6.4 days; $p < 0.05$; prospective, 2.3 versus 8.5 days; $p < 0.0005$).

Treggiari and colleagues[50] studied outcomes for patients with acute lung injury in open versus closed ICUs. A total of 24 ICUs were evaluated, and complete data were available for 23; 13 units were closed and 11 were open. The hospital mortality rate was improved significantly in the closed versus open units (adjusted OR, 0.68; 95% CI, 0.53 to 0.89; $p = 0.004$). The presence of a consulting pulmonologist, presumably with critical care training and thus an "intensivist," did not appear to confer benefit in open ICUs.

Cooke and colleagues[51] conducted a secondary analysis of the data presented by Treggiari and colleagues[50] that examined the effect of a closed staffing model on tidal volume in patients with acute lung injury. The authors reviewed day 3 tidal volumes in open and closed units and found that those patients in closed ICUs received tidal volumes that were 1.40 mL/kg predicted body weight (PBW) lower than patients in open model ICUs (95% CI, 0.57 to 2.24 mL/kg PBW). Patients in closed ICUs were more likely (OR, 2.23; 95% CI, 1.09 to 4.56) to receive lower tidal volume (6.5 mL/kg PBW or less) and were less likely (OR, 0.30; 95% CI, 0.17 to 0.55) to receive a potentially injurious tidal volume (12 mL/kg PBW or greater) compared with patients cared for in open ICUs, independent of other variables.

Using data from a prospective cohort study, Nathens and colleagues[52] looked at mortality rates in trauma patients across 68 ICUs. After adjustment for differences in baseline characteristics, the relative risk of death in intensivist-model ICUs was 0.78 (95% CI, 0.58 to 1.04) compared with an open ICU model. The effect was greatest in the elderly (RR, 0.55; 95% CI, 0.39 to 0.77), in units led by surgical intensivists (RR, 0.67; 95% CI, 0.50 to 0.90), and in designated trauma centers 0.64 (95% CI, 0.46 to 0.88). It is worth noting that in this study, as in other studies of SICUs, high-volume surgical centers are more likely to have intensivists, and these factors may reinforce one another.[4,53,54]

Petitti and colleagues[55] assessed the association between the change to a closed-unit, intensivist-led system and mortality in injured patients at an urban Level I trauma center. A total of 18,918 patients were admitted to the ICU during periods of preintensivist, partial intensivist, and full-intensivist care. Mortality for patients older than age 65 years in the partial intensivist period was decreased relative to the preintensivist period (OR, 0.51; 95% CI, 0.31 to 0.84, $p < 0.05$); however, no added benefit was seen with the addition of a full-time intensivist. Changing to a closed unit configuration brought about improved survival rates in patients with less severe injuries and patients older than 65 years, but no improvement was seen in the survival of the group as a whole.

Tai and colleagues[56] retrospectively studied quality of patient care and procedure use in a MICU over two 3-month periods before ($n = 112$) and after ($n = 127$) change in unit organization. In the first period, an open model prevailed. In the second, an intensivist provided daytime care, acting as primary physician and gatekeeper, with rotational medical cover at night. There was a reduction in median LOS. Interestingly, the use of invasive monitors increased from 0% to 24% for arterial lines and from 0% to 5.5% for pulmonary artery catheters, without evidence of improvements in outcomes.

The introduction of a physician–manager for intensive care services (ICU director) has become universal. However, significant variability exists in the director's day-to-day involvement in medical care, protocols, bed management, and audit.

Manthous and colleagues[57] studied outcomes and educational standards in a medium-sized community hospital

in the year before (n = 459) and after (n = 471) the appointment of a director of critical care. The ICU mortality rate was reduced from 21% to 15% (ARR, 6%; NNT, 16; OR, 0.66; 95% CI, 0.47 to 0.93). This reduction in mortality rate was consistent for most disease processes and severity of illness. In addition, a significant reduction was seen in the hospital mortality rate from 34% to 25% (ARR, 9%; NNT, 11; OR, 0.63; 95% CI, 0.48 to 0.84). There was a concomitant reduction in mean stays in the ICU (from 5.0 ± 0.3 days to 3.9 ± 0.3 days; $p < 0.05$) and in the hospital (from 22.6 ± 1.4 days to 17.7 ± 1.0 days), along with an improvement in standard of knowledge of residents.

Mallick and et al[58] examined a 1991 survey by the Society of Critical Care Medicine of nearly 3000 ICUs to determine the effectiveness of the role of the ICU director. They concluded that significant involvement of the ICU director in the day-to-day operation of the unit reduced inappropriate bed occupancy, thus improving efficiency. Strosberg and colleagues[59] questioned nurse managers from 137 ICUs on the involvement of ICU directors in bed management at their hospitals. This revealed a perception of limited nocturnal availability, even though many hospitals had ICU directors.

Zimmerman and colleagues[40] looked at organizational issues in nine ICUs and determined that superior organization was characterized by a patient-centered culture, strong medical and nursing leadership, effective communication and coordination, and open, collaborative approaches to solving problems and managing conflict. They failed to equate superior organization to improved risk-adjusted survival rates.

Shortell and colleagues[60] examined risk-adjusted mortality rates in 42 ICUs involving 17,440 patients using APACHE III. They found that high-quality organization was associated with a lower risk-associated mortality rate, lower risk-adjusted LOS, lower nurse turnover, and higher patient and family member satisfaction. Examples of organizational excellence included technological availability, lack of diagnostic diversity, and caregiver interaction comprising the culture, leadership, coordination, communication, and conflict management abilities of the unit.

A large European study of ICU organization, EURICUS-1,[61] published in 1998, looked at the organizational characteristics of 89 ICUs in 12 European countries. It was determined that the optimal model of ICU organization—where the strategic apex of shared medical-nursing administration lies within the ICU—existed in only 12% of ICUs studied. Further, there was no clear concept of "intensive care," little planning or purposeful organization, and few defined objectives.[41]

In the pediatric ICU setting, Nishisaki and colleagues[62] conducted a retrospective study to monitor the impact of a transition from a 12-hour (n = 10,182) to a 24-hour (n = 8520) attending physician coverage model of in-hospital pediatric critical care. They found that implementation of 24-hour in-hospital pediatric critical care attending coverage was associated with a shorter duration of mechanical ventilation (median, 42 hours versus 56 hours; $p < 0.001$) and a shorter length of ICU stay (median, 2 days [interquartile range, 1 to 4] versus 2 days [interquartile range, 1 to 5]; adjusted $p < 0.001$). However, there was no difference in unit mortality (2.2% versus 2.5%; $p = 0.23$).

The Leapfrog group has proposed that intensive care services provided by telemedicine, involving an intensive care specialist covering several ICUs from a remote location,[63] constitute a reasonable surrogate for a full-time intensivist.[64] This has been a widely embraced approach to alternative intensivist staffing,[65] and some outcome benefit has been demonstrated.[66] Breslow and colleagues[63] showed that tele-ICU services improve outcomes (reduced hospital mortality rate, 9.4% versus 12.9%; RR, 0.73; 95% CI, 0.55 to 0.95) and reduce LOS (3.63 days [95% CI, 3.21 to 4.04] versus 4.35 days [95% CI, 3.93 to 4.78]). This approach should be envisioned as complementing and extending organized ICU services rather than manifesting an alternative model for critical care service delivery.

Telemedicine has been touted as a viable option to alleviate the increased demand for intensivist presence in ICUs. The data that exist on the impact of telemedicine indicate decreased mortality rates and ICU LOS.[63,67-70] However, some studies report conflicting results.[71,72]

Willmitch and colleagues[14] examined the institution of a telemedicine service in five separate hospitals and 10 ICUs. Charts of 24,566 patients were reviewed retrospectively for the baseline year and 3 years after telemedicine implementation. The results demonstrated statistically significant decreases in severity-adjusted hospital LOS of 14.2%, ICU LOS of 12.6%, and relative risk of hospital mortality of 23% in a multihospital health care system.

Young and colleagues[73] conducted a meta-analysis on the impact of telemedicine ICU coverage on in-hospital mortality rates, ICU LOS, and hospital LOS. A total of 41,374 patients were included in the meta-analysis, and tele-ICU coverage was associated with a reduction in the ICU mortality rate (OR, 0.80; 95% CI, 0.66 to 0.97; $p = 0.02$). There was no change in the overall in-hospital mortality rate. Similarly, tele-ICU coverage was associated with a reduction in ICU LOS (mean difference –1.26 days; 95% CI, –2.21 to –0.30; $p = 0.01$) but not in-hospital LOS.

Lilly and colleagues[74] performed a prospective stepped-wedge clinical practice study of 6290 adults admitted to both MICUs and SICUs. These patients were then monitored before and after the institution of an adult telemedicine unit. The hospital mortality rate was 13.6% during the preintervention period compared with 11.8% during the tele-ICU intervention period. The tele-ICU intervention period compared with the preintervention period was associated with higher rates of best clinical practice adherence as well as shorter hospital LOS (9.8 versus 13.3 days).

Evidence-based literature increasingly supports the value of telemedicine on ICU outcomes, but the actual volume of data supporting claims of lower mortality rates and decreased LOS is limited. Some fear that telemedicine will draw intensivists away from rural settings and toward more academic centers that are capable of supporting such programs. This change may exacerbate ICU staffing issues in rural areas and in smaller community hospitals.

In conclusion, the conversion of ICUs from open to closed formats and the appointment of an ICU medical director appears to confer modest benefits in terms of mortality rate, morbidity, resource utilization, and LOS. At least in part, these outcome benefits relate to more advanced critical care built on the intensivist model. Although telemedicine's fate remains unknown, it may well be a feasible option to offset the work hour burden of the 24-hour intensivist model.

AREAS OF UNCERTAINTY

The limited volume of published literature supports the appointment of intensive care specialists alongside the development of multidisciplinary critical care teams, standards-based care, and an integrated organizational structure. However, a number of significant limitations remain. The majority of reports were cohort studies using historical control subjects. Hawthorne effects cannot be discounted. Only one group, that by Hanson and colleagues,[25] concurrently studied patients in the same ICU. This study was limited by lack of randomization and multiple potentially confounding variables relating to selection bias. Similarly, the large cross-sectional studies by Pronovost and colleagues,[29] Dimick and colleagues,[28] and Nathens and colleagues[52] were limited by single diagnoses and the possibility that poorer outcomes related not to critical care but to hospital volume and expertise.[54] However, Pronovost and colleagues,[29] having corrected for these factors, demonstrated a threefold increase in mortality rate in hospitals without daily intensivist rounds. A number of the studies required statistical adjustments to demonstrate mortality rate differences.[19,22,27,47,52] This is consistent with validated prediction models.[75]

Another potential limitation is publication bias. Studies of this nature are performed by intensivists to promote their specialty. It is unlikely that studies published demonstrating worse outcomes will reach print. Conversely, a number of studies have been published in abstract form alone. When these are systematically reviewed with published data, support for the intensivist model persists.[34] Moreover, Pronovost and colleagues[29] have been unable to demonstrate publication bias in the literature.

The study by Levy and colleagues[35] may lead to a reassessment of the entire intensivist paradigm. Although the article reflects data-mining designed to examine workload, not outcomes, the results appear to be robust. However, the self-selection of highly functioning ICUs to the Project IMPACT database is problematic when applied to the population as a whole ("we measure what we value"), and the approach may examine an alternative model of ICU organization rather than a repudiation of the critical care concept.[36] Guidelines and standards used in these units were developed by intensivists in academic medical centers and adopted by community hospitals, and this may represent the ultimate example of the effectiveness of evidence-based medicine.

Wallace and colleagues[17] recently published an article examining the impact that a night-time intensivist has on ICU outcomes. They examined this impact in the setting of low-intensity daytime intensivist units versus high-intensity daytime staffing. With the use of the APACHE database, the authors retrospectively reviewed 65,752 admissions to 49 ICUs in 25 hospitals. Those ICUs with low-intensity staffing, defined as optional consultation with an intensivist, were shown to have a reduction in risk-adjusted in-hospital mortality rates (OR, 0.62; $p = 0.04$). However, those units with high-intensity staffing, defined as mandatory consultation with an intensivist or an intensivist as the primary decision maker, saw no added benefit with respect to the risk-adjusted in-hospital mortality rate (OR, 1.08; $p = 0.78$). These data mandate a reappraisal of the need for 24-hour staffing and add increased importance to the value of high-intensity daytime staffing. Although the choice of 24-hour coverage over intensive daytime coverage seems an obvious one, it is important to define what 24-hour coverage really adds to our repertoire as intensivists.

Intensivists appear to be valuable, but are they available? In 1997 intensivists cared for only 37% of critically ill patients.[2] This figure is expected to decline significantly over the next 20 years. Currently, 78.9% of intensivists are pulmonologists, 11.9% are internists, 6.1% are anesthesiologists, and 3.2% are surgeons. The percentage of intensivists who are anesthesiologists is declining.[13] In spite of these data, the Committee on Manpower for Pulmonary and Critical Care Services has determined that SICUs are particularly underserved by intensivists compared with MICUs.[2] In 1996 there were 130 graduates (50% were anesthesiologists) from surgically oriented critical care training programs compared with 464 from internal medicine–based programs.[2]

In 2000, 72% of the 1374 critical care fellows nationwide in training were in combined pulmonary and critical care programs. The number of internal medicine–trained fellows had fallen from 110 in 1998 to 86 in 2003. The number of critical care anesthesia fellows had fallen from 110 in 1998 to 86 in 2003.[76] This reflects the high opportunity cost of practicing critical care versus operating room activity.[13] Nevertheless, economically powerful patient advocate organizations[64] are demanding intensivist involvement in patient care. The conservative estimate by the Health Resources and Services Administration suggests that in 2000, we needed 3200 intensivists and had 1800, and by 2020, we will need 4300 but will have only slightly more intensivists than in 2000.[77,78] Some improvement may be forthcoming; for the 2011-2012 academic year, a total of 1957 trainees were enrolled in adult critical care medicine fellowships (i.e., surgery, anesthesia, medical critical care, and pulmonary/critical care).[16] Nonetheless, it is unlikely that this demand can be met[2,12] for the foreseeable future. Novel concepts such as telemedicine[66] may provide a bridge.

GUIDELINES

Although no specific guidelines exist, groups such as Leapfrog recommend that ICUs be staffed by dedicated intensivists.

AUTHORS' RECOMMENDATIONS

Most data support the contention that patient outcomes improve with the provision of an intensivist as part of an intensive care team. However, it is important to note that the data are heterogeneous, varying from daytime availability of an intensivist,[56] to "not consulted but available,"[25] to 24-hour coverage,[45] to complete service closure.[47] It is tempting to suggest that outcome improvement is related to the degree of involvement and responsibility of the critical care team, and, indeed, a dose–response relationship has been described[79,80]; however, more proof is required. Although recent data indicate that the institution of telemedicine may improve outcomes, the study by Wallace and colleagues[17] provides strong evidence that the main imperative is the transition to high-intensity coverage for the critically ill patient and night-time intensivist coverage; these associations appear only in settings with low-intensity coverage.

Although the intensivist model is ubiquitous outside the United States, the geographic variability in outcomes is significant.[75,81,82] Identifying the reason is difficult. Some factors worth considering are bed availability,[81] nurse and physician workload,[21,83] and practice patterns and resource availability.[84] Emerging evidence suggests that subspecialist intensive care units further improve outcomes.[85] Conversely, there is evidence that, in certain circumstances, intensivists may be associated with worse outcomes.[35] Perhaps this illustrates the paradox of intensive care: hospital mortality rates of intensive care patients can be manipulated by admission and transfer criteria and end-of-life decision making. By "cherry picking" admissions with likely more favorable outcomes, by transferring the sickest patients to alternative (specialist) units, and by delaying end-of-life decision making (e.g., by using long-stay ventilator facilities), more favorable outcomes may be presented without better health care delivered.

In summary, focused, standardized care with clear leadership, rapid specialist availability, and a well-developed team approach appears to be the optimal model for critical care organization.[27] Unquestionably, the demand for intensivists trained in anesthesiology will increase; the question is—are you in or are you out?[13]

A list of Accreditation Council for Graduate Medical Education (ACGME) accredited programs and sponsoring institutions can be found at www.acgme.org/adspublic [accessed 20.08.12].

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CHAPTER 42

Fast-Track Cardiac Anesthesia: What Works Best for Safety and Efficacy?

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INTRODUCTION

Opioid-based anesthesia emerged as a safe and effective way to maintain hemodynamic stability in patients undergoing cardiac surgery in the early 1970s.[1] This traditional anesthetic technique used large doses of long-acting opioids such as morphine and resulted in patients requiring postoperative endotracheal intubation and mechanical ventilation for up to 24 hours.[2] Limitations of morphine-based cardiac anesthesia (typical doses were 0.5 mg/kg to 1.0 mg/kg) included delayed anesthetic emergence and histamine-induced hypotension.[1-3] In an effort to address these limitations, fentanyl-based cardiac anesthesia (typical doses were 50 mcg/kg to 100 mcg/kg) was introduced in the late 1970s.[4] Fentanyl-based opioid anesthesia gradually became the standard cardiac anesthetic in the 1980s because of its comparatively shorter time to anesthetic emergence and its hemodynamic stability.[5] Titration of short-acting benzodiazepines such as midazolam was subsequently added to this technique in the early 1990s to enhance amnesia, lower the total fentanyl requirement, and shorten the stay in the intensive care unit (ICU).[6]

Throughout the 1990s coronary artery bypass grafting (CABG) case volumes soared and challenged concepts of postoperative care such as hospital costs and resource utilization.[7] Fast-track cardiac anesthesia (FTCA) emerged as a possible solution for streamlining perioperative care with a management protocol for rapid recovery after cardiac surgery.[8] FTCA involves tailoring the anesthetic plan to facilitate tracheal extubation within 6 hours after completion of cardiac surgery. Anesthetic design options to achieve this goal include limitation of the total dose of long-acting opioid and balanced anesthetic techniques with inhalational anesthesia, neuraxial blockade, or both.[9-12] A vital component for successful FTCA is the systematic implementation of an early tracheal extubation and an accelerated recovery protocol in the ICU.[13]

OPTIONS

The current time standard for defining FTCA varies between 4 and 8 hours after ICU admission.[14] Tracheal extubation within the operating room at the conclusion of cardiac surgery is termed *ultra-fast-track cardiac anesthesia* (UFTCA), and initial series have documented its feasibility and safety in select patients.[15,16] The possible additional clinical benefits of UFTCA and FTCA include early ambulation and a lower risk of infection through a decrease in ventilator exposure, requirements for invasive lines, and exposure to infection in the ICU setting.

EVIDENCE

Safety of Fast-Track Cardiac Anesthesia

Two large meta-analyses have analyzed the evidence for the safety of FTCA.[17,18] The first meta-analysis (total $N = 1800$; 10 randomized trials) reviewed morbidity and mortality in patients undergoing CABG or valve surgery with cardiopulmonary bypass.[17] Clinical trials that included off-pump CABG or neuraxial anesthetic techniques were excluded from this analysis. In this pooled dataset, FTCA significantly reduced the mean time to tracheal extubation by 8.1 hours, and the trend was toward reduced perioperative mortality (1.2% versus 2.7%; $p = 0.09$).[17] Furthermore, FTCA resulted in equivalent rates of major morbidities such as prolonged ICU stay, stroke, myocardial infarction, major bleeding, sepsis, major wound infection, and renal failure.[17]

The second meta-analysis (total $N = 871$; four randomized trials) included clinical trials with patients undergoing CABG or valve procedures.[18] Pooled data from all four trials demonstrated that FTCA significantly reduced the length of stay in both the ICU (weighted mean difference, 7.02 hours; 95% confidence interval [CI], −7.42 to −6.61; $p < 0.00001$) and hospital (weighted mean difference, 1.08 days; 95% CI, −1.35 to −0.82; $p < 0.05$).[18-22] Furthermore, FTCA resulted in equivalent perioperative mortality, myocardial ischemia, and risk of tracheal reintubation within the first 24 postoperative hours.

These favorable data from these two meta-analyses have led to the widespread implementation of FTCA.[23] A recent single-center retrospective analysis ($N = 7989$) confirmed the safety of FTCA in a real-world setting.[24] In this clinical study, FTCA resulted in equivalent mortality (odds ratio [OR], 0.92; 95% CI, 0.65 to 1.32;

$p = 0.66$), stroke (0.9% versus 1.3%; $p = 0.06$), myocardial infarction (5.2% versus 5.5%; $p = 0.61$), and acute renal failure (average incidence, 0.8%; $p = 0.84$).[24] The investigators concluded that FTCA adds no additional outcome risk in adult cardiac surgical patients.

An important limitation in FTCA is that the landmark clinical trials demonstrating its perioperative safety did not include high-risk patient groups. Collectively, these trials excluded patients with severe left ventricular systolic dysfunction, advanced lung disease, and advanced age (defined as age older than 70 years). Advanced age has been shown to be a risk factor for increased mortality rates and prolonged hospital stays in patients undergoing cardiac surgery.[25,26] A randomized FTCA trial showed that elderly patients (defined as age older than 70 years) had significantly prolonged tracheal extubation times ($p < 0.03$) and hospital stays ($p < 0.001$).[27] A second clinical trial confirmed that advanced age remains a risk factor for prolonged hospital stay after FTCA.[28] A third clinical trial ($N = 319$) noted that advanced age significantly delayed hospital discharge after cardiac surgery in a rapid recovery model ($p < 0.01$).[29] Even in a dedicated FTCA clinical milieu, advanced age remains a significant independent predictor for delayed tracheal extubation and prolonged ICU stay.[30] Anesthetic design can offset some of this excessive risk in the elderly after cardiac surgery. In the elderly, a randomized FTCA trial[31] demonstrated that propofol infusion and limitation of benzodiazepine significantly improved time to tracheal extubation ($p < 0.02$), time to readiness for ICU discharge ($p < 0.02$), and time to readiness for hospital discharge ($p < 0.04$).

Interest is growing in UFTCA, which has been defined as including tracheal extubation in the operating room after cardiac surgery.[31-34] Although multiple clinical trials have demonstrated the safety of UFTCA, randomized trials demonstrating clear advantages of UFTCA over FTCA are lacking.[31-34] The emergence of off-pump CABG within the last 15 years has facilitated the implementation of UFTCA.[35] In a large single-center series ($N = 1196$), 89% of patients undergoing off-pump CABG with UFTCA were successfully extubated in the operating room.[35] The tracheal reintubation rate was 2.5%. Independent predictors for avoiding operating room extubation included reoperation (OR, 3.9; $p < 0.001$), pre-existing renal disease (OR, 3.1; $p < 0.0001$), diabetes (OR, 1.7; $p < 0.007$), intra-aortic balloon pump placement (OR, 7.4; $p < 0.0001$), and total surgical time (OR, 3.7; $p < 0.0001$).[35] Recent single-center series have expanded the scope of this anesthetic approach by demonstrating the feasibility and safety of UFTCA for patients undergoing aortic valve replacement and surgery for congenital heart disease.[36-38]

Cost-Effectiveness of Fast-Track Cardiac Anesthesia

Given that FTCA is safe, the evaluation of its cost-effectiveness becomes relevant. The costs of a cardiac surgical procedure are significantly determined by operating room time, perioperative complications, and length of stay, in both the ICU and hospital. A randomized trial ($N = 100$ elective CABG cases) demonstrated that FTCA reduced total costs per case by 25%.[39] These significant savings were predominantly in reduced nursing and ICU costs. Furthermore, FTCA reduced ICU and hospital length of stay without increasing the perioperative complications, which add significantly to total cost per procedure.[39] A subsequent analysis by the same investigators demonstrated that FTCA significantly decreased resource utilization in the first year after CABG.[40]

The cost-effectiveness of FTCA depends on the implementation of a fast-track recovery protocol in the ICU and cardiac surgical ward.[13] FTCA is an essential component of a cost-effective fast-track recovery model.[41-43] Reduction of ICU length of stay in FTCA depends on reducing tracheal intubation times but also on a highly efficient hospital staffing model and smooth discharge ICU procedures.[44] This requires multidisciplinary collaboration and effective communication that is the basis for the recommendations in the recent multisociety CABG guidelines (Tables 42-1 and 42-2).

The maturation of minimally invasive mitral valve surgery has also resulted in multiple studies that document its safety, outcome advantages, and cost-effectiveness as compared with traditional mitral valve surgery via full

TABLE 42-1 Class I Recommendations for Anesthetic Considerations for CABG Surgery

Recommendation	Class and Evidence
Anesthetic management directed toward early postoperative extubation and accelerated recovery of low- to medium-risk patients undergoing uncomplicated CABG is recommended	I (Level B)
Multidisciplinary efforts are indicated to ensure an optimal level of analgesia and patient comfort throughout the perioperative period	I (Level B)
Efforts are recommended to improve interdisciplinary communication and safety in the perioperative environment (e.g., formalized checklist-guided multidisciplinary communication)	I (Level B)
A fellowship-trained anesthesiologist (or experienced board-certified practitioner) credentialed in the use of perioperative transesophageal echocardiography is recommended to provide or supervise anesthetic care of patients who are considered to be at high risk	I (Level C)

CABG, coronary artery bypass graft.

Adapted from the following guideline: Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:2610–42.

TABLE 42-2 Classes II and III Recommendations for Anesthetic Considerations for CABG Surgery

Recommendation	Class and Evidence
Volatile anesthetic-based regimens can be useful in facilitating early extubation and reducing patient recall	IIa (Level A)
The effectiveness of high thoracic epidural anesthesia/analgesia for routine analgesic use is uncertain	IIb (Level B)
Cyclooxygenase-2 inhibitors are not recommended for pain relief in the postoperative period after CABG	III (Level B)
Routine use of early extubation strategies in facilities with limited backup for airway emergencies or advanced respiratory support is potentially harmful	III (Level C)

CABG, coronary artery bypass graft.
Adapted from the following guideline: Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:2610–42.

sternotomy.[45-49] This surgical evolution is also under way in aortic valve replacement and off-pump CABG, further reducing operative time and anesthetic requirements and hastening postoperative recovery.[50-53] This paradigm shift in cardiac surgery will likely continue to result in significant reductions in health resources utilization and enhanced cost-effectiveness. Because UFTCA and FTCA are linked to this changing perioperative cardiovascular paradigm, they will also further contribute to this robust cost-effectiveness.

Optimal Anesthetic Technique for Fast-Track Cardiac Anesthesia

The evidence base for FTCA demonstrates that it is safe and cost-effective, as already outlined. The cardiac anesthetic has evolved significantly since the emergence of high-dose opioid anesthesia in the 1970s and 1980s.[1-5] In the 1990s, the rapidly growing costs of health care and the soaring volume of cardiac surgery provided the impetus for the birth of FTCA and now UFTCA. The purpose of this section is to review the evidence base for the various anesthetic options in FTCA and UFTCA.

A major trend in FTCA has been to reduce the total dose of the long-acting opioid component of the general anesthetic. Multiple clinical trials have demonstrated the clinical safety and efficacy of this approach with shorter-acting intravenous opioids such as alfentanil, sufentanil, and remifentanil.[54-58] Although this approach has become important in FTCA and UFTCA, it is essential that the anesthetic design not compromise postoperative analgesia.[59] Adequate pain control is essential to safe FTCA. Increased pain will expose patients to unnecessary tachycardia and myocardial oxygen demand, putting the patient at risk for myocardial ischemia.

Intrathecal morphine has been studied as a component of FTCA for its ability to both reduce the systemic opioid dosage and provide sustained postoperative analgesia.[60-62] A recent meta-analysis (cumulative $N = 1106$; 25 randomized trials)[11] documented that spinal analgesia in cardiac surgery does not significantly reduce perioperative mortality (risk difference, 0.00; 95% CI, –0.02 to 0.02; $p = 1.0$), perioperative myocardial infarction (risk difference, 0.00; 95% CI, –0.03 to 0.02; $p = 0.77$), and hospital length of stay (weighted mean difference, –0.28 days; 95% CI, –0.68 to –0.13; $p = 0.18$). Given the concern about neuraxial hematoma in anticoagulated cardiac surgical patients, the investigators concluded that these neutral data discourage further randomized clinical trials of spinal analgesia for cardiac surgery. Furthermore, a recent meta-analysis of remifentanil in cardiac surgery (cumulative $N = 1473$; 16 randomized trials)[63] demonstrated significantly decreased duration of postoperative mechanical ventilation (weighted mean difference, –139 minutes; 95% CI, –244 to –32; $p = 0.01$), cardiac troponin release (weighted mean difference, –2.08 ng/mL; 95% CI, –3. 93 to –0.24; $p = 0.03$), and hospital length of stay (weighted mean difference , –1.08 days; 95% CI, –1.60 to –0.57; $p < 0.0001$). Despite these advantages, remifentanil exposure did not significantly reduce perioperative mortality (OR, 0.76; 95% CI, 0.17 to 3.38; $p = 0.72$).[63]

The role of thoracic epidural analgesia (TEA) in FTCA has also received considerable recent attention. A recent randomized trial in off-pump CABG ($N = 226$; single-center) demonstrated that TEA as a component of FTCA significantly reduced arrhythmias (OR, 0.41; 95% CI, 0.22 to 0.78; $p = 0.006$), median duration of mechanical ventilation (hazard ratio, 1.73; 95% CI, 1.31 to 2.27; $p < 0.001$), perioperative pain (OR, 0.07; 95% CI, 0.03 to 0.17; $p < 0.001$), and hospital length of stay (hazard ratio, 1.39; 95% CI, 1.06 to 1.82; $p = 0.017$).[64] In contrast, a second recent randomized controlled trial[65] demonstrated that TEA as a component of FTCA failed to reduce important clinical outcomes such as mortality, stroke, myocardial infarction, pulmonary complications, and renal failure either at 30 days ($P = 0.23$) or at 1 year ($p = 0.42$) postoperatively. An accompanying editorial[66] suggested that the evidence base currently supports TEA in FTCA for quality of postoperative recovery rather than for major organ-based clinical outcome improvement.

This controversy about TEA as a component of FTCA has not been resolved by recent meta-analyses.[12,67] The first recent meta-analysis (cumulative $N = 2366$; 33 randomized trials)[12] determined that TEA in cardiac surgery reduced duration of mechanical ventilation (weighted mean difference, –2.48 hours; 95% CI, –2.64 to –2.32; $p < 0.001$), mortality and myocardial infarction as a composite endpoint (OR, 0.61; 95% CI, 0.40 to 0.95; $p = 0.03$), and the risk of acute renal failure (OR, 0.56; 95% CI, 0.34 to 0.93; $p = 0,02$). In contrast, the second meta-analysis (cumulative $N = 2731$; 28 studies)[67] demonstrated that TEA in cardiac surgery did not reduce mortality (risk ratio, 0.80; 95% CI, 0.40 to 1.64),

myocardial infarction (risk ratio, 0.80; 95% CI, 0.52 to 1.24), and stroke (risk ratio, 0.59; 95% CI, 0.24 to 1.46). In this analysis, TEA did significantly reduce the risk of respiratory complications (risk ratio, 0.53; 95% CI, 0.40 to 0.69) and arrhythmias (risk ratio, 0.68; 95% CI, 0.50 to 0.93).[67] This ongoing controversy in the evidence base for TEA in FTCA is the rationale for the Class IIb recommendation in recent multisociety CABG guidelines (see Table 42-2).[68] Furthermore, the risk of neuraxial hematoma cannot be assessed in this evidence base because the cumulative cohort size is still too small.[66]

The possibility of UFTCA with high TEA as the sole anesthetic has recently gained attention.[69-71] Although this technique is feasible and appears safe so far, current trials demonstrate that it is still in the pilot phase.[69-71] This type of FTCA has not yet become part of mainstream practice; thus it cannot be advocated at this point.

Transcatheter Aortic Valve Replacement and Fast-Track Cardiac Anesthesia

Patients with severe aortic stenosis and excessive operative risk are now eligible for transcatheter aortic valve replacement (TAVR), principally via the transfemoral and transapical approaches.[72] This revolutionary therapy has given high-risk patients the option to receive a prosthetic aortic valve replacement without the stress of sternotomy and cardiopulmonary bypass.[72] Because TAVR uses a minimally invasive surgical approach, the role of FTCA and UFTCA has been discussed and debated.[73-76] Because transapical TAVR requires a minithoracotomy for surgical access to the left ventricular apex, the typical anesthetic design has entailed a balanced general anesthetic.[73] Transarterial TAVR via the subclavian or femoral approach is feasible with general anesthesia or sedation with a local anesthetic.[77-80] The choice of anesthetic technique varies according to patient criteria and heart team preference and experience.

Sedation for transarterial TAVR is not only feasible but it can also improve cost-effectiveness and shorten patient recovery.[77-80] A limitation of this technique may be the difficulty in performing transesophageal echocardiography.[81,82] One solution is to use transesophageal echocardiography during transarterial TAVR with noninvasive ventilation that uses a tailored mask.[78] A second solution is to relinquish imaging with transesophageal echocardiography in this setting, as it is not absolutely required during transarterial TAVR because the prosthetic valve can be adequately positioned with fluoroscopy.[81] A second limitation of sedation for transarterial TAVR is the significant possibility of procedure-related complications requiring urgent conversion to general anesthesia (Box 42-1).[79] Furthermore, in addition to procedural complications, general anesthesia may be indicated when patient suitability for sedation may be significantly compromised by comorbidities such as borderline mental status, chronic back pain, severe chronic lung disease, and morbid obesity.

At this time, no randomized prospective controlled trials have compared sedation and general anesthesia for transarterial TAVR. Retrospective analyses have demonstrated the feasibility of sedation at multiple centers.[77-80]

BOX 42-1 Complications Associated with Transcatheter Aortic Valve Replacement Requiring Possible Conversion to General Anesthesia

- Persistent ventricular fibrillation after rapid ventricular pacing
- Coronary artery occlusion
- Major arterial bleeding
- Structural valve failure
- Prosthesis embolization
- Aortic root rupture
- Aortic dissection
- Pericardial tamponade
- Lung injury
- Prolonged procedure

It is important to realize that this technique is also a function of heart team experience: typically, sedation is introduced after the learning curve with TAVR has been completed in the setting of general anesthesia.[76,77] The experienced anesthesia TAVR team is ideally best suited to introduce sedation for select patients scheduled for transarterial TAVR.[76,77] In summary, sedation with local anesthesia for transarterial TAVR should be considered for suitable patients at experienced centers. In patients requiring general anesthesia, FTCA techniques should be used to facilitate prompt tracheal extubation and rapid recovery.

AREAS OF UNCERTAINTY

The mainstream application of off-pump CABG has significantly aided the generalization of FTCA.[35] Debate is still ongoing about the clinical advantages of each technique for CABG.[83,84] While this controversy continues, little doubt exists that off-pump CABG significantly reduces resource utilization and cost per procedure due to clinical effects such as reduced bleeding and transfusion, decreased ventilator times, faster recovery, as well as shorter ICU and hospital stays.[85,86] The integration of FTCA for patients undergoing off-pump CABG will only further augment the overall cost-effectiveness of this procedure, especially in high-volume settings.[35,43]

GUIDELINES

Based on global clinical experience and safety with FTCA, the recent multisociety CABG guidelines include recommendations about FTCA (refer to Tables 42-1, 42-2, 42-3, and 42-4).[68] This guideline set is available at www.americanheart.org (section on statements and practice guidelines [accessed 25.06.12]). The level I recommendations support FTCA in non–high-risk CABG patients (see Table 42-1). It is essential that the perioperative practice milieu for FTCA be characterized by

TABLE 42-3 Definition of Classification Scheme for Clinical Recommendations

Clinical Recommendations	Definition of Recommendation Class
Class I	The procedure/treatment should be performed (benefit far outweighs the risk)
Class IIa	It is reasonable to perform the procedure/treatment (benefit still clearly outweighs risk)
Class IIb	It is not unreasonable to perform the procedure/treatment (benefit probably outweighs the risk)
Class III	The procedure/treatment should not be performed because it is not helpful and may be harmful (risk may outweigh benefit)

From American Heart Association. Methodologies and Policies from the ACC\AHA Task Force on Practice Guidelines, <http://my.americanheart.org/professional/StatementsGuidelines/PoliciesDevelopment/Development/Methodologies-and-Policies-from-the-ACCAHA-Task-Force-on-Practice-Guidelines_UCM_320470_Article.jsp>; 2012 [accessed 08.07.12].

TABLE 42-4 Definition of Supporting Evidence for Clinical Recommendations

Level of Evidence	Definition of Evidence Level
Level A	Sufficient evidence from multiple randomized trials and/or meta-analyses
Level B	Limited evidence from a single randomized trial or multiple nonrandomized studies
Level C	Case studies and/or expert opinion

From American Heart Association. Methodologies and Policies from the ACC\AHA Task Force on Practice Guidelines, <http://my.americanheart.org/professional/StatementsGuidelines/PoliciesDevelopment/Development/Methodologies-and-Policies-from-the-ACCAHA-Task-Force-on-Practice-Guidelines_UCM_320470_Article.jsp>; 2012 [accessed 08.07.12].

multidisciplinary approaches to communication, safety, and patient comfort (see Table 42-1). Furthermore, the involvement of fellowship-trained anesthesiologists is strongly recommended (see Table 42-1). The guidelines also stress that early tracheal extubation strategies in FTCA must take place in clinical settings with advanced respiratory support and adequate backup for airway emergencies (see Table 42-2). Cardiac anesthesia teams that are interested in implementing FTCA must integrate their anesthetic design and perioperative care with the rest of the health care team to ensure optimal safety and success in the delivery of this streamlined perioperative approach.

AUTHORS' RECOMMENDATIONS

Fast-track cardiac anesthesia (FTCA) is feasible, safe, and effective. This anesthetic design should be strongly considered in low-to-medium risk patients undergoing coronary artery bypass grafting (CABG), single valve repair or replacement, or combined CABG–single valve repair/replacement. Furthermore, FTCA and ultra-fast-track cardiac anesthesia are increasingly relevant in the mainstream application of minimally invasive cardiac surgery. FTCA should be used for patients undergoing transcatheter aortic valve replacement, regardless of the surgical approach. Careful consideration is required to tailor and translate anesthetic design for success at a given medical institution. Current principles of FTCA include a balanced technique, use of shorter acting opioid alternatives, an expanded role for volatile anesthetics, and a limited role for major regional techniques. The success of FTCA as an integrated component for rapid recovery after cardiac surgery depends on multidisciplinary collaboration with careful attention to detail and team communication in the operating room, intensive care unit, and throughout the subsequent hospital stay. These principles have been summarized in the accompanying tables.

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CHAPTER 43

Can We Prevent Recall during Anesthesia?

T. Andrew Bowdle, MD, PhD

INTRODUCTION

Three large prospective studies of the incidence of intraoperative awareness from Australia, Europe, and North America suggest that the overall rate is in the range of 0.1% to 0.2% or 1 to 2 per 1000 patients.[1-3] Intraoperative awareness can be a minor or a major complication, depending on the severity and the response of the individual patient; in severe cases post-traumatic stress disorder may occur.[4-6] In select patient populations the rate of intraoperative awareness may be substantially higher, such as in cardiac surgery patients, in which the rate has been reported to be in the range of 0.4% to 1%.[3,7-12] Prospective studies of intraoperative awareness in children found a rate of 0.8% to 1.1%.[13, 14] Conversely, the rate of intraoperative awareness may be lower in a particular setting. A retrospective analysis of quality assurance data from a single medical center suggested that the incidence of intraoperative awareness was 0.0068% or 1 per 14,560 patients.[15] Methodologic criticisms can be made of all of these studies of the incidence of intraoperative awareness.[16] However, as a whole, the literature suggests that intraoperative awareness is a significant problem. Many anesthesiologists find a rate of intraoperative awareness in the vicinity of 0.1% to be unacceptably high. Most patients affected by intraoperative awareness find the experience to be unacceptable, especially if they experience pain and anxiety.[1] Can we prevent recall during anesthesia or, at least, lower the rate substantially?

OPTIONS

Some episodes of intraoperative awareness are caused by specific, identifiable errors in anesthetic drug administration. Examples of these errors include the following:

1. Administration of a muscle relaxant instead of a hypnotic during induction of anesthesia, resulting in an awake, paralyzed patient
2. Unrecognized failure of a pump to deliver an intravenous hypnotic drug such as propofol (see Rowan[17] for a particularly vivid example)
3. An unrecognized empty vaporizer

Thus prevention of drug administration errors could be useful for reducing intraoperative awareness. Discussion of drug administration errors and strategies for prevention are beyond the scope of this chapter, and readers are referred to previous publications.[18-23]

Many, if not most, cases of intraoperative awareness occur without a specific error in drug administration and are probably related to an unusually large anesthetic dose requirement, due to either lower than average sensitivity to one or more drugs or faster than average clearance of one or more drugs. Large variation between individuals in anesthetic drug effect or anesthetic drug clearance is well-documented for a variety of anesthetic drugs.[24] Identification of higher risk individuals in advance and administration of larger doses of anesthetic to these individuals might reduce the rate of intraoperative awareness. Unfortunately, a practical clinical method for identifying such individuals does not currently exist.

Patients receiving nondepolarizing muscle relaxants during the maintenance phase of anesthesia may be at greater risk of intraoperative awareness, presumably because they may not be able to move as readily, thereby giving a clue to the anesthesiologist that the anesthetic depth is inadequate.[2] Some anesthesiologists take the approach of using as small a dose of muscle relaxant as possible to provide surgical exposure, with the idea that if patients are too lightly anesthetized they will still be able to move. This practice probably makes sense, although it is clear from case reports that patients may not move during an episode of intraoperative awareness even in the absence of neuromuscular blocking drugs.[25]

Another option could be to give all patients very large doses of anesthetic drugs that would be adequate for even the least sensitive patient. The drawbacks to this approach are numerous, including cost, the potential for slow wake up, and cardiovascular side effects, not to mention that there are no data that show what dose of anesthetic drug would be large enough to prevent intraoperative awareness under every circumstance in every patient.

Likewise, no particular drug has ever been shown to be uniquely reliable for preventing awareness in every circumstance in every patient; intraoperative awareness has been reported in patients receiving apparently adequate doses of almost every possible anesthetic agent. The available evidence suggests that total intravenous anesthesia has the same risk of intraoperative awareness as inhalational anesthesia.[2,26-28]

Finally, there is the option to somehow monitor the depth of anesthesia and titrate anesthetic drugs accordingly. Hypothetically, such an approach might prevent intraoperative awareness by identifying the patients who require larger doses of anesthetic drugs. The rest of this chapter will focus on this last approach.

EVIDENCE

Electroencephalography (EEG) has been the most widely applied technology for measuring anesthetic depth. Auditory evoked potentials have also been used either alone or in combination with EEG. For a comprehensive review of the methodology of EEG and auditory evoked potentials to measure anesthetic depth, the reader is referred to previous publications.[29,30]

Although it may seem reasonable that depth of anesthesia monitoring would reduce the incidence of intraoperative awareness, that outcome was certainly not assured. The opposite hypothesis was entertained by some—that depth of anesthesia monitoring would actually increase the incidence of intraoperative awareness because numerous studies had previously shown that, on average, patients received less anesthetic drug when monitored with an EEG depth of anesthesia monitor.[31]

Four studies have suggested that intraoperative monitoring with EEG (specifically, the bispectral index [BIS] monitor) can significantly reduce the incidence of intraoperative awareness (Table 43-1). The first was a retrospective case-comparison study of 5057 consecutive BIS-monitored patients from two hospitals in Sweden compared with 7826 non–BIS-monitored patients from the same institutions.[32] Two cases of intraoperative awareness occurred in the BIS-monitored series compared with 14 in the non–BIS-monitored case-matched control group. This difference was statistically significant ($p < 0.039$).

The second study was a prospective, randomized, international multicenter trial of 2463 patients at high risk of intraoperative awareness (e.g., cardiac, trauma, obstetric patients) assigned randomly to BIS or non-BIS groups (the so-called B-AWARE trial).[9] High-risk patients were chosen for this trial for the purpose of increasing the statistical power of the study. Two cases of intraoperative awareness occurred in the BIS-monitored group compared with 11 in the non–BIS-monitored group. Again, the difference was statistically significant ($p = 0.022$).

Avidan's group has published two prospective, randomized trials[33,34] that compared two interventions intended to reduce the incidence of awareness: BIS monitoring (target BIS range, 40 to 60) and analysis of targeted end-tidal anesthetic gas concentration (ETAC) (target range, 0.7 to 1.3 minimum alveolar concentration [MAC], with gas analyzers audibly alarmed at these limits). The first of these trials was a single center study involving approximately 2000 patients,[33] and the second was a multicenter study involving approximately 5800 patients.[34] The patients were required to be at "high risk" of intraoperative awareness, estimated to be perhaps 1%, based on a specific set of criteria. Approximately 25% to 30% of the patients underwent cardiac surgery. BIS and ETAC data were collected for both groups, but BIS values were not visible in the operating room for the ETAC group. Patients were assessed for intraoperative awareness three times, at 0 to 24 hours, 24 to 72 hours, and 30 days after extubation. Classification of no awareness, possible awareness, or definite awareness was made by a panel of reviewers unaware of monitoring allocation.

There were 13 cases of definite awareness in the two studies by Avidan et al combined, which yielded an overall incidence of 0.17%. There were nine cases of definite awareness in the BIS-monitored groups and four cases in the ETAC groups. No significant difference was found in the incidence of definite awareness between BIS and ETAC groups in either study. Among the patients with definite awareness in the BIS-monitored groups, four of the patients had some BIS values greater than 60 (BIS values less than 60 are generally considered to be desirable for the purpose of avoiding intraoperative awareness), and five of the patients did not have any BIS values greater than 60. All patients with definite awareness in the ETAC groups had some ETAC values less than 0.7 MAC (although there were patients with "possible awareness" without any ETAC values less than 0.7 MAC). Interpretation of the data is complicated by substantial amounts of missing ETAC and BIS data. Six of the BIS-monitored patients with definite awareness had epochs of missing BIS data lasting as long as 90 minutes. No explanation for the missing data was provided. One cannot help but wonder whether intraoperative awareness may have occurred during an epoch of missing BIS data in the BIS-monitored patients, and whether the availability of BIS data would have enabled

TABLE 43-1 **Summary of Clinical Trials of Bispectral Index (BIS) Monitoring for Reduction of Intraoperative Awareness**

Ekman et al, 2004[32]	5057 consecutive BIS-monitored patients compared with 7826 non–BIS-monitored case-control patients	Two hospitals in Sweden	Two cases of intraoperative awareness in BIS-monitored group versus 14 in non–BIS-monitored group ($p < 0.039$)
Myles et al, 2004, "B-AWARE" trial[9]	Randomized, prospective; patients at high risk of awareness: 1225 BIS-monitored, 1238 non–BIS-monitored standard practice	International, 21 hospitals, most in Australia	Two cases of intraoperative awareness in BIS-monitored group versus 11 in non–BIS-monitored group ($p = 0.022$)
Avidan et al, 2008[33]	Randomized, prospective; patients at high risk of awareness: 967 BIS-guided, 974 target end-tidal anesthetic gas–guided	Single center	Two cases of definite intraoperative awareness in BIS group; two cases in targeted end-tidal anesthetic group
Avidan et al, 2011[34]	Randomized, prospective; patients at high risk of awareness: 2861 BIS-guided, 2852 end-tidal anesthetic gas–guided	Three centers	Seven cases of definite awareness in BIS group, 2 cases in targeted end-tidal anesthetic group ($p = 0.98$)

the anesthesia providers to prevent awareness in these patients. The argument can be made that no monitoring device is able to provide usable data under all circumstances, and the prevalence of missing data contributes (negatively) to the overall performance and usefulness of any monitor. Nevertheless, it would be very valuable to distinguish intraoperative awareness that occurs with BIS values in the target range (less than 60) from intraoperative awareness that occurs in the absence of usable BIS data.

The B-AWARE trial by Myles and colleagues[9] was a comparison of BIS monitoring with "standard practice" in high-risk patients. The standard practice group had an incidence of awareness of approximately 1%, which was the expected incidence, compared with approximately 0.2% in the BIS-monitored group, which was a statistically significant difference in favor of BIS monitoring. The studies by Avidan and colleagues[33,34] were not a comparison of BIS monitoring with standard practice; rather, they were a comparison of BIS monitoring with another intervention in which practitioners were instructed to keep ETACs within a particular range with the use of gas monitor audible alarms set to activate when the concentrations were outside the prescribed range. Given that the expected incidence of awareness in the studies by Avidan and colleagues[33,34] was approximately 1% (as estimated by the authors), and the observed overall incidence of definite awareness was less than 0.2% with BIS monitoring or ETAC, one could conclude that BIS monitoring and targeted ETAC analysis were similarly effective in reducing the expected incidence of intraoperative awareness. Unfortunately, Avidan and colleagues[33,34] did not have a true standard practice control group for comparison, so one cannot know with certainty what the incidence of intraoperative awareness would have been in their patients without either BIS monitoring or targeted ETAC analysis.

It may be instructive to look more closely at patients who have had intraoperative awareness, despite the use of a BIS monitor. In the Swedish case-control study, two BIS-monitored patients had intraoperative awareness, both of which occurred during intubation, with a BIS value greater than 60.[32] In the first multicenter randomized prospective trial (B-AWARE), two BIS-monitored patients had intraoperative awareness, one during laryngoscopy with a BIS value of 79 to 82 and one during cardiac surgery with a BIS value of 55 to 59.[9] In this later case, intraoperative awareness occurred despite BIS values in the recommended range. In the studies by Avidan et al,[33,34] two patients with intraoperative awareness had a complete record of BIS data (no missing data) and no BIS values greater than 60. Despite the possibility that intraoperative awareness can occur with a BIS value less than 60, the use of BIS resulted in reduction of the incidence of intraoperative awareness from about 1% (either an actual measured incidence as reported by Myles and colleagues[9] or an expected incidence from Avidan et al[33,34]) to about 0.2% in both the Myles and Avidan studies, which suggests that BIS is useful.

Given that intraoperative awareness can occur at a BIS value less than 60 (or ETACs greater than 0.7 MAC), it is important to use the traditional methods of detecting light anesthesia (e.g., movement and vital signs) and give reasonable doses of anesthetic drugs, regardless of the BIS value—those who understand BIS technology have never seriously suggested otherwise. As a general principle, the wise practitioner realizes that no monitoring device, single number, or data point should be used as the sole guide to patient care.

Intraoperative awareness appears to be less likely at depth-of-anesthesia monitoring values in the recommended range (e.g., less than 60 for BIS); however, it is evidently possible for BIS values to exceed the recommended range without the occurrence of intraoperative awareness. In addition, the sufficient conditions to produce intraoperative awareness are not known. The Swedish case-control study[32] reported the distribution of BIS values greater than 60, as found in 5057 consecutive BIS-monitored patients. They found average times with BIS values greater than 60 to be 1.9 minutes during induction of anesthesia (range, 0 to 10 minutes) and 2.0 minutes during maintenance (range, 0 to 178 minutes). As noted previously, only two of these patients had intraoperative awareness.

There have been very few published case reports of individual patients with intraoperative awareness in the presence of BIS values in the recommended range, that is, less than 60. In two published case reports of purported intraoperative awareness with BIS values less than 60, the BIS data were taken retrospectively from an anesthesia record, not from the continuous record stored in the memory of the monitor.[35,36] Because BIS values are recorded intermittently on a handmade anesthesia record, it is possible that the BIS values pertinent to the episode of intraoperative awareness may not have appeared on the anesthesia record. In the instance of one of the case reports,[34] when the complete record was obtained at a later time from the flash memory of the monitor, there were substantial time periods with BIS values greater than 60 that were not recorded on the anesthesia record.[37]

AREAS OF UNCERTAINTY

Whether the studies discussed previously constitute a convincing argument that BIS monitoring reduces the incidence of intraoperative awareness depends perhaps on whether one thinks the glass is half empty or half full. It would be desirable to have additional trials of depth of anesthesia monitoring for the prevention of intraoperative awareness. However, by historical standards, the fact that four studies suggest better outcomes for patients monitored with a particular device is significant. By comparison, it has not been possible to demonstrate that pulse oximetry affects outcome,[38-40] and most studies suggest that the use of pulmonary artery catheters produces worse outcomes or outcomes that are no better than when pulmonary artery catheters are not used.[41-43] The BIS monitor is probably the only monitoring device used in anesthesiology that has been shown by a clinical trial to improve outcome.

The BIS monitor is not the only depth of anesthesia monitor available today. Several other monitors use EEG,

auditory evoked potential monitoring, or both to assess anesthetic depth.[30] Although similar in principle to BIS, each of these monitors uses different hardware and software. Whether the use of non-BIS depth of anesthesia monitors will result in a reduction in the rate of intraoperative awareness is unknown.

As noted previously, intraoperative awareness can occur during the use of a BIS monitor. There are limitations to the monitor that have to be taken into account.[30] An assessable, suitably artifact-free EEG signal is not available under all circumstances. A time lag of approximately 15 to 30 seconds is related to EEG processing; thus the BIS number lags slightly behind the current anesthetic state. This may be especially important during induction and intubation, when events occur relatively quickly and BIS processing may lag significantly behind. Interestingly, in the four studies of BIS for the prevention of intraoperative awareness, at least three cases of intraoperative awareness associated with BIS values greater than 60 occurred during laryngoscopy or intubation in patients monitored with BIS. The circumstances under which intraoperative awareness occurs in some patients with BIS values greater than 60, but not others, are not understood. Clearly, not all patients having values greater than 60 experience intraoperative awareness. Some patients with BIS values less than 60 may experience intraoperative awareness.

One wonders whether the combined, simultaneous application of BIS monitoring and ETAC (as described by Avidan et al[33,34]) would result in a lower incidence of intraoperative awareness than either modality alone. A major shortcoming of the ETAC approach is that it does not take into account the effects of intravenous anesthesia drugs. An unpublished trial[44] is comparing BIS monitoring with a calculated anesthetic dose that attempts to take intravenous and inhaled anesthetics into account.

The first of the trials by Avidan et al, the B-Unaware trial,[33] has also been subjected to a subanalysis of the relationship between BIS values and volatile anesthetic concentrations.[45] The results of this subanalysis have been interpreted by the authors to suggest that BIS does not accurately reflect the effects of volatile anesthetics because they found that BIS correlated poorly with anesthetic concentration. They concluded that "BIS is insensitive to clinically significant changes in ETAC." These conclusions should be interpreted cautiously: 841 of 1941 patients were excluded from the subanalysis because of "manually-recorded or undersampled ETAC recordings"; interestingly, these issues regarding the quality of ETAC data were not mentioned in the original reports of the two clinical trials by Avidan et al.[33,34] More importantly, the authors may have misinterpreted some fundamental aspects of monitoring anesthetic depth with EEG. Intravenous anesthetics, such as opioids, benzodiazepines, propofol, and other agents, have significant effects on the EEG and BIS. These drugs were not accounted for in the subanalysis, except that patients receiving greater than 2 mg of midazolam or greater than 50 mg of morphine (or equivalent) were called out in the general estimating equation that was fit to the data. Clearly, doses of morphine less than 50 mg (or equivalent) can have a substantial effect on the EEG and the BIS; for example, Bouillon et al[46] found that remifentanil and propofol had additive effects on BIS. In addition, the level of surgical stimulation has a substantial effect on the responsiveness of the patient during anesthesia, and this can be reflected in the EEG and the BIS; for example, Ropcke et al[47] found that surgical stimulation shifted the desflurane concentration–EEG effect curves for BIS toward higher desflurane concentrations (Figure 43-1). Therefore because of the effects of intravenous anesthetic drugs on BIS and the effects of surgical stimulation on BIS, a close correlation between BIS and ETAC would not necessarily be expected.

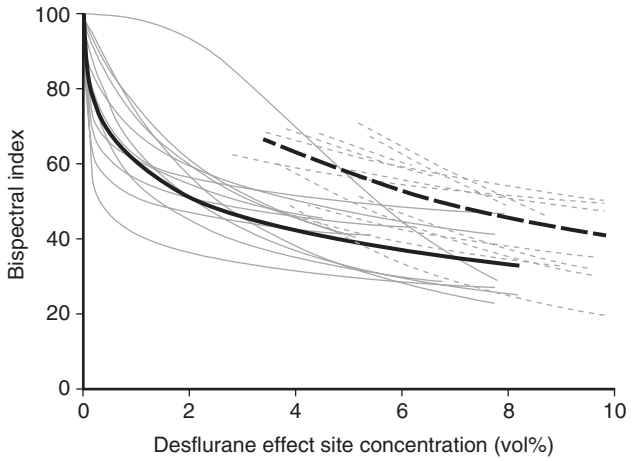

FIGURE 43-1 ■ Desflurane Concentration–Electroencephalographic Effect Curves with and without Surgical Stimulation. *Light solid line,* individual patients without surgical stimulation; *light dashed line,* individual patients during surgical stimulation; *heavy solid line,* model for patients without surgical stimulation; *heavy dashed line,* model for patients during surgical stimulation.

GUIDELINES

The American Society of Anesthesiologists published a practice advisory on intraoperative awareness and monitoring in 2006.[48] It is important to note that an advisory does not have the force of a practice guideline or standard of care. As noted in the publication, "Practice advisories are not supported by scientific literature to the same degree as are standards or guidelines because sufficient numbers of adequately controlled studies are lacking." The reader is urged to read the complete text of the advisory, but the bottom-line recommendation follows: "It is the consensus of the Task Force that the decision to use a brain function monitor should be made on a case-by-case basis by the individual practitioner for selected patients….It is the opinion of the Task Force that brain function monitors currently have the status of the many other monitoring modalities that are currently used in selected situations at the discretion of individual clinicians."

The Joint Commission on Accreditation of Healthcare Organizations has published a "sentinel event alert"

concerning intraoperative awareness (available at www.jointcommission.org/sentinel_event_alert_issue_32_preventing_and_managing_the_impact_of_anesthesia_awareness/ [accessed 11.06.12]). The reader is urged to read the complete text of the sentinel event alert. The portion relevant to depth of anesthesia monitoring follows:

To overcome the limitations of current methods to detect anesthesia awareness, new methods are being developed that are less affected by the drugs typically used during general anesthesia. These devices measure brain activity rather than physiologic responses. These electroencephalography (EEG) devices (also called level-of-consciousness, sedation-level and anesthesia-depth monitors) include the Bispectral Index (BIS); spectral edge frequency (SEF) and median frequency (MF) monitors. These devices may have a role in preventing and detecting anesthesia awareness in patients with the highest risk, thereby ameliorating the impact of anesthesia awareness. A body of evidence has not yet accumulated to definitely define the role of these devices in detecting and preventing anesthesia awareness; the Joint Commission expects additional studies on these subjects to emerge.

SUMMARY

Intraoperative awareness is a significant clinical problem. Several large studies suggest that the incidence is approximately 0.1% overall, and higher and lower rates are possible in specific circumstances. There is no simple, completely reliable way to prevent intraoperative awareness. Prevention of intraoperative awareness requires a comprehensive approach, including meticulous attention to correct drug administration, careful clinical observation of the patient for movement or autonomic responses to surgical stimulation, avoidance of muscle relaxant overuse, and appropriate use of monitors of anesthetic depth. Four studies have indicated that BIS monitoring may significantly reduce the incidence of intraoperative awareness. Two of these four clinical studies have suggested that ETAC (targeted volatile anesthetic gas administration with anesthetic gas monitors alarmed at 0.7 to 1.3 MAC) may also reduce the incidence of intraoperative awareness, although the lack of a standard practice control group limits to some degree the conclusions that can be drawn from these trials.

AUTHOR'S RECOMMENDATIONS

- Because some cases of intraoperative awareness are related to errors in drug administration, do everything possible to avoid these errors. See previous publications for suggestions of methodology for avoiding drug administration errors.[18-23]
- Use only the smallest dose of neuromuscular blocking drugs necessary to achieve adequate surgical exposure.
- If available, bispectral index (BIS) monitoring may help reduce the incidence of intraoperative awareness, as suggested by four studies.[9,32-34] As with any monitor, BIS monitors have limitations. Users of BIS monitors (or other depth of anesthesia monitors) are encouraged to be very familiar with the correct operation of the monitor, interpretation of the data, and inherent limitations. Whether the use of non-BIS monitors of anesthetic depth can result in reduced incidence of intraoperative awareness is currently unknown.
- Awareness during intubation appears to be relatively common. Therefore if depth of anesthesia monitoring is available, it may be valuable to initiate monitoring before induction of anesthesia. Nevertheless, it is important to note that monitors typically lag behind the current anesthetic state by at least 15 to 30 seconds because of the time required for processing the raw electroencephalographic signal, which may limit the usefulness of monitoring during induction or at other times when rapid changes in the electroencephalogram are taking place.
- Prevention of intraoperative awareness requires a comprehensive approach, including meticulous attention to correct drug administration, careful clinical observation of the patient for movement or autonomic responses to surgical stimulation, avoidance of muscle relaxant overuse, and appropriate use of monitors of anesthetic depth.

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CHAPTER 44

Are Patients with Sleep Apnea Appropriate for Ambulatory Surgery?

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INTRODUCTION/BACKGROUND

Obstructive sleep apnea (OSA) is a chronic condition that is characterized by recurrent episodes of partial or complete collapse of the upper airway during sleep. The reduction or cessation of airflow during these obstructive episodes may result in significant decreases in oxyhemoglobin saturation and hypercarbia and eventual arousal from sleep. Patients with sleep apnea may have a variety of nocturnal symptoms, such as loud disruptive snoring, choking, and gasping, and they may have observed pauses in breathing. Because sleep is fragmented, daytime symptoms include excessive daytime sleepiness, mood disorders, and neurocognitive impairment, which lead to an increased likelihood of accidental injury or death.[1] Additionally, it is well accepted that the abnormalities in gas exchange that result from OSA are associated with adverse cardiovascular, endocrine, and cerebrovascular consequences.[2-6]

Public awareness of OSA and its health consequences is increasing, and concern among health care providers is growing that patients with sleep apnea may be at risk of adverse perioperative outcomes, including death. General population studies suggest that 5% of middle-aged women and 9% of middle-aged men have OSA, and data suggest that the prevalence of OSA is even higher in the elderly population.[7,8] Unfortunately, the prevalence of OSA in adult patients undergoing outpatient surgery is still unknown. Furthermore, it has been estimated that up to 90% of those with the disease carry no formal diagnosis.[7,9] With 15 million patients undergoing outpatient surgeries in free-standing ambulatory surgical centers each year, statistically, more than 1 million of them may have disordered breathing.

The presence of OSA in the surgical patient is thought to lead to potential problems with mask ventilation, tracheal intubation, extubation, and the ability to provide adequate analgesia without respiratory compromise.[10] When the diagnosis of OSA is known, there is an opportunity to arrange for additional resources to deal with anticipated potential airway complications and the need for possible prolonged postoperative monitoring. However, the patient who has signs and symptoms of OSA but does not have a formal diagnosis poses a particular problem for the ambulatory anesthesiologist who must decide whether to proceed with surgery or delay the case until the patient undergoes a formal evaluation. Additionally, the anesthesiologist must decide whether the patient is a candidate for a free-standing ambulatory surgical center.

The gold standard test used to determine the presence of OSA is polysomnography (PSG). PSG is a relatively expensive, time-consuming, and labor-intensive test that cannot be performed on the day of the surgical procedure. The patient who undergoes PSG is brought to a sleep laboratory in the evening, monitors are applied, and simultaneous recordings of several physiologic signals are acquired over an 8-hour period while the patient sleeps. Most sleep laboratories define an abnormal breathing episode of obstructive apnea as the complete cessation of airflow for a minimum of 10 seconds during sleep while the patient makes persistent efforts to breathe. Although the definition of hypopnea is less uniform, the most common description is a decrease in airflow of greater than 30% associated with a decrease in oxyhemoglobin saturation of 4% or more. The apnea–hypopnea index (AHI) is the total number of all recorded episodes of apneas and hypopneas per hour of total sleep time, and if sleep-disordered breathing is detected, it is reported as mild, moderate, or severe, based on the AHI. It is important to note that the criteria for diagnosis and the presentation of OSA differ between the adult and pediatric populations, and what is discussed in this review applies only to the management of adults.

OPTIONS

At present, there is no consensus to define the specific additional risk, if any, that the presence of OSA poses to the ambulatory surgical patient. Because the risk of potential OSA during outpatient surgery is poorly defined, postponement of a surgical procedure to define the patient's risk may seem unreasonable to the patient and the surgeon. There are both financial and social pressures to proceed because the patient may have made arrangements for time away from work, as well as provisions for family members to help during the recovery period. Additionally, even though the procedure may have been scheduled as an elective outpatient procedure, the nature of the surgery may still be considered relatively

urgent, as in the case of a breast biopsy to rule out cancer. Delay of this type of procedure can have tremendous psychological consequences for the patient and may result in delay of treatment. Although no large-scale, randomized trials have compared perioperative adverse outcomes of patients with OSA with those of healthy patients, several observational studies have examined this question. Therefore current perioperative care is based on clinical judgment and an understanding of the pathophysiologic mechanism and consequences of OSA.

PATHOPHYSIOLOGY/MECHANISM OF ACTION

The occurrence of pharyngeal collapse during sleep suggests that sleep onset is associated with functional alterations in airflow in the upper airway that reduce patency and increase resistance to airflow. The point of obstruction can occur anywhere in the upper airway, from the soft palate and nasopharynx to the base of the tongue and epiglottis, and frequently occurs at different sites during the various stages of sleep.[11] Bachar and colleagues[12] demonstrated sites and patterns of obstruction with the use of sleep endoscopy in 55 surgical patients. They found that the most common site of obstruction was uvulopalatine and also noted that many patients (72%) had multiple sites of obstruction.[12] Regardless of where the obstruction occurs, two subsequent effects are thought to follow. First, with repetitive episodes of hypoxia and hypercapnia and the reoxygenation that occurs during arousal, oxidative stress ensues and systemic inflammation follows.[13] Reactive oxygen species are formed and cause injury to the surrounding tissue. Although these molecules trigger pathways that are adaptive to hypoxia, they have also been found to have an association with harmful inflammatory and immune responses. Among the changes are activation of endothelial cells, leukocytes, and platelets.[14,15] Sympathetic activity is increased, which, after repetitive cycles of hypoxia and hypercarbia, results in upregulation of both alpha- and beta-receptors. This may have a role in the pathogenesis of coronary and cerebrovascular disorders.

One of the most commonly recognized cardiac sequelae of OSA is right-sided heart dysfunction. The increased sympathetic activity associated with the hypoxia and hypercarbia leads to an increase in pulmonary vascular resistance. The endothelial wall thickens, and pulmonary hypertension can ensue. The right ventricle hypertrophies to meet the demand and, if unremedied, can eventually dilate and enlarge. However, although historically most attention has been directed toward the status of the right side of the heart during a preoperative assessment in the patient suspected of having OSA, there is a far greater association with systemic hypertension and, more specifically, uncontrolled hypertension.[16] Of patients with documented OSA, 60% to 70% have a concomitant diagnosis of systemic hypertension, whereas only about 20% of those with OSA have progression of the disease resulting in pulmonary hypertension severe enough to cause right ventricular dysfunction.

OSA has been implicated in the pathogenesis of various other comorbidities, including coronary artery disease, congestive heart failure, cardiac arrhythmias, sudden death, stroke, and impaired glucose metabolism.[14,15,17]

EVIDENCE

To date, there is a paucity of outcome data generated from surgical patients with diagnosed or undiagnosed OSA and even less that addresses outcomes in the ambulatory surgical population. Recent studies suggest that 24-hour observation in a monitored environment confers a minimal, if any, advantage in risk reduction for ambulatory surgical patients with uncomplicated OSA.

Most available data arise from otolaryngologic studies, specifically patients undergoing uvulopalatopharyngoplasty (UPPP). Several studies have addressed the question of whether patients with OSA undergoing upper airway procedures should be monitored in an intensive care unit (ICU) postoperatively, but the data are retrospective and inconclusive. Mickelson and Hakim[18] retrospectively analyzed 347 consecutive patients who underwent UPPP. Of the 14 patients who had complications, five involved the airway, and the episodes occurred in the immediate perioperative period. Additionally, no correlation was seen between the rate of complication and the severity of OSA. Of the five patients with airway complications, three required reintubation. One patient had bronchospasm immediately after extubation, one patient was thought to have been prematurely extubated in the operating room and experienced subsequent respiratory arrest, and one patient was reported to have respiratory distress in the recovery room of unknown etiology. Respiratory complications developed in two of the five patients after admission to the ward; however, neither required reintubation. The authors concluded that ICU care postoperatively was not required for most patients undergoing UPPP and that the rate of complication was substantially higher in patients who had undergone simultaneous otolaryngologic procedures in addition to UPPP. Hathaway and Johnson[19] examined the outcomes of 110 patients scheduled for outpatient UPPP. Twenty of the 110 patients required admission (18%); however, no patient required transfer to an ICU. Although three patients were admitted for postoperative oxygen desaturation, this did not correlate with the severity of AHI. Additionally, the majority of admissions were for control of pain and nausea. The authors emphasized that appropriate patient selection is essential in minimizing the risk of perioperative complications in patients undergoing UPPP, and in their study, any patient with severe cardiopulmonary comorbidities was eliminated as a candidate for UPPP. Terris and colleagues[20] found similar results when they performed a retrospective analysis of 109 patients with OSA who were scheduled for 125 upper airway procedures. The rate of airway complications was 0.9% (1 of 109), and the one patient who experienced airway obstruction did so in the immediate postoperative period. Again, the authors concluded that ICU monitoring for all patients undergoing UPPP was unnecessary and that the decision for discharge to the floor or home

could be made based on the patient's status in the recovery room within 2 hours of the surgical procedure. In another retrospective analysis of OSA patients undergoing airway procedures, Spiegel and Tejas[21] found that, if airway complications were to occur, they could be identified within 2 to 3 hours postoperatively and also concluded that same-day discharge was an option for some patients. Although it appears that select patients with OSA can be safely discharged to home after UPPP, it seems prudent that this be done in a facility with provisions for transfer to an overnight ward for observation.

Studies in the literature examining nonotorhinolaryngologic surgeries in patients with OSA are scant. However, studies that retrospectively analyze outcomes of inpatient surgical procedures have suggested that OSA is an independent risk factor for adverse outcomes. Gupta and colleagues[22] studied 110 patients with OSA diagnosed either before or after total hip or knee replacement and matched the population with control subjects. OSA was associated with an increased incidence of "serious" adverse perioperative events requiring transfer to an ICU.[22] Although the severity of OSA or AHI was not related to the incidence of complications, OSA patients who were compliant with continuous positive airway pressure (CPAP) preoperatively were noted to have a decreased incidence of complications when compared with patients with OSA who did not use CPAP.

Sabers and colleagues[23] at the Mayo Clinic in Rochester, Minnesota, designed a retrospective study to determine whether the preoperative diagnosis of OSA was an independent risk factor for perioperative complications after outpatient surgery. A total of 234 patients who had been previously diagnosed with OSA by PSG were scheduled for ambulatory surgical procedures and were matched with control subjects. All types of surgery were included with the exception of otorhinolaryngologic procedures. The primary outcome measured was unplanned hospital admission or readmission; however, recorded data included episodes of bronchospasm, airway obstruction, and reintubation during the recovery period. Previously diagnosed OSA was not found to be an independent risk factor for unplanned admissions or for other adverse perioperative events.

We have examined the prevalence of OSA and propensity to OSA in our own outpatient surgical population at Johns Hopkins Hospital.[24] A previously validated prediction model[25] was used to determine the pretest probability for OSA in 3557 consecutive adult patient undergoing ambulatory surgery of all types except ophthalmologic procedures. Propensity to OSA was determined by logistic regression analysis. Relevant perioperative data such as anesthetic technique, difficulty with endotracheal intubation, need for supplemental oxygen, need for assisted ventilation, reintubation, unplanned admission, and death were recorded; 2.6% of the patients had a greater than 70% propensity for OSA but had not yet been given a diagnosis. Of these high-risk patients, only 28.2% (31 of 110) of male patients and 21.6% (11 of 51) of female patients had a previous self-reported diagnosis of possible OSA. The results of the study suggested that OSA is relatively common in an ambulatory surgical population and that the majority of patients with a propensity for OSA who undergo ambulatory surgery remain undiagnosed. There was a positive correlation of patients with a higher propensity to OSA (versus non-OSA) and increased difficulty of intubation, administration of intraoperative ephedrine, metoprolol, and labetolol, and need for prolonged supplemental oxygen. However, we found no relationship between unplanned admission or readmission, life-threatening events such as reintubation, cardiac arrhythmia, or death in patients with either a diagnosis or higher propensity for OSA. Therefore our data suggest that patients with OSA may require additional perioperative interventions; however, they can be treated safely in an ambulatory care center.[24]

Acknowledging the weakness of the data available to guide the perioperative management of patients with uncomplicated OSA, it appears that these patients can be safely managed as outpatients. However, those patients with comorbid illnesses may need to be managed differently. Moreover, as the complexity and invasiveness of ambulatory surgical procedures increase with advances in technique and technology, the appropriateness of care of patients with OSA in an ambulatory surgical center may need further exploration.

CONTROVERSIES

The greatest controversy in the management of surgical patients with known or suspected sleep apnea involves the postoperative disposition of the patient. Although current recommendations suggest prolonged postoperative monitoring, there are no data to show what type of monitoring or duration is necessary to decrease risk.

GUIDELINES

The American Society of Anesthesiologists (ASA) task force approved practice parameters for the perioperative management of patients with OSA in October 2005.[26] The systematically developed guidelines were intended as recommendations aimed at reducing adverse outcomes; although based on a review of current literature, they have not been validated and are not intended to replace the judgment of the practitioner. The recommendations are consensus based.

The ASA practice parameters include a scoring system based on the documented severity of the patient's sleep apnea and the invasiveness of the surgical procedure, combined with the perioperative opioid requirements.

The task force recognized that the majority of patients with OSA may not carry a formal diagnosis and therefore provided recommendations for the preoperative identification of patients who may be at risk of OSA. Determination of risk of OSA is ascertained by assessment of predisposing physical characteristics, a history of apparent airway obstruction during sleep, and the presence of daytime somnolence. If the patient is found to have signs and symptoms from two or more of these categories, the guidelines state that patients should be treated as though they have moderate sleep apnea. If any of the signs and symptoms are extraordinarily severe, patients should be

treated as though they have severe OSA. Although the literature was insufficient to construct guidelines for recommended criteria for discharge to home for patients with OSA, the consensus opinion was that outpatient procedures could be safely performed if regional or local anesthesia was administered. The consultants were equivocal regarding whether minor-risk procedures could be safely performed under general anesthesia in patients at risk of OSA in an ambulatory setting. Furthermore, they stated that otorhinolaryngologic surgery such as UPPP should not be performed in patients with OSA on an ambulatory basis. Moreover, the consultants acknowledge that the literature is insufficient to determine the efficacy of postoperative monitoring in reducing perioperative risk in patients with OSA. The consultants did agree that intermittent pulse oximetry was of little use in reducing patient risk. Although the guidelines recommend monitoring a patient with OSA for 3 hours longer than their non-OSA counterparts before discharge from a facility, they also indicate that monitoring of patients with OSA should be continuous for a median of 7 hours after the last episode of obstruction of the airway or documented hypoxemia while the patient is breathing room air. Again, it should be emphasized that this is a consensus of expert opinion based on a relative paucity of published literature.

AUTHORS' RECOMMENDATIONS

Ambulatory patients with known or suspected obstructive sleep apnea (OSA) should be scheduled early in the day to allow for potential prolonged postoperative observation. Additionally, those who have been prescribed continuous positive airway pressure should be instructed to bring the device with them to the facility on the day of surgery for postoperative use. Provisions should be made to deal with a potential difficult airway, and a plan should be in place for transfer to a monitored care environment if necessary. A validated optimal anesthetic technique is not available for patients with diagnosed or suspected OSA. Local and regional anesthesia seem to be logical choices because they may decrease the amount of postoperative systemic narcotic required for adequate analgesia. Neuraxial blockade with local anesthetic may also confer the advantage of avoidance of further airway compromise; however, it must be recognized that a high block may exacerbate cardiopulmonary dysfunction. Additionally, epidural narcotics have been implicated in postoperative respiratory arrest.[27,28]

If general anesthesia is required, consideration should be given to securing the airway with the patient awake and spontaneously ventilating. Obese patients should be placed in the semiupright position during induction, and consideration should be given to aspiration prophylaxis. On tracheal extubation, there should be unequivocal confirmation of reversal of neuromuscular blockade, and extubation should occur with the patient returned to the semiupright position, breathing 100% oxygen, and fully awake.

On arrival to the postanesthesia care unit, the patient with OSA requires constant surveillance for airway obstruction, hypoxemia, dysrhythmias, and hypertension. During the immediate postoperative period, the patient is particularly at risk of the residual effects of anesthetics in the absence of a secured airway. Supplemental oxygen therapy should be continued and weaned cautiously. However, because respiratory status is frequently based on pulse oximetry readings, the patient may experience hypercarbia due to unrecognized hypoventilation. Hypercarbia should be suspected if the patient exhibits persistent hypertension or dysrhythmia, and arterial blood gas analysis should be considered.

In addition to narcotics, other sedating drugs such as benzodiazepines, antihistamines, and phenothiazines should be administered only if required and then only judiciously to the patient with OSA. Before discharge, we recommend administration of the patient's first dose of prescribed narcotic analgesic while the patient is still in the recovery room, followed by a period of observation for hypersomnolence and airway compromise, which might necessitate overnight observation. Additionally, the patient should be counseled about the potentiated respiratory depressant effects of alcohol consumption or other over-the-counter sedating medications in conjunction with narcotic analgesics.[29]

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CHAPTER 45

What Criteria Should Be Used for Discharge after Outpatient Surgery?

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INTRODUCTION

The concept of ambulatory procedure with admission, operation, and discharge on the same day has evolved considerably over the last two decades. The number of ambulatory surgical procedures has grown tremendously throughout the world. The rapid growth of ambulatory surgical care worldwide is attributed to its multiple advantages, such as early return to preoperative physiologic state, fewer complications, reduced physical and mental disturbance, early resumption of normal activities, and reduced hospital costs. The major advance in anesthetic techniques includes the use of rapidly dissipated anesthetic agents and the increasing use of regional anesthetic techniques. It is expected that the number, diversity, and complexity of operations performed in the outpatient setting will continue to increase.

Time to discharge from an ambulatory surgical unit is considered to be a measure of the efficiency of the unit. Counterbalancing efficiency, patient safety is also an important issue in terms of a good practice. Hence, for a successful ambulatory surgical unit, emphasis is not only on patient selection but also on scientifically sound and safe discharge criteria. This chapter outlines the current literature available on discharge criteria and reviews the factors affecting the discharge.

EVIDENCE

The knowledge regarding the process of recovery and the concept of fast-tracking are essential in understanding the application of the appropriate discharge criteria that are presently available. Recovery is an ongoing process that begins from the end of intraoperative care until the patient returns to his or her preoperative physiologic state. This process is divided into three distinct phases: early, intermediate, and late recovery. Early recovery (phase 1) is from the discontinuation of anesthetic agents to the recovery of the protective reflexes and motor function. At most institutions, the phase 1 recovery occurs in the postanesthesia care unit (PACU).

Intermediate recovery (phase 2) occurs when the patient achieves criteria for discharge from the PACU and occurs mostly in the step-down or ambulatory surgical unit (ASU). Late recovery (phase 3) continues at home under the supervision of a responsible adult and continues until the patient returns to his or her preoperative physiologic state.[1]

Traditionally, most patients are transferred from the operating room to the PACU and then to the ASU before they are discharged home. However, the recovery care after ambulatory surgery is now in a state of change with advances in surgical and anesthetic techniques. This has facilitated an early recovery process. It is now possible to have patients who are awake, alert, and comfortable in the operating room to bypass the labor-intensive PACU directly into the step 2 recovery area. This new concept is referred as *fast-tracking* in ambulatory surgery.[2]

DISCHARGE CRITERIA

The many discharge criteria commonly employed are identified in Box 45-1. There are discharge criteria for the PACU, the ASU, and fast-tracking.

Discharge Criteria for the Postanesthesia Care Unit

The Aldrete score has been successful in addressing the early phase 1 recovery. This score, created in 1970, is a modification of the Apgar score used in neonates.[3] This score assesses five parameters: respiration, circulation, consciousness, color, and level of activity. Each parameter is scored 0, 1, or 2, and patients scoring 9 or greater are eligible to be transferred from the high-dependency PACU to the ASU. However, with the advent of pulse oximetry, the Aldrete score was modified in 1995 to include this technologic improvement (Table 45-1).[4]

Although the Aldrete score is an effective screening tool, it has a few limitations.[5] It does not provide an assessment for home-readiness, and it does not address some of the common side effects seen in the PACU, such as pain, nausea and vomiting, and bleeding at the incision site.

Discharge Criteria for the Ambulatory Surgical Unit

Discharge criteria applied in the ASU are designed to assess home-readiness of patients, and hence strict

BOX 45-1 Common Discharge Criteria

Discharge Criteria Applied at Different Phases of Recovery

- Discharge criteria at postanesthesia care unit (phase 1 recovery)
  - Aldrete score
- Discharge criteria at ambulatory surgical unit (phase 2 recovery)
  - Postanesthesia discharge score
  - Outcome-based discharge criteria
- Discharge criteria for fast-tracking
  - White fast-tracking score

Discharge Criteria Used for Research Purposes

- Psychomotor test of recovery (phase 3 recovery)

Discharge Criteria Used under Specific Circumstances

- Discharge home criteria after neuraxial blockade
- Discharge home criteria after peripheral nerve block
- Discharge home criteria for suspected malignant hyperthermia

TABLE 45-1 **Modified Aldrete Scoring System***

	Discharge Criteria from Postanesthesia Care Unit	Score
Activity	Able to move voluntarily or on command	
	Four extremities	2
	Two extremities	1
	Zero extremities	0
Respiration	Able to breathe and cough freely	2
	Dyspnea, shallow or limited breathing	1
	Apneic	0
Circulation	Blood pressure 20 mm of preanesthetic level	2
	Blood pressure 20-50 mm of preanesthesia level	1
	Blood pressure –50 mm of preanesthesia level	0
Consciousness	Fully awake	2
	Arousable on calling	1
	Not responding	0
O_2 saturation	Able to maintain O_2 saturation >92% on room air	2
	Needs O_2 inhalation to maintain O_2 saturation >90%	1
	O_2 saturation <90% even with O_2 supplementation	0

*To determine readiness for discharge from postanesthesia care unit. A score >9 is required for discharge.

From Aldrete JA. The post-anesthesia recovery score revisited. J Clin Anesth 1995;7:89–91.

adherence to the criteria to ensure patient safety is important. There are a number of available criteria, but the most common criteria that are applied at the ASU are the safe discharge criteria proposed by Korttila[6] and the post-anesthesia discharge score (PADS) devised by Chung and colleagues.[7]

BOX 45-2 "Safe Discharge" Criteria*

- Patient alert and oriented to time, place, and person
- Stable vital signs
- Pain controlled by oral analgesics
- Nausea and emesis controlled
- Able to walk without dizziness
- No unexpected bleeding from the operating sites
- Discharge instruction and prescription received
- Patient accepts readiness for discharge
- Responsible escort

*A set of typical discharge criteria to determine readiness for discharge from postanesthesia care unit. All parameters of safe discharge criteria need to be met before discharge.

From Awad IT, Chung F. Factors affecting recovery and discharge following ambulatory surgery. Can J Anaesth 2006;53:858–72.

The safe discharge criteria use outcome-based clinical observations, and all parameters have to be met before discharge. It is important to note that clinical observations such as the need to drink and void before discharge, which were initial prerequisites in "safe discharge criteria," are no longer applicable. Current outcome-based discharge criteria are listed in Box 45-2.[1]

Chung and colleagues[7] devised the PADS in 1993. The PADS was later modified to eliminate the requirements for oral fluid intake and urinary output before discharge.[8] It has been demonstrated that the implementation of PADS as a criterion for discharge from the ASU facilitates expeditious discharge, with 80% of patients able to be discharged within 1 to 2 hours.[9] PADS is a cumulative index that measures the home-readiness of patients based on five major criteria: (1) vital signs, (2) ambulation, (3) pain, (4) postoperative nausea and vomiting, and (5) surgical bleeding.[1] The pain criteria have been further refined to score pain with a visual analog scale ranging from 1 to 10 (Table 45-2). Patients who achieve a score of 9 or greater are considered fit for discharge with an adult escort. PADS also provides for an objective determination of the optimal length of patient stay following ambulatory surgery (see Table 45-2).

Discharge Criteria for Fast-Tracking

The success of fast-tracking depends on the appropriate modification of anesthetic technique, which would allow rapid emergence from anesthesia and the prevention of common postoperative complications such as pain, nausea, and vomiting using a multimodal approach. White and Song[2] devised a fast-tracking score, which incorporated assessment of pain and emetic symptoms, to the original Aldrete score. The maximum possible score is 14. A score of 12 (with no score less than 1 in any category) is considered sufficient for discharge from the operating room to the ASU (Table 45-3).

Studies have shown that outpatients who are fast-tracked can be discharged earlier without any increase in complications or side effects.[10-12] Apfelbaum and colleagues[12] undertook a multicenter prospective study to determine the safe bypass of PACU by patients after ambulatory surgery. After education of the health

TABLE 45-2 **Postanesthetic Discharge Scoring System**

Vital Signs	
Within 20% of preoperative baseline	2
20%-40% of preoperative baseline	1
40% of preoperative baseline	0
Activity Level	
Steady gait, no dizziness, consistent with preoperative level	2
Requires assistance	1
Unable to ambulate/assess	0
Nausea and Vomiting	
Minimal: mild, no treatment required	2
Moderate: treatment effective	1
Severe: treatment not effective	0
Pain	
VAS = 0-3: the patient has minimal or no pain before discharge	2
VAS = 4-6: the patient has moderate pain	1
VAS = 7-10: the patient has severe pain	0
Surgical Bleeding	
Minimal: does not require dressing change	2
Moderate: required up to two dressing changes with no further bleeding	1
Severe: required three or more dressing changes and continues to bleed	0

VAS, visual analog scale.
Maximum score = 10: patients scoring >9 are fit for discharge.
From Awad IT, Chung F. Factors affecting recovery and discharge following ambulatory surgery. Can J Anaesth 2006;53: 858–72.

TABLE 45-3 **White Fast-Tracking Score**

Discharge Criteria	Score
Level of Consciousness	
Awake and oriented	2
Arousable with minimal stimulation	1
Responsive to tactile stimulation	0
Physical Activity	
Able to move all extremities on command	2
Some weakness in movement of extremities	1
Unable to voluntarily move extremities	0
Hemodynamic Stability	
Blood pressure <15% of baseline MAP value	2
Blood pressure 15%-30% of baseline MAP value	1
Blood pressure >30% below the baseline MAP value	0
Respiratory Stability	
Able to breathe deeply	2
Tachypnea with good cough	1
Dyspneic with good cough	0
Oxygen Saturation Status	
Maintains value >90% on room air	2
Requires supplemental oxygen	1
Saturation <90% with supplemental oxygen	0
Postoperative Pain Assessment	
None, or mild discomfort	2
Moderate to severe pain controlled with intravenous analgesics	1
Persistent severe pain	0
Postoperative Emetic Symptoms	
None, or mild nausea with no active vomiting	2
Transient vomiting	1
Persistent moderate to severe nausea and vomiting	0
Total possible score	**14**

MAP, mean arterial pressure.
Scoring system to determine whether outpatients can be transferred directly from the operating room to the step-down unit. A minimum score of 12 (with no score <1 in any individual category) would be required for patients to be fast-tracked after general anesthesia.
From White PF, Song D. New criteria for fast-tracking after outpatient anesthesia: a comparison with the modified Aldrete's scoring system. Anesth Analg 1999;88:1069–72.

personnel, the PACU bypass rate of patients having general anesthesia increased from 15.9% at baseline to 58%. These patients had a significantly shorter duration of recovery when compared with patients who had a standard recovery at the PACU.

However, the advantages of a faster recovery and saving time may not reflect the true nursing workload and real cost savings. A recent randomized control trial compared fast-tracking of bypassing PACU with no bypassing of PACU.[13] In this study, patients were randomly assigned to either a routine or a fast-tracking group. Patients in the fast-tracking group were transferred from the operating room directly to the ASU (i.e., bypassing the PACU) if they achieved the fast-tracking criteria. All other patients were transferred to the PACU and then to the ASU. The mean time to discharge was 17 minutes less in the fast-tracking group, but the overall nursing workload and the associated cost were not significantly different between the two groups.[13]

A number of psychomotor tests are available[14-21] (Table 45-4) to determine recovery of patients; however, the tests have a number of disadvantages. They require equipment and trained personnel to use and interpret the equipment. The tests are time consuming and usually only assess one area of brain function. Therefore they are mostly used for research purposes rather than for clinical use.

Evaluation of the Scores

Various scores have been devised to guide the process of discharge and home-readiness to ensure patient safety, but none have been formally evaluated. An ideal discharge score should be practical, simple, and easy to remember and should be applicable to all postanesthesia settings.[22] Use of common physical signs with scores assigned to each parameter makes the assessment more objective. The presently available discharge criteria in literature have been successful to a very large extent but have some limitations. The Aldrete scoring system and the PADS are widely used.

TABLE 45-4 **Common Psychomotor Tests***

Test	Description
Simple reaction time[14]	Time to press a keyboard in response to a stimulus (e.g., buzzer)
Choice reaction time[14]	Involves choice of optical stimulus (e.g., green/red)
Critical flicker fusion time[15]	Involves the time it takes for the patient to notice a flickering light at a particular frequency that appears and becomes continuous
Digital symbol substitution test[16]	
Perceptive accuracy test[17]	
Digital span	The ability to recall strings of numbers
California verbal test[18]	Ability to remember a list of words from a previously presented list
Trieger dot test (Gestalt test)[19]	Ability to connect a series of dots on paper to form a pattern; the more dots the patient misses, the lower the recovery score
Driving simulation test[20]	
Maddox wing test[21]	A device to test extraocular muscle balance

*Used as discharge criteria for research purposes.

BOX 45-3 Risk Factors for Postoperative Urinary Retention

Low Risk for Urinary Retention

Low-risk patients can be defined as having the following characteristics:

- General anesthesia, peripheral nerve block, monitored anesthesia care
- Nonpelvic and nonurologic surgeries
- Most outpatient gynecologic surgeries (transvaginal or pelvic laparoscopy who undergo intraoperative bladder drainage)
- Most patients having spinal or epidural anesthesia with short-acting local anesthetic such as lidocaine, procaine, or 2-chloroprocaine

High Risk for Urinary Retention

High risk of urinary retention can be defined as having:

- Pelvic surgery (hernia, rectal, penile, urologic)
- Positive family history of retention or spinal cord disease
- Spinal or epidural anesthesia with agents of long-acting duration such as bupivacaine, tetracaine, and ropivacaine
- The use of neuraxial opioids combined with local anesthetics

From Souter KJ, Pavlin DJ. Bladder function after ambulatory surgery. J Ambulatory Surg 2005;12:89–97.

Shift from the Traditional Discharge Criteria

Traditionally, clinical parameters such as oral intake and urinary output were considered a prerequisite for discharge criteria from the ASU. However, this practice is increasingly being questioned.

Urinary retention is defined by the inability to void at a bladder volume of 600 mL, a volume at which there is a strong desire to void.[23] The risk for postoperative urinary retention can be classified as high and low risk.[24] The identified risk factors for postoperative urinary retention are presented in Box 45-3.

The incidence of urinary retention is 1% in low-risk ambulatory surgical procedures and ranges from 3% to 20% in high-risk patients.[24] Prolonged urinary retention can cause bladder atony and may also cause impaired voiding after return of function.[24] Prolonged urinary retention can also cause delay in discharge in 5% to 11% of ambulatory care patients.[25] Mulroy and colleagues[26] undertook a prospective study to determine the risk of developing postoperative urinary retention in the low-risk group. In this study standard patients were required to void before discharge. Accelerated-pathway patients were discharged home if the bladder volume was less than 400 mL as evidenced by ultrasound. Patients who had bladder volume greater than 400 mL were reassessed after 1 hour and catheterized if they did not void. All patients were advised to return to the emergency department if they were not able to void after 8 hours. Mean discharge time in patients with the accelerated pathway was 22 minutes shorter than the standard pathway. No patients reported urinary retention after they were discharged home.[26]

In summary, low-risk patients can be discharged home without voiding. They should be instructed to return to the hospital if they are unable to void within 6 to 8 hours. Patients at high risk of urinary retention should be required to void before discharge and display a residual volume of less than 400 mL. If the bladder volume is greater than 500 to 600 mL, catheterization should be performed before discharge. It is important to note that the use of ultrasound in detecting bladder volume is better than clinical judgment.[27]

Patients are no longer required to drink fluids before discharge. The studies that questioned mandatory oral fluids before discharge were Schreiner and colleagues[28] and Kearney and colleagues[29] in the pediatric population and Jin and colleagues[30] in the adult population. Schreiner assigned children undergoing ambulatory surgery into either mandatory drinker or elective drinker.[28] Children in the mandatory drinker group experienced a higher incidence of vomiting and prolonged hospital stay. Kearney evaluated the incidence of vomiting in 317 children undergoing day surgery.[29] Children were randomized into two groups: either drinking oral fluids or having oral fluids withheld for 4 to 6 hours. Vomiting was assessed in the hospital and throughout the first postoperative day. The incidence of vomiting in the group with fluids withheld was significantly less than that of the group that drank (38% versus 56%, $p < 0.004$). The greatest effect of withholding fluids was seen in patients receiving opioids ($p < 0.004$), where vomiting was reduced from 76% to 36%.

To answer the question of whether adult outpatients should drink before discharge after minor surgical procedures, 726 patients were randomized to either drinking oral fluids or not drinking after surgery.[30] Neither drinking nor nondrinking worsened postoperative nausea or vomiting or prolonged hospital stay. Therefore drinking oral fluids is not a requirement before discharge. These changes have been incorporated in the American Society of Anesthesiologists' practice guidelines for postanesthetic care. Mandating oral fluid intake before discharge should be done only for select patients on a case-by-case basis.

Discharge Criteria after Regional Anesthesia

The role of regional anesthesia in ambulatory surgery is very promising and has demonstrated benefits of better pain control, lower incidence of nausea and vomiting,[31] and potentially faster discharge and reduction in the incidence of chronic pain syndrome.[32]

Spinal anesthesia is a simple and reliable technique, widely used in ambulatory surgical care. There has been ongoing effort to refine anesthetic technique to tailor faster recovery with minimal side effects. Two specific low-dose techniques, unilateral[33,34] and selective spinal anesthesia,[35] have been described, although there is an overlap between the two. With adequate doses of local anesthetic agents, the time to home-readiness after unilateral spinal anesthesia,[36] or selective spinal anesthesia[37-40] with bupivacaine, or low-dose spinal anesthetic with lidocaine and fentanyl,[41] or sufentanil,[42] has been equal to that for general anesthesia maintained with propofol or desflurane.[40,41]

Lidocaine was previously the agent used for short-acting spinal anesthesia until it was reported to cause transient neurologic symptoms.[43-45] These neurologic problems have made anesthesiologists seek alternative suitable local aesthetic agents. The incidence of transient neurologic symptoms has been highest after lidocaine spinal anesthesia (37%) and in patients undergoing knee arthroscopy (22%) or surgery in the lithotomy position (0% to 3%),[46] whereas after bupivacaine or ropivacine it has been as low as 0% to 3%.[38,39,47,48] Recently the use of 2-chloroprocaine as an alternative to lidocaine in ambulatory anesthesia has been revisited.[49] In this study, volunteers received either 40 mg of 2% lidocaine or 40 mg of 3% 2-chloroprocaine intrathecally. The quality of surgical anesthesia and motor block was similar in the two groups. No patient developed transient neurologic symptoms in the 2-chloroprocaine groups. Patients in this group also experienced faster resolution of sensory block, and achieved discharge criteria earlier. In another study, 40 mg of 3% 2-chloroprocaine produced similar motor block compared with 7.5 mg bupivacaine. Low-dose 2-chloroprocaine may be the local anesthetic for short-acting bilateral procedures in the future, but its safety has not been proved.[50]

The main factor restricting the popularity of spinal anesthesia is postdural puncture headache (PDPH). The incidence of PDPH is less than 1% with the use of a standard 25 G Whitacre spinal needle.[51] This complication is reduced to a large extent by choosing an appropriate needle, decreasing to 0.4% with a 27 G Whitacre needle versus 1.5% with a 27 G Quincke needle.[52]

There are limited reports in the literature on epidural anesthesia for ambulatory care because it is generally regarded as a time-consuming technique when compared with other techniques. Mulroy and colleagues[26] showed a faster discharge after epidural with either lidocaine or 2-chloroprocaine versus spinal lidocaine or low-dose bupivacaine. Other studies have used epidural successfully for hemorrhoidectomy and lower abdominal surgery,[53,54] with observation time in the hospital ranging from 5 to 6 hours, respectively. However, there is an isolated case report of epidural hematoma in a patient receiving nonsteroidal antiinflammatory drugs (NSAIDs) after discharge from an ambulatory arthroscopy after epidural anesthesia.[55]

Patients undergoing regional anesthesia should expect the same discharge criteria and standard postoperative care as those who have undergone general anesthesia. It is important to ensure that motor, sensory, and sympathetic blocks have regressed; suitable criteria to judge block regression include normal perianal (S4-S5) sensation, plantar flexion of the foot, and proprioception in the big toe.[56]

Discharge after Single Shot Peripheral Block

For peripheral nerve block, it is safe to discharge patients home before full regression of motor and sensory block. Although the risk of accidental injury is very low,[57] patients should be given written instructions advising them (1) to avoid driving while the leg is insensate, (2) to avoid placing hot pads on the numb limb, (3) to keep the limb elevated as much as possible in the first 24 hours to avoid swelling, (4) to use walkers or crutches when the leg is numb, and (5) to take analgesic medication as soon as the numbness starts to subside and is replaced by a tingling sensation.[1,58]

Discharge after Continuous Peripheral Block

The ability to provide continuous peripheral nerve block to patients safely on an outpatient basis has been a major advance in ambulatory surgery over the past several years. There are more studies showing the efficacy and safety of ambulatory continuous interscalene blocks,[59,60] infraclavicular blocks,[61] axillary block,[62] sciatic nerve blocks,[63-65] femoral nerve block,[66] psoas compartment blocks,[67] and paravertebral block.[68] However, these techniques have the potential for significant complications such as nerve injury, catheter migration leading to local anesthetic toxicity, and unintentional spread of blockade epidurally or intrathecally.[69-71] Discharge in patients with regional anesthesia should include clear instructions with a written copy regarding cautions and limitation of continuous regional blocks.[72] Telephone communication must be available to the patient at all times. The instructions should also vary depending on the site of catheter placement. Patients with an upper-extremity catheter should

be instructed to protect their arm in a sling. Patients with a lower-extremity catheter must be instructed to have aid for ambulation and to avoid weight-bearing on the surgical extremity. These precautions, along with standard discharge criteria, are an essential part of good practice.

Discharge for Patients with Suspected Malignant Hyperthermia

Malignant hyperthermia (MH) is a rare condition and does not lend itself to large prospective studies. Knowledge of this condition and its management in the ambulatory setting is largely derived from case reports, audits, and retrospective cases, and hence the level of evidence is poor. Traditionally, overnight hospitalization of the patient with suspected or confirmed MH was a common practice. To determine whether hospitalization for MH-susceptible (MHS) patients is required, the charts of 303 children labeled MHS who underwent surgery with trigger-free anesthesia on 431 occasions were reviewed.[73] Ten patients developed fever, but none were considered to be MH. The authors recommend that MHS is not an indication for postoperative hospital admission. These findings are again confirmed in a large prospective audit investigating possible adverse reactions in patients suspected of MH.[74] The incidence of MH after a trigger-free anesthetic has been estimated to be less than 1%.[75,76] In a large population of MHS patients, the charts of 2124 who underwent elective muscle biopsy for MH were reviewed.[75] Five patients (0.46%) had MH-like reactions, and all the reactions were seen in the immediate recovery room; four of these patients received intravenous dantrolene as a part of therapy. Current available literature suggests that overnight hospitalizations may not be required as long as a trigger-free anesthetic is provided and body temperature is monitored and remains normal for at least 4 hours postoperatively. These are recommendations in keeping with the guidelines of the Malignant Hyperthermia Association of the United States. It is important to give written instructions regarding how to monitor temperature of the patient at home and how to recognize signs of malignant hyperthermia with contact details to seek medical attention if necessary before discharge of patients.

Reliable Escort

Meeting a set of standard discharge criteria before discharge is not the end of quality ambulatory surgical care. The presence of an escort, clear verbal instructions, and written postoperative instructions are crucial for safety of patients before discharge. A recent study reported that 0.2% of ambulatory surgical patients did not have an escort.[77] Another survey indicated that 11% of anesthesiologists would be willing to anesthetize patients for ambulatory surgery without the availability of an escort to take patients home.[78] This is in contrast to the guidelines issued by professional associations such as the American Society of Anesthesiologists (ASA), Canadian Anesthesiologists Society (CAS), Association of Anaesthetists of Great Britain and Ireland (AAGBI), and Australian Day Surgery Council.[79-82] The major concern with an absence of an escort is that the patient may drive, operate machinery, or become involved in unsafe activities that are not intended. These may lead to serious consequences such as car accidents and may have medicolegal implications for the anesthesiologist. A number of factors can impair performance of patients[83-87] (Box 45-4).

BOX 45-4 Common Factors That Impair Driving

- Lack of sleep
- Stress of surgery
- Residual effects of anesthetic[87-90]
- Type of surgery[91]
- Residual motor block after local or regional anesthesia

Chung and colleagues[88] compared the driving performance in a simulator in patients who had their surgery performed under general anesthesia with healthy, nonanesthetized controls. In this study, simulated driving in patients was impaired both preoperatively and postoperatively. Performance was worst 2 hours postoperatively, a crucial time, because many patients met discharge criteria within 2 to 3 hours. Within 24 hours, driving simulation performance had returned to normal. The results of this trial support the current recommendations not to drive for 24 hours after ambulatory surgery.[88]

In another study, the brake response time for driving returned to normal at 3 weeks in patients who underwent total knee arthroplasty for osteoarthritis.[89] These studies denote that the degree of functional recovery may vary depending on the type of anesthetic and the type of surgery. In the context of the available literature, if no escort is available before surgery, the elective procedure should be canceled or the patient should be admitted overnight. If an escort is not available after anesthesia is given, elective hospital admission should be arranged.

Most ambulatory surgical units verify the presence of an escort, but it may be difficult to ensure the compliance of postoperative instruction. Correa and colleagues[90] reported that 4% of patient drove within 24 hours and 4% of patients were alone despite a clear postoperative instruction.[90] These results were confirmed by another survey where 1.3% of patients spent the night alone and 4.1% drove home within 24 hours after ambulatory surgery.[91] Although it is impossible to ensure compliance with postoperative instructions, it is essential to educate patients, and their caregivers, regarding the potential hazards of not complying with the recommendation.

POSTANESTHESIA CARE

The safe transition of patients through the three phases of recovery requires standard patient care in the PACU and ASU. Postanesthesia care refers to those activities undertaken to manage patients following the completion of surgical procedures and the concomitant primary anesthetic.[92] The American Society of Anesthesiologists Task Force provides a practice guideline for standard

postanesthesia care.[92] The guideline emphasizes the need for periodic perioperative patient assessment and monitoring and recommends treatment during emergence and recovery in the PACU. Perioperative patient assessment includes monitoring of respiratory and cardiovascular function, neuromuscular function, mental status, temperature, pain, nausea and vomiting, drainage and bleeding, and urine output. Treatment recommendations during emergence and recovery in the PACU include prophylaxis and treatment of nausea and vomiting, administration of supplemental oxygen, fluid administration and management, normalizing patient temperature, and pharmacologic agents for reduction of shivering and antagonism of the effects of sedatives, analgesics, and neuromuscular blocks.

The guidelines do not recommend any specific discharge criteria but focus on the need to adopt discharge criteria that are suitable to the local ambulatory surgical setting. The guidelines also suggest that a discharge scoring system may be helpful in documentation of fitness for discharge.

AREAS OF UNCERTAINTIES

Anesthesiologists, to a large extent, have focused on patient care to the point of the patient's discharge. Unfortunately, postdischarge symptoms such as nausea and vomiting are aspects of ambulatory anesthesia that have been overlooked. Relatively little research to date has examined these unpleasant and distressing symptoms. The incidence of postdischarge nausea and vomiting (PDNV) can be as high as 30% to 50%.[93,94] This high incidence of PDNV is clinically important, especially when recognizing that 65% to 70% of surgeries are performed in the ambulatory surgical setting. The treatment of this complication should extend beyond discharge from the hospital because one third of patients continue to have PDNV after returning home. More research needs to be conducted in this area. The scope for further study includes identification of specific risk factors, antiemetic efficacy in postdischarge settings, the effectiveness of a detailed education program for patients, and the possible economic impact.

The presence of a reliable escort before the patient is discharged is emphasized by most anesthesia professional associations. However, the presence of a responsible caregiver at home, who can cater to the needs of the discharged patient in the postdischarge setting, is not clear. The functional status of these discharged patients may be reduced for up to 7 days, which is both unpleasant and disturbing.[95] More studies are needed to address the functional status of patients during the postdischarge period and the need for a responsible adult during those times.

GUIDELINES

The major concern for patients without an escort is that they may drive home after ambulatory surgery. Patients may be noncompliant with postoperative instructions, which can lead to potential hazards. The American Society of Anesthesiologists' guidelines do not comment on the issue of driving. The minimum duration required for patients to resume driving based on the type of surgery is still an area of uncertainty, which emphasizes the need for further focused research.

AUTHORS' RECOMMENDATIONS

- The success of safe ambulatory surgical care depends on appropriate patient selection and timely discharge.
- Discharge scoring systems such as the Aldrete score, the postanesthesia discharge score, and fast-tracking can facilitate safe transition through the three phases of recovery.
- Shifting from previous traditional discharge criteria by excluding mandatory drinking and voiding will enhance the speedy discharge.
- Patients at low risk for urinary retention can be discharged home without voiding, and should be instructed to return to the hospital if they are unable to void within 6 to 8 hours. Patients at a high risk of urinary retention should be required to void before discharge and display a residual volume of less than 400 mL. If the bladder volume is more than 500 to 600 mL, catheterization should be performed before discharge.
- Patients are no longer required to drink fluids before discharge.
- Regional anesthetic techniques are well-suited for ambulatory surgery, but discharging such patients requires specific considerations and patient education, apart from the standard discharge criteria.
- Inclusion of antiemetics in the postdischarge prescription, along with analgesics and other required medication, may improve the patient's overall comfort in postdischarge settings.
- Discharge criteria and discharge scores assess home-readiness but not street fitness, as functional recovery may vary depending on the type of anesthetic and type of surgery.
- The presence of a reliable escort, clear written instructions, and clear verbal instructions are crucial for patient safety before discharge.
- If an escort is not available after anesthesia is given, elective admission should be arranged.
- Patients should not drive or operate machinery for 24 hours after ambulatory surgery.

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CHAPTER 46

What Must I Consider in Order to Safely Anesthetize Someone in the Office Setting?

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INTRODUCTION

A hospital and a freestanding ambulatory surgery center (ASC) were once considered the only locations in which to perform a safe anesthetic and surgical procedure. However, since the latter part of the twentieth century, this assumption has been challenged. Private surgical offices have become increasingly viable anesthetizing and surgical and procedural locations. This has been made possible, in part, because of the introduction of "shorter-acting" anesthetics with fewer hemodynamic side effects,[1,2] as well as the development of minimally invasive surgical techniques.[3-5] The American Society of Plastic Surgeons (ASPS) estimated that in 2004, 9.2 million cosmetic procedures were performed in plastic surgeons' private offices.[6] By 2005, the American Hospital Association reported that 82% of all procedures were performed on an ambulatory basis, and of these, 16% were performed in a private office.[7]

Office-based procedures offer many advantages over traditional procedures at hospitals or freestanding ASCs. These include cost containment, patient privacy, ease of scheduling, and decreased risk of nosocomial infection.[8,9] This improvement in surgical convenience is not without its potential costs. The lay press has reported that an office-based surgical procedure may not be as safe as the same procedure performed in a traditional hospital or ASC.[10] After analyzing data from Florida office-based surgery, Vila and colleagues[11] reported as much as a 10% increase in morbidity and mortality rates associated with surgery in an office when compared with a hospital or ASC. However, contradictory data do exist.[12-15] An article by Hoefflin and colleagues[13] found no complications after 23,000 procedures conducted in an office under general anesthesia (GA). Fletcher and colleagues[16] retrospectively reviewed the outcomes of an office performing more than 5000 surgical procedures by five independent surgeons, and no deaths occurred over the 5-year period. A retrospective study of adverse outcomes in 3615 consecutive patients undergoing 4778 procedures in offices between 1995 and 2000, using monitored anesthesia care, reported no deaths.[17] Determining the true safety record of procedures performed in an office is difficult because of the relative lack of data. Currently, the incidence of morbidity and mortality for an anesthetic is approximately 1/400,000. Thus to illustrate whether an office-based anesthetic is equivalent, a large sample size would be required (Tables 46-1 and 46-2). These tables illustrate the concept that even if the risk of a complication is very small (1/100,000), very large sample sizes are required to give a true estimation of the risk. Thus for example, if 50,000 procedures were done safely, one could inaccurately determine the risk to be zero.

Safety in any office-based setting is contingent on a number of factors, all of which must be ensured before an anesthetic procedure is undertaken. Metzner and colleagues[18] recently reported on the safety concerns for anesthesia performed outside the traditional hospital operating room. They observed that 50% of all cases of lawsuits involving a nonoperating room location resulted from the use of monitored anesthesia care. They also reported that adverse outcomes due to respiratory events were more common in this remote location when compared with a traditional operating room, and better monitoring could have prevented these injuries (approximately 32%). Finally, the proportion of claims for death was 54% as opposed 29% in the hospital operating room.[18]

COMPONENTS OF OFFICE SAFETY

Physical Considerations

The physical design of the office (i.e., ensuring adequate space for all operating room functions; consideration for anesthesia equipment, particularly the availability and placement of oxygen lines and venting opportunities; and emergency egress for an anesthetized patient), perioperative monitoring capabilities, office staffing, governance, policies and procedures (including emergency admission planning, fire safety, and infection control), and accreditation status are important components of office safety. Presently, there are several nationally recognized agencies that can accredit an office-based surgical site. These agencies include The Joint Commission (TJC), the American Association for Accreditation of Ambulatory Surgery Facilities (AAAASF), and the Accreditation Association for Ambulatory Health Care (AAAHC). Most states that regulate office-based surgery and anesthesia require that every office be accredited by one of these bodies or that the office be Medicare-certified

TABLE 46-1 **Likelihood of Detecting a Complication When the Risk is 1 per 10,000**

Risk	Risk of "Failure"	Sample Size	Likelihood of "Failure"*	Risk of Complication Occurring
1:10,000	0.9999	10	99.9%	0.1%
1:10,000	0.9999	100	99.0%	1.0%
1:10,000	0.9999	1000	90.5%	9.5%
1:10,000	0.9999	10,000	36.8%	63.2%
1:10,000	0.9999	100,000	0.0%	100.0%

*Failure to see the complication.

TABLE 46-2 **Likelihood of Detecting a Complication When the Risk is 1 per 100,000**

Risk	Risk of "Failure"	Sample Size	Likelihood of "Failure"*	Risk of Complication Occurring
1:100,000	0.99999	10	100.0%	0.0%
1:100,000	0.99999	100	99.9%	0.1%
1:100,000	0.99999	1000	99.0%	1.0%
1:100,000	0.99999	10,000	90.5%	9.5%
1:100,000	0.99999	100,000	36.8%	63.2%

*Failure to see the complication.

under Title XVIII. Additionally, the ASPS has required that all its members operate exclusively in accredited offices or forfeit their societal membership since 1996. It must be noted, however, that accreditation is on a cycle of between 6 months and 3 years, and between site visits, it is imperative that practitioners be constantly vigilant in maintaining a safe anesthetizing location.[19]

Physician Qualifications

The physician performing the office-based procedure should be certified by one of the boards recognized by the American Board of Medical Specialties or the American Osteopathic Association. It is also recommended that the surgeon or proceduralist have privileges to perform the proposed procedure at a local hospital. They should also have admitting privileges in a nearby hospital for an unplanned emergency admission.

For both the anesthesiologist and proceduralist, active license, registration, and Drug Enforcement Administration (DEA) certificate as well as adequate malpractice coverage must be maintained and continuing medical education (CME) credit earned. Peer review and performance improvement must occur.

Patient and Procedure Selection

A determination of the procedures to be performed and appropriateness of individual patients to undergo that procedure in this venue must be clearly defined.[20] Patients with significant comorbidities are not ideal candidates and should be excluded from this type of surgical environment.[21] Specifically, only American Society of Anesthesiologists (ASA) physical status (PS) 1 and 2 patients should undergo GA, although occasionally an ASA 3 patient may be acceptable.

The patient with the anticipated difficult airway may cause a problem for the office-based practitioner. One of the earliest steps in the difficult airway algorithm endorsed by the ASA is to call for help. In the office-based setting, there will likely be no other experienced individuals present. It is therefore intuitive that patients with anticipated difficult airways not be anesthetized in this venue. It would, however, be difficult to design a randomized prospective study to evaluate this issue.

Certain procedures are not suitable to be performed in an office.[17] Procedures that create significant physiologic derangements, including significant pain or large fluid shifts, are better suited for a hospital or ASC. Determining whether a particular procedure is appropriate involves consideration of the patient's comorbidities. For example, an obese, asthmatic ASA PS 3 patient may safely undergo a cataract extraction in an office with local anesthesia, whereas this patient may not be suitable for a rhytidectomy under GA.

EVIDENCE

The ASA is a strong proponent of patient safety. Consequently, it has become a leader in advocating that all anesthetizing locations meet the same safety standards and has published recommendations specifically for the office-based anesthesiologist.[22] The ASPS has, likewise, published guidelines for its members.[23,24] However, the field of office-based surgery and anesthesia is completely unregulated in many states; it thus becomes the joint responsibility of the individual surgeon or proceduralist and the anesthesia provider to ensure that patient safety is a priority in each office and to follow all applicable local, state, and society-mandated regulations.

BOX 46-1 Risk Factors for Deep Vein Thrombosis (DVT)

- Age greater than 40 yr
- Anti-thrombin III deficiency
- Central nervous system disease
- Family history of DVT
- Heart failure
- History of a DVT
- Hypercoagulable states
- Lupus anticoagulant
- Malignancy
- Obesity
- Oral contraceptive use
- Polycythemia
- Previous miscarriage
- Radiation therapy for pelvic neoplasms
- Severe infection
- Trauma
- Venous insufficiency

The field of office-based anesthesia is primarily conducted outside academic medical centers, and the reporting of adverse outcomes is often voluntary; therefore prospective scientific data about the field of office-based anesthesia and surgery in the literature are sparse.[25] One can only extrapolate data regarding procedure and patient selection from the specialty of ambulatory anesthesia and apply it to the office-based setting. Much of the available literature regarding office-based anesthesia comes from a retrospective analysis of the experience in Florida,[26,27] which looks at perioperative deaths and what may have been done to prevent them. Vila and colleagues[11] determined that adverse incidents occurred at a rate of 5.3 per 100,000 procedures in ASCs, but they occurred at a rate of 66 per 100,000 in offices. Similarly, the death rate per 100,000 procedures was 0.78 in ASCs and 9.2 in offices.

One certainty in office-based anesthesia (OBA), as well as anesthesia delivered in more traditional locations, is the direct relationship between a patient's preoperative health and the potential for developing perioperative deep vein thrombosis (DVT).[18] Pulmonary embolism has been shown to be a significant cause of death after office-based surgical procedures.[28,29] Reinisch and colleagues[28] found that 0.39% of patients (37/9493) who underwent rhytidectomy developed DVT. Of these, 40.5% (15/37) subsequently had pulmonary embolism. Further, it was noted that although GA had accounted for only 43% of the anesthetic techniques used for the rhytidectomy, 83.7% of the embolic events were associated with the patient having undergone GA. Risk factors for the development of DVT appear in Box 46-1.[28]

When unfavorable outcomes do occur, they are most often secondary to inadequate perioperative patient monitoring, oversedation, and thromboembolic events.[30,31]

AREAS OF UNCERTAINTY

Because there is little scientific data to exclude any particular patient from undergoing an office-based anesthetic procedure, there are no set standards for patient selection. However, the ASA does recommend that the anesthesia provider specifically consider coexisting diseases, previous adverse reactions to anesthesia, current medications and allergies, NPO (nothing by mouth) status, potential difficult airway status, substance abuse, and the availability of an escort when considering a patient for an office-based surgical procedure.[22]

GUIDELINES

The ASPS has published a practice advisory dealing with patient and procedure selection for the office-based practitioner.[23,24] It should be noted that although there are few data to support the *exclusion* of specific procedures or specific patient populations from an office-based surgical setting, certain basic physiologic principles can be applied to these venues.

Acute blood loss will limit oxygen-carrying capacity and may lead to hemodynamic instability. It is therefore recommended that procedures with anticipated blood loss exceeding 500 mL be conducted only in centers where blood products are readily available.[24]

Hypothermia is associated with marked physiologic impairment, including platelet dysfunction, altered drug metabolism, tissue hypoxia, and increased incidence of postoperative infection. GA will routinely cause some degree of hypothermia because of redistribution of body heat from the core to the periphery secondary to vasodilation. Additionally, thermoregulation of the hypothalamus is directly inhibited by most general anesthetic agents.[32] The ASPS recommends that active patient warming equipment such as forced-air warming devices and fluid warmers be used. If warming equipment is not available, it is recommended that the procedures be less than 2 hours in duration and be limited to 20% of body surface area.[13]

A plastic surgery procedure commonly performed in the office environment is liposuction.[33,34] Surprisingly, very little scientific evidence is available about its safety. However, one of the physiologic changes associated with the procedure is well-understood.[35] Large-volume liposuction (more than 5 L of lipoaspirant) is associated with significant derangements in normal physiology.[36] Although the data to exclude specific volumes of aspirant from an office-based procedure are not available, the ASPS recommends limiting total aspirant to 5000 mL or less. It also cautions against performing large-volume liposuction when combined with another procedure.[37]

There is debate among clinicians about the suitability of patients with obstructive sleep apnea syndrome (OSAS) for ambulatory-based procedures.[38] This group has a high incidence of perioperative respiratory difficulty.[39] Although evidence-based data are sparse, the ASA has published "Practice Guidelines for the Perioperative Management of Patients with Obstructive Sleep Apnea."[40] The scientific data for the ASA recommendations regarding patient selection are considered insufficient (too few studies to investigate a relationship between intervention and outcome). However, the consultants offer recommendations regarding patient and

TABLE 46-3 Stratification of the Risk of Thromboembolism

	Cohort	Treatment
Low risk	No risk factors Uncomplicated surgery Short duration	Comfortable position Knees flexed at 5 degrees Avoid constriction and external pressure
Moderate risk	Age > 40 with no other risks Procedure > 30 min Oral contraceptive use	Proper positioning Intermittent pneumatic compression of calf or ankle (prior to sedation and continued until patient is awake and moving) Frequent alterations of the operating room table
High risk	Age > 40 with concomitant risk factors Procedure > 30 min	Treatment as per patients with moderate risk Preoperative hematology consultation with consideration of perioperative antithrombotic therapy

procedure suitability for an ambulatory anesthetic. Most agree that superficial surgery or minor orthopedic procedures under local or regional anesthesia and lithotripsy are acceptable ambulatory procedures. They also recommend that airway surgery (such as uvulopalatopharyringoplasty), tonsillectomy in patients younger than 3 years, and upper abdominal laparoscopy should not be performed on an outpatient basis. They were equivocal in their opinions about the suitability of superficial surgery under GA, tonsillectomy in patients older than 3 years, minor orthopedic procedures under GA, and pelvic laparoscopy. These recommendations were created for ambulatory procedures, but it is intuitive that they, at a minimum, should be adhered to in an office setting when the risks of treating patients with OSAS are being considered.

The ASPS recommends that patients be stratified according to risk and that the prophylactic treatment be directed by risk (Table 46-3).

Duration of the procedure has long been correlated with the need for hospital admission. Originally, procedures lasting more than 1 hour were found to be associated with a higher incidence of unplanned hospital admission.[41] More recent data suggest that procedure duration alone is not predictive of an unplanned admission; rather, the patients' pre-existing comorbidities and the procedure itself are more predictive.[42] It is also important to note that longer procedures are often associated with postoperative nausea and vomiting, postoperative pain, and bleeding.[43,44] These conditions may subsequently warrant admission. For these reasons, the ASPS has recommended that procedures be limited to 6 hours and be completed by 3 PM, which will allow a full patient recovery with maximum office staffing.[25]

AUTHORS' RECOMMENDATIONS

Before an office-based anesthetic procedure is undertaken, many considerations must be discussed and agreed on by the anesthesiologist and surgeon or proceduralist, remembering that many of the safeguards inherent in a hospital system will not be present. The checklist provided in Box 46-2 should serve as a template for the delivery of safe office-based anesthesia.

BOX 46-2 Safety Checklist for Office-Based Anesthesia Providers

Office
- Accreditation status
- Design and layout
  - Adequate space for procedure
  - Adequate space for recovery
  - Safe emergency egress for an anesthetized patient
- Policies and procedures manual
  - Office governance
  - Infection control
  - Emergency preparedness
  - Narcotic storage and maintenance
  - Gas transport and storage
- Perioperative monitoring capabilities and defibrillator Maintenance and servicing
- Oxygen, suction, positive pressure ventilation (anesthesia machine)
- "Crash cart"
- Emergency/anesthetic drugs and supplies
- Staffing

Proceduralist/Surgeon/Anesthesia Provider
- Active license and registration
- Current Drug Enforcement Administration number
- Malpractice
- Evidence of proficiency/board certification
- Admitting privileges
- Current curriculum vitae
- Continuing medical education
- Peer review/performance improvement
- Admitting privileges
- BLS/ACLS/PALS certification

Patient Selection
- American Society of Anesthesiologists physical status
- Coexisting diseases
- Difficult airway
- Deep vein thrombosis prophylaxis

Procedure Selection
- Duration
- Risk of hypothermia
- Risk of blood loss
- Postoperative pain
- Postoperative nausea and vomiting
- Fluid shifts

BLS/ACLS/PALS, Basic Life Support/Advanced Cardiac Life Support/Pediatric Advanced Life Support.

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CHAPTER 47

Is Propofol Safe If Given by Nonanesthesia Providers?

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INTRODUCTION

Propofol is a sedative–hypnotic that was commercially introduced into U.S. anesthetic practice in 1989.[1] Released under the trade name of Diprivan, it rapidly gained acceptance in the anesthesia community as an induction agent because of its rapid onset of action and other favorable pharmacokinetic properties. Because propofol undergoes a two-phase distribution, with the first phase lasting only 4 to 6 minutes, the sedative effects of a single bolus dissipate rapidly.[1] Thus it was soon recognized that the "rapid-on, rapid-off" profile of propofol also made it an ideal agent for sedation either as a continuous infusion or in small boluses.[2,3]

OPTIONS

Even before its commercial release in the United States, specialties outside anesthesiology began to report on the use of propofol for procedures requiring sedation.[4] Standard agents for procedures occurring in radiology and endoscopy suites, dental offices, and emergency departments were opioids and long-acting sedatives such as benzodiazepines. However, recovery from the prolonged effects of these medications was troublesome, and clinically significant side effects such as respiratory depression limited the amounts administered. The rapid redistribution properties of propofol and its minimal effects on most patients' hemodynamic variables made it appear to be a much safer alternative.

The pharmacokinetic properties of propofol allow patients to emerge more quickly after administration, and they appear less sedated compared with other barbiturate or benzodiazepine combinations, even though complete elimination from the body can take hours or even days.[1] It also may produce amnesia and has a dose-dependent, mood-altering effect that can be euphorogenic.[5] Studies have shown that mood and psychomotor function return to baseline within an hour or less after brief infusions of the medication are stopped in healthy volunteers,[5,6] which is similar to other modern general anesthetics.[7] Propofol also has an antiemetic effect[1] that further supports its selection for procedures in an outpatient setting.

Unfortunately, the ideal anesthetic agent does not exist, and propofol has its share of undesirable side effects. Most notable is the dose-dependent respiratory depression that can abruptly result in apnea or airway obstruction. This effect ends quickly when administration is stopped,[1] which gives a false sense of safety to those providing or directing the sedation. Another commonly encountered effect is the decrease in mean arterial pressure that is similar[8,9] or somewhat more pronounced[6,10] when compared with other sedative–hypnotics. Again, these observed effects end quickly when dosing stops.

EVIDENCE

Investigators in three medical specialties and dentistry have compared propofol with other traditional options and currently recommend propofol as a safe addition to everyday practice, supporting its administration by practitioners who are not anesthesia professionals. In nearly every instance, studies conclude that propofol is associated with minimal postprocedural sedation, which results in a faster recovery, provides amnesia and comfort to the patient, delivers better procedural conditions, and has a better safety profile than traditional choices.

Evaluation of the data on propofol use by nonanesthesia providers is complex because of several factors, the foremost of which is the lack of adequately powered studies that statistically support the conclusions made. In addition, a direct comparison among the different specialties cannot be made. Procedural needs, patient presentation, and defined endpoints are quite different for each specialty. Gastroenterology has evolved from simple procedures such as colonoscopy and diagnostic esophagogastroduodenoscopy (EGD) that require only moderate sedation, to more invasive and stimulating ones such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS). The diagnostic and therapeutic value of these newer endoscopic methods has led to a substantial increase in annual procedural numbers,[11] but by their very nature, they require deeper sedation for patient acceptance and optimal conditions. The traditional approach has been to combine a benzodiazepine with or without an opioid,[12] and this is the combination against which propofol-based sedation protocols with or without adjuvants are compared. Similarly, physicians in the specialty of emergency medicine are often faced with the need for deep sedation and analgesia to perform short, painful procedures such as the reduction of a dislocated joint or closed fracture.[13] The specialty of radiology has supported the

development of pediatric sedation units (PSUs) primarily for radiologic procedures. The sedation teams are supervised at times at a distance by pediatric intensivists[14] or emergency department physicians.[15] Because these cases can require hours of sedation,[14,15] propofol is one of several options used. Finally, dentistry has long been associated with painful procedures. Although local infiltration or nerve blocks remain the techniques of choice, patients may receive supplemental sedation to accompany the procedure, especially at the time of the nerve block or local infiltration.[16] Current studies report sedation being maintained throughout the entire procedure, albeit at a more responsive level.[17]

The American Society of Anesthesiologists (ASA) House of Delegates approved a document in 1999 describing the continuum of depth of sedation.[18] However, the aforementioned specialties had already begun to report on sedation with propofol against other traditional medications and, in so doing, used the definitions for sedation depth to which they were accustomed. This makes comparisons between fields difficult (Table 47-1). Studies often report the use of basic monitors such as a pulse oximeter and automated blood pressure cuff (except in dentistry), but supplemental oxygen and capnography are not standard. Even though propofol is commonly used for sedation in the critical care unit, there is often input from the available anesthesiology service and patients receive ventilation under heightened monitoring conditions; therefore the critical care unit setting will not be considered in this chapter.

Gastroenterology

There are two meta-analyses and a Cochrane Database review on the administration of propofol by nonanesthesia personnel for moderate sedation in endoscopic procedures.[22-24] Of these, the Cochrane review discusses the use of propofol for colonoscopy only; one meta-analysis reviews the use of propofol for diagnostic EGD and colonoscopy but not for those procedures requiring deep sedation such as ERCP, enteroscopy, or EUS[22]; and the other analysis reviews studies that included colonoscopy, EGD, and ERCP.[23]

The Cochrane Review analyzed 22 studies published since 1989, of which most were small, randomized controlled trials (RCTs) of limited power.[24] The review's primary objective was to appraise studies that evaluated the safety and efficacy of propofol, either alone or in combination with adjuvants, in comparison with the traditional medications of benzodiazepines, opioids, or both. A secondary objective was to assess studies that compared the administration of propofol by nonanesthesia personnel to that by anesthesia professionals, but only one study reported that comparison. Although several of these studies show similar outcomes between providers, they do not have sufficient power to detect a statistical difference in the outcomes of interest. The Cochrane review authors noted that the studies were generally of poor quality and concluded that studies of better design, sufficient power, and standardized outcome reporting are needed, as well as comparative data about propofol administration by nonanesthesia personnel versus anesthesia professionals.

The meta-analysis by Qadeer et al[23] evaluated 12 studies that specifically compared the incidences of hypoxia (defined as a pulse oximetry reading of less than 90), hypotension (defined as a systolic pressure less than 90 mm Hg), arrhythmias, and apnea from sedation with the use of propofol against traditional techniques for colonoscopy, EGD, and ERCP. Anesthesiologists administered the sedation in two of the studies; in one of these, the propofol arm was a patient-controlled design that was compared with traditional sedation by the anesthesiologist. Two other studies did not specify the sedation administrator, one used a nurse directed by the endoscopist, and the remaining seven used an endoscopist dedicated to the sedation. Hypoxia and hypotension occurred frequently with both sedation techniques, and arrhythmias and apnea were rare but of equal frequency when reported, which makes a statistical comparison of frequency not possible. One study of the 12 markedly favored propofol, and when the authors removed that study in a sensitivity analysis, they acknowledged an implied influence. Nonetheless, they reported that the pooled analysis demonstrated a 26% lower incidence of the defined complications when propofol was used, which led them to conclude that propofol had a lower risk profile than traditional methods for colonoscopy but not for EGD or ERCP. Of note, they added that better studies are needed to prove its superiority.

TABLE 47-1 **Sedation Scales**

Ramsay Sedation Scale[19]		ASA Continuum of Depth of Sedation (Responsiveness)[18]	Observer's Assessment of Alertness/Sedation (OAA/S)[20]	
6	No response	General anesthesia	0	No response to pain
5	Sluggish to light glabellar tap/noise	Deep sedation/analgesia	1	No response to mild prodding/shaking
4	Response to light glabellar tap/noise	Moderate sedation/analgesia	2	Responds to mild prodding/shaking
			3	Responds to loud noise or repeated name
3	Responds to commands only		4	Lethargic response to name called
2	Cooperative, oriented, calm	Minimal sedation to awake	5	Responds to name, alert
1	Anxious, agitated, restless	Not defined	6*	Anxious, agitated, restless

*The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) includes level 6.[21]

The meta-analysis by McQuaid et al[22] compared sedation techniques used for diagnostic EGD and colonoscopy. Inclusion criteria were studies in which protocols included both traditional and propofol-based practices used in healthy, adult, outpatient populations with the goal of moderate sedation. Thirty-six RCTs, systematic reviews, and the Qadeer et al meta-analysis were included for assessment, in which the primary goal was to evaluate patient satisfaction, physician satisfaction, and efficiency metrics. In this analysis, who administered the sedation was not specifically reported other than to state it was a health care professional. It also rated the methodologic quality of each study using a tool called the Jadad scale.[25] This scale assigns a score of 0 to 5, and a score of 3 or less means the study is of relatively poor quality. Of the studies meeting inclusion criteria, 23 of the 36 rated a 3 or less on the Jadad quality scale. The authors concluded that traditional sedation protocols and those that use propofol have similar outcome profiles when the goal is moderate sedation; the only exception is that recovery times for propofol-based methods are significantly shorter. Moreover, they acknowledged that higher quality RCTs are needed to better assess the role of propofol either alone or with adjuvants for moderate sedation.

Aside from the studies included in the meta-analyses and Cochrane review, the number of RCTs published within the past decade that compared propofol with or without other medications against traditional protocols and that used nonanesthesia professionals to administer the sedation is difficult to determine. Many do not report who gave the sedation in the newer publications. More concerning, one survey from 2006 noted 25% of endoscopy units in the United States use propofol for routine procedures, and of those not yet doing so, 68% plan to move to it in the future with proper staff training.[26] This same survey reported that 82% of propofol-based sedation was provided by an anesthesia professional at that time but that, in some European countries, such as Switzerland, the incidence of nonanesthesia personnel administering propofol was 34%. The recent literature suggests this shift may be happening.

Earlier RCTs focused on the safety of propofol as an alternate sedation strategy in endoscopy units and whether nonanesthesia personnel could safely administer it either under endoscopist direction, by protocol, or via patient-control. These studies tended to use healthy patients undergoing routine procedures requiring moderate sedation. Table 47-2 summarizes these earlier studies, of which two were designed to demonstrate the safety of using registered nurses to administer the sedation while under the direction of the endoscopist,[27,28] one compared patient-controlled sedation (PCS) against nurse-administered sedation (arguing that nurse administration was preferred),[29] and one other argued that the use of another endoscopist to administer the propofol was not cost-effective.[30] Trained nurses were identified as the most cost-effective providers of propofol.[30,31] Hypoxia was the most common complication, yet supplemental oxygen was not given in one study[30] and only 2 L/min was delivered in four.[28,29,32,33] The incidence of hypoxia and other defined complications were similar with either sedation technique, but valid statistical evaluations could not be made. Recovery was faster in the groups that received combination therapy and were kept to a moderate level of sedation. These early reported findings in the endoscopy literature laid the foundation for two more recent RCTs that studied propofol use for more invasive procedures in sicker patients.[35,36] Although these studies were underpowered, they concluded that nurse-administered propofol sedation in this sicker population was not associated with a higher incidence of complications and thus was safe[35]; patients given propofol had faster recovery times and propofol was more efficient[36]; and propofol was better tolerated in an elderly population with liver disease.[35,36]

Among the prospective, non–evidence-based studies reviewed, several trends are apparent. Within the endoscopy literature, depth of sedation is most often assessed with the use of either the Observer's Assessment of Alertness/Sedation (OAA/S) scale or its modified version (MOAA/S) (see Table 47-1). The ASA sedation continuum scale is not used. The deepest sedation level on the OAA/S scale is 0, defined as no response to painful stimulation. This corresponds to the ASA definition of general anesthesia. In studies in which sedation levels were reported, intraprocedural levels were often in the 0 to 2 range of the OAA/S scale,[21,37,38] except when patients controlled their own level of sedation.[39] Hypoxia is the most frequent complication and is defined as a measured pulse oximetry reading of less than 90%. Despite this, some studies did not report the use of supplemental oxygen,[40,41] and only a few studies monitored respiratory activity. Two did so using a capnograph[41,42] to look for the presence of a waveform, another did so by "visual inspection,"[43] and in another, the sedating nurse only felt for a breath on the back of her hand.[40] None of the other studies monitored ventilations or respiratory effort,[21,37-39,44,45] and one report went so far as to claim that additional monitoring beyond pulse oximetry is unnecessary for routine diagnostic procedures.[46] This was recommended despite the current statement on respiratory monitoring during endoscopic procedures[47] and the revised ASA basic monitoring standards.[48] More recent publications report on the use of propofol as the primary sedative for more stimulating procedures requiring deeper sedation, under monitoring and administration conditions similar to those applied to healthier patients having diagnostic procedures.[42,43,45] These and older studies consistently report that the clinical and recovery profile of propofol is better than more traditional agents and that death or significant morbidity have not occurred. This has led to recently published guidelines on the use of propofol by nonanesthesia personnel for endoscopic procedures by major gastrointestinal societies.[49,50]

A frequently studied and reported variable in both the RCT literature and nonrandomized articles is the use of nurse-administered propofol sedation (NAPS).* The concept has evolved from that of a nurse solely devoted to the process of sedation following endoscopist direction to the nurse following a set protocol with less input from the endoscopist.[21,40] More recently, an article reported on

*References 21, 27, 29, 40, 42, 43, 45, 51.

TABLE 47-2 **Randomized Clinical Trials of Endoscopic Literature**

Author (Date)	Study	Responsible for Administration of Medications	Medications	Population *(N)*	Mean Dose (mg/kg)	Hypoxia <90% (%)	Hypotension <25% (%)	Heart Rate Changes (%)	Study Conclusions
Lee (2002)[28]	Colonoscopy in >65-yr-olds	Patient-controlled	Pfl and A	50	0.79 NR	0	4	NR	Total Pfl dose was low and allowed a faster recovery. Patient satisfaction was high in both.
		Endoscopist-directed RN	D and Mep	50	5.8 30.1	8	28	NR	
Vargo (2002)[30]	ERCP/EUS	Endoscopist	Pfl	38	4.67	37	16	0	Cost analysis study. End-expired CO_2 measured. No differences in cardiopulmonary parameters. Pfl
		Endoscopist	Mid and Mep	37	0.12 1.54	57	19	8	
Sipe (2002)[27]	Colonoscopy	RN	Pfl	40	2.61	0	0	0	Pfl had faster onset, greater sedation (unresponsive to pain versus response to verbal), and faster
		RN	Mid and Mep	40	0.06 1.09	0	5	5	
Heuss (2004)[29]	Colonoscopy	PCS	Pfl	36	1.78	2	23	NR	Similar cardiopulmonary changes regardless of technique, but 35% of
		NAPS	Pfl	40	1.53	2	25	NR	
Riphaus (2005)[32]	ERCP in >80-yr-olds	Intensivists	Pfl	75	322 mg mean total	9	4	8	ASA III and IV elderly patients. No statistical difference in clinical parameters except desaturation during recovery was less and recovery faster with Pfl.
		Intensivists	Mid and Mep	75	6.3 mg and 50 mg mean totals	11	5	4	
Chen (2005)[33]	ERCP	Intensivists	Pfl	35	NR	6	20	6	With Pfl, 43% had significant changes in blood pressure versus 60%. Heart
		Intensivists	Mid and Mep	35	NR	9	0	11	
VanNatta (2006)[34]	Colonoscopy	Endoscopist-directed RN	Pfl	50	215 mg median dose	0	Cannot interpret	Occurred but cannot interpret data as presented	The mean sedation score (MOAA/S) with Pfl was 0.9 but was >3.0 for the three combinations. The Pfl + F group had the lightest mean sedation score and never reached deep sedation. None had O_2 desaturation below 90%. Shorter recovery times occurred with the mixtures versus Pfl alone.
		Endoscopist-directed RN	Pfl + F	50	140 mg Pfl median dose F: NR	0			
		Endoscopist-directed RN	Pfl + Mid	50	125 mg Pfl median dose Mid: NR	0	0		
		Endoscopist-directed RN	Pfl + Mid + F	50	82.5 mg Pfl median dose F and Mid: NR	0	Cannot interpret		

A, alfentanil; *D*, diazepam; *ERCP*, endoscopic retrograde cholangiopancreatography; *EUS*, endoscopic ultrasound; *F*, fentanyl; *Mep*, meperidine; *Mid*, midazolam; *MOAA/S*, modified Observer's Assessment of Alertness/Sedation; *NAPS*, nurse-administered propofol sedation; *NR*, not recorded; *PCS*, patient-controlled sedation; *Pfl*, propofol; *RN*, registered nurse.

the success of NAPS for endoscopy in which the nurse was no longer only devoted to sedation with propofol but was also performing the other nursing aspects of the endoscopic procedure.[46] Causing a countertrend, in December 2009 the Centers for Medicare & Medicaid Services (CMS) reaffirmed that registered nurses may not administer anesthesia and deep sedation (42 CFR §482.52(a)).

Too recent to be included in the Cochrane review or meta-analyses, two studies compared anesthesiologist-administered propofol sedation with that by nonanesthesia personnel; an endoscopist administered propofol in one study, and PCS was used in the other.[52,53] Both studies reported that the anesthesiologist-based sedation resulted in larger propofol amounts given, which resulted in unnecessarily greater sedation that was without benefit yet did not produce any negative outcomes. In contrast, a cohort study using a large national database comparing anesthesiologist-provided sedation with that given by endoscopists for colonoscopies and EGDs found that the adjusted relative risk of a significant adverse event was 0.5 if an anesthesia professional rather than the endoscopist provided sedation.[54]

Emergency Medicine

Multiple RCTs have been published comparing the use of propofol with traditional and nontraditional medications for sedation and analgesia since 1999.[13,55-63] The conclusion by all these studies is that propofol has an equivalent or improved safety profile over traditional choices after measurement of the incidence of adverse events such as hypoxia and hypotension. The focus of more recent studies is on sedation-to-recovery times, suitability of procedural conditions, and patient satisfaction. The most common types of emergency department procedures used in these studies are major lacerations and fracture and dislocation reductions.

Of the RCTs published, an early study in 1999 evaluated closed fracture reduction and casting in a pediatric population ranging in age from 2 to 18 years.[55] Patients were randomly assigned to receive propofol or midazolam, and all received morphine before the procedure. Hypoxia, defined as an SpO_2 less than 93%, occurred at similar rates for both propofol and midazolam (11.6% and 10.9%, respectively), and oversedation, as defined by a Ramsay score of 6 for 10 minutes or more (see Table 47-1), was the most common complication, occurring at rates of 32.6% for propofol and 34.8% for midazolam.

Three other early RCTs by the same emergency medicine group evaluated the safety and outcomes of propofol against different sedation techniques in the adult population undergoing fracture and dislocation reductions.[13,56,57] Protocols in these studies suggested a routine use of basic monitoring by emergency physicians during procedures that require deep sedation. This is not apparent in the gastroenterology literature. These particular studies also included capnography as a monitor to identify respiratory depression under clearly defined parameters as one of the measured events. In addition, only nonanesthesia personnel administered the sedation, as is common practice in the specialty. In the earliest publication, propofol was compared with methohexital, and bispectral index (BIS) readings were included with their basic monitoring protocol.[56] Of 103 patients, a total of 50 experienced respiratory depression; each group had 25 cases. Of that 50, 61.5% registered a BIS score of less than 70 at some point during the procedure, leading the authors to note that the BIS monitor was not helpful in preventing respiratory depression. The other variables measured were comparable; thus the authors concluded that propofol was as safe as methohexital for sedation in the emergency department. This same group published another study that was similar in design and in endpoint criteria but compared etomidate with propofol.[57] The number of patients who met respiratory depression criteria was not statistically significant: 34.3% in the etomidate group and 42.2% in the propofol group. Need for bag-valve mask assistance (3.8% versus 4.6%), airway repositioning (13.3% versus 11%), and stimulation to induce breathing (11.4% versus 11.9%) were also similar between etomidate and propofol. The BIS monitor was used again in conjunction with the MOAA/S scale and, again, did not add any clinical information beyond that provided by the scale. The study concluded that, although the use of either medication was a safe option, etomidate produced more myoclonus and was associated with a nonsignificant lower procedural success rate. A third study by this group was designed to determine whether aiming for a preprocedural sedation level made a difference in outcome or complications.[13] Patients were assigned to receive deep or moderate sedation as defined by the ASA,[18] and propofol was the only sedative used. The total dose of propofol administered was 1.69 mg/kg in the moderate group and 1.82 mg/kg in the deep group. Of the moderate sedation group, 31% reached deeper than intended levels of sedation, and 46% of the deep sedation group achieved only a moderate level. The mean minimum BIS scores were 67.7 in the moderate group and 59.2 in the deep group. Respiratory depression was similar (49% versus 50%), as were all other measured variables. The authors concluded that targeting to maintain a moderate sedation level and to avoid a deeper level was difficult to accomplish and did not mitigate the occurrence of complications or the risk of respiratory depression. With this study, the authors also concluded that BIS monitoring did not aid in the prevention of respiratory depression and should not be used as a standard monitor.

Emerging in the more recent literature of protocol comparisons for procedural sedation is the use of ketamine. These trials examined outcomes and procedural conditions when ketamine was combined with propofol, a mixture termed *ketofol*, and compared with propofol[58-60] or ketamine.[61] Investigators also studied ketamine compared with propofol as single agents[62] and ketamine plus another medication compared with propofol.[63] No study comparing ketofol with another agent showed a reduction in adverse respiratory events. When ketamine was compared with propofol, patients had longer recovery times with more agitation and a higher rate of subclinical respiratory depression, as noted by capnography.[62] Orthopedic residents with undisclosed training compared the use of ketamine with midazolam against propofol for painful orthopedic manipulations, and although the incidence of

hypotension, apnea, hypoxia, and bradycardia was 20% in the propofol group versus 10% in the midazolam–ketamine group, the authors concluded that propofol was a safe alternative.[63]

Unique to emergency medicine is the issue of the patient with a full stomach requiring deep sedation for painful, albeit short, procedures. Few articles report an occurrence of periprocedural emesis. Of three recent reviews that included emesis as an adverse event, the reported incidences ranged from a high of 8.4% in one pediatric population[64] to a combined low of 1.5% to 1.6%.[65,66] Despite this significant frequency, propofol is considered safe because it produces the same or a lower incidence of vomiting as other sedation protocols.[67,68] Although the specialty acknowledges the risk, it draws a distinction between procedural analgesia and operative anesthesia, noting that aspiration is exceedingly rare; evidence is not sufficient to support the extrapolation of guidelines from operative anesthesia to procedural sedation. Green et al[69] released a consensus-based advisory in 2007 to guide procedural sedation in patients who had not fasted.

Radiology and Pediatric Sedation Units

The first report of a PSU that provided services for radiologic procedures without direct anesthesia professional involvement occurred in 1998.[14] Within this body of literature, only one RCT is published[70]; all other studies are of a retrospective[14,15] and observational nature.[71] The RCT compared propofol sedation with a protocol using pentobarbital–midazolam–fentanyl for magnetic resonance imaging (MRI) scans of the brain in the pediatric population.[70] All patients had pulse oximetry, nasal capnography, and blood pressure monitoring, and all received supplemental oxygen. Both a specially trained nurse and a pediatric emergency medicine physician were present through the sedation period, and the desired level of sedation to achieve was more than 4 on the Ramsay scale (see Table 47-1). The mean total dose of propofol given throughout the procedure was 7.6 mg/kg. For the pentobarbital, midazolam, and fentanyl group it was 4.1 mg/kg, 0.089 mg/kg, and 0.3 mcg/kg, respectively. All adverse events were considered minor and were too few to compare. The authors concluded propofol has a favorable induction and recovery profile while demonstrating efficacy equal to the pentobarbital–midazolam–fentanyl protocol.

Of the early non-RCT literature, two descriptive articles used propofol as a component of the sedation regimen along with opioids, benzodiazepines, and ketamine,[14,15] and one used only propofol.[71] In all three, the physicians involved in drug selection and administration were pediatric intensivists or emergency department physicians. They were not the primary caregivers for the child during transport or the procedure, and specially trained nurses who had varying levels of contact with the supervising physician often performed the maintenance monitoring. In two of the articles, the PSUs were established in consultation with the anesthesia department.[14,71] The other study in which emergency department physicians were providing the sedation service did not state whether the anesthesia department was involved at any time.[15] Deep levels of sedation were intentionally achieved to prevent movement. One study did not report complications from the sedation medications used, but the authors concluded that the practice was safe.[15] Another reported a 4.4% incidence of hypotension, 2.6% incidence of hypoxia, 1.5% incidence of apnea, and 1.3% incidence of airway obstruction. Most interventions for these complications were performed by the sedation nurse, who was present and acting under a protocol with a radio communication device at hand.[14] In the study in which propofol was the only medication used, desaturation occurred in 12.7%, and 0.8% required assisted ventilation for a short period.[71] The authors concluded that propofol for sedation in a PSU with rapid availability of anesthesia personnel, as needed, was safe.

Dentistry

The RCT studies reported in the dentistry literature compared propofol with other traditional medications[72,73] or focused on the effectiveness of different patient delivery modes for sedation using propofol.[16,17] Patients having simple outpatient tooth extraction procedures comprised the study groups in all four articles reviewed, and patients served as their own comparison over two separate sessions. The goal of each design was to achieve satisfactory sedation before local infiltration or a nerve block. Either the patient using a device or a baseline infusion initiated by the practitioner then determined further sedation.

Two studies compared propofol with methohexital[72] or midazolam.[73] One study reported that propofol had a superior recovery profile and better patient acceptance without an increased complication rate,[73] and the other found no difference between the two medications[72]; however, neither study was adequately powered to support its conclusions.

The delivery systems compared for dental sedation used propofol only.[16,17] A continuous infusion was evaluated against two patient-controlled techniques. Variables measured were pulse, respiratory rate, blood pressure, oxygen saturation, sedation levels, recovery time, and patient satisfaction. No cardiopulmonary complications were reported, and recovery times were similar. All patients receiving the continuous infusion of propofol achieved a moderate sedation level where they could be aroused to command,[16] and in neither patient-controlled system did patients reach a level of sedation where they could not be aroused. As seen with other patient-based techniques, the patient-controlled groups used less propofol overall and satisfaction remained high.[16,17]

AREAS OF UNCERTAINTY

It is evident from the literature that propofol use is growing among nonanesthesia professionals. It is equally evident from the more recent literature that propofol is considered a safe alternative with an acceptable profile, and adverse events are no longer the focus of these newer studies. This raises concern because the majority of the studies reviewed are not powered well enough to support

the conclusions, and this lack of power is cited frequently in the meta-analyses as well as the Cochrane review.[22-24] Such confidence in the safety of propofol and growing pressure from payers to justify the increased cost of an anesthesia professional prompted the American College of Gastroenterology (ACG) to petition the U.S. Food and Drug Administration (FDA) to lift the ban on propofol administration by nonanesthesia professionals in 2010. The FDA denied the petition on the grounds that the dosing range required to maintain sedation for endoscopic procedures as described in studies provided by the ACG overlaps that used for general anesthesia.[74] The FDA also reaffirmed that persons administering propofol should not be involved in the conduct of the surgical or diagnostic procedure. Areas of controversy within the anesthesia community continue to revolve around the acceptability of outcomes, adequate monitoring, consistent definitions of sedation depth, and whether the individual administering the medications and monitoring the patient has the necessary education and skills to identify developing problems and implement corrections.

The types and quantities of procedures requiring sedation and analgesia are increasing,[11] and economic and social pressures are mounting for nonanesthesia specialties to provide procedural sedation without an anesthesia professional present.[68,75-77] Studies outside the anesthesiology literature claim that propofol has a comparably safer recovery profile when compared with traditional protocols. However, the FDA in its denial noted that the narrow therapeutic window of propofol makes it easier to overdose the patient, which increases the risk of a significant adverse event, and that the frequency and extent of adverse events were quite significant in all treatment groups.[74] The denial also contains the FDA assessment of the inadequacies of the studies provided by the ACG. Whether with sedation by propofol or by traditional medications, these studies reported periods of apnea, hypotension, hypoxia, and the loss of response to stimulation as acceptable intraprocedural conditions. Unfortunately, no data show whether such short-term events are insignificant and without morbidity over the long term, as assumed by the studies' authors.

Anesthesia professionals believe that well-defined monitoring is the key to maintaining patient safety, and intraprocedural variations in cardiopulmonary variables should be treated promptly. Unfortunately, other specialties differ on which cardiopulmonary variables are monitored, how changes are defined as significant, and whether they are treated. Although basic heart rate, blood pressure, and oxygen saturation measurement, as well as simple observation, are commonly employed, other variables such as adequate ventilation are not routinely assessed. Emergency medicine is one specialty that has actively defined monitoring requirements, including capnography.[56] Researchers have identified that the routine use of supplemental oxygen may delay recognition of apnea or airway obstruction[68] because not all chest wall movement means air exchange, and the measurement of end-expired CO_2 via nasal cannulae may signal the presence of subclinical respiratory depression. Aside from emergency medicine, other nonanesthesia fields do not routinely use more than basic monitoring, if that.[46] Despite hopes that electroencephalographic monitoring such as the BIS would correlate with perceived sedation levels and perhaps reduce adverse events related to oversedation, studies have not shown a correlation.[20,21,56,57] This suggests that the technology as it now exists offers very little, and its use is not recommended by any anesthesia or nonanesthesia specialty.

Another area of concern is the many ways by which sedation depth is defined. Definitions are loosely similar among the scales used, but the numeric designations may cause confusion when comparing the literature (see Table 47-1). To avoid such confusion, it would be helpful if only one scale describing the range of sedation, including the extremes of no sedation and general anesthesia, were universally accepted among the specialties. One-word descriptors such as *minimal*, *moderate*, or *deep* with an explicit, accepted description of the term would give a more comprehensive understanding of the level of sedation than occurs with a numeric value. The ASA has explicit definitions,[18] but providers in other specialties do not universally accept their use. Furthermore, knowledge of the depth at which cardiopulmonary variables may be affected or protective airway reflexes lost would provide better sedation endpoints and might reduce the incidence of adverse events. Unfortunately, the physician's desire to have an unresponsive patient during a procedure may concur with the patient's desire to be unaware and result in oversedation, even though several studies established that deep sedation is not a necessary endpoint for patient satisfaction or procedural success.*

Who is actually administering the medications and how they decide when and what dose is another area of concern to the professional anesthesia community. Endoscopy has been advocating the use of NAPS for some time as a cost-effective and efficient mode.[21,27-31,34,51] However, studies show that the depth of sedation achieved can slip beyond moderate and deep levels into what is commonly understood to be general anesthesia,[21,37,38] and it is sometimes unclear who is ordering the drug doses and their timing. Although the nurse involved in NAPS is separate from the nurse assisting with the procedure in the United States, in one European article, this situation may be changing.[46] Also, patient-controlled computerized infusion systems to provide sedation such as described in the dental literature[17,73] are under development. If these are the coming trends, the need for better monitoring standards, better sedation assessments, and education on the adverse effects of propofol and their treatment are underscored.

GUIDELINES

The ASA has published a number of documents on the use of propofol by nonanesthesia professionals. The most relevant here are "Continuum of Depth of Sedation,"[18] "Statement on the Safe Use of Propofol,"[80] "Statement on Respiratory Monitoring during Endoscopic Procedures,"[81] "Statement for Basic Anesthetic Monitoring,"[48]

*References 17, 28, 34, 39, 41, 73, 78, 79.

"Statement on Granting Privileges for Administration of Moderate Sedation to Practitioners Who Are Not Anesthesia Professionals,"[82] "Advisory on Granting Privileges for Deep Sedation to Non-Anesthesiologist Sedation Practitioners,"[83] and "Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists."[84] Although these documents have not yet gained universal acceptance outside anesthesiology and competing documents are promoted by other specialties,[85,86] the ASA classifications and guidelines are being acknowledged in the more recent nonanesthetic literature.[34,68,87]

AUTHORS' RECOMMENDATIONS

- It is unlikely that the use of propofol by nonanesthesia professionals will cease. In many ways, propofol may be as safe or safer than more traditional medications. However, education of nonanesthesia professionals, especially those responsible for the patient, is needed to advance patient safety. Understanding the risks for nonfasted patients and providing the training to avoid and rescue from deep levels of sedation are essential. The American Society of Anesthesiologists (ASA) provides documents to assist in the educational and credentialing process, and these should be at the core of any training program.
- Monitoring must be standardized and adequate. Given their training, experience, and everyday environment, anesthesiologists should be at the forefront to determine protocols, initiate training, perform or oversee competency reviews, and set up quality assurance programs. All data should undergo periodic review, and appropriate responses should be given about sentinel events.
- All specialties using sedation should agree on a consistent set of definitions of sedation depth. This would help to advance research and develop evidence-based recommendations on patient safety. The ASA has published a document defining the continuum of depth of sedation that describes physiologic changes, as well as responsiveness at different depths, including general anesthesia. The use of such a document should be universal as it would promote discussion and provide comparison of data between fields.
- Anesthesiologists did not anticipate such ready acceptance of a new anesthetic medication outside the specialty. However, this is unlikely to be the last time such a scenario occurs. With a growing emphasis on ambulatory procedures and short-acting medications, a similar circumstance may occur again. Anesthesia professionals need to be better prepared to address the use of such potent drugs by nonanesthesia professionals in a more proactive manner. The ASA has started to establish the necessary documentation to address future events.

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CHAPTER 48

Aspiration: Is There an Optimal Management Strategy?

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INTRODUCTION

Aspiration is a recognized risk of anesthesia. Although a relatively rare complication of anesthesia, aspiration contributes to perioperative morbidity and mortality. It can occur whenever a patient is unable to adequately protect the airway, either as a result of underlying disease or with loss of normal airway protective reflexes as a result of sedation or anesthesia. Although aspiration can occur at any time during the perioperative period, the risk of aspiration is greatest when the patient is rendered unconscious as occurs during deep sedation or general anesthesia.[1] Other situations also put the patient at risk of aspiration. For example, recent ingestion of food, obesity, and underlying gastroesophageal reflux disease increase the likelihood of aspiration. Supine or lithotomy positioning increases the likelihood of regurgitation and subsequent aspiration. Swallowing disorders, which are relatively common in elderly patients,[2] and a reduced coughing reflex[3] also increase the risk of aspiration.

Anesthesiologists take precautions to minimize the likelihood of aspiration in the perioperative period, but, in spite of these efforts, aspiration can occur. Aspiration can be benign, depending on the quantity and characteristics of the aspirate, but it is often associated with significant physiologic implications as well as an increased cost of care. Because aspiration is mistakenly assumed to be a preventable complication, potential professional liability issues are also associated with aspiration and its complications. Anesthesiologists therefore go to great lengths to identify patients at risk of aspiration, to reduce the risk, and to treat the complication when it occurs. A number of approaches are used for reduction of the risk of aspiration and treatment, although the evidence to support most therapies is limited.

To clarify the current state of knowledge regarding the risks, complications, and treatment for aspiration during anesthesia care, this chapter will review the available data regarding the diagnosis of aspiration and its clinical significance and will address some of the controversial areas surrounding management of aspiration.

THERAPEUTIC OPTIONS

Minimizing the Risk

Anesthesiologists should first take appropriate steps to reduce the likelihood of aspiration but, should it occur, management strategies to reduce the risk of complications from the aspiration should be initiated. Because the complications of aspiration are rare and many patients may have silent aspirations that are neither witnessed nor apparent, the incidence of aspiration is probably significantly underestimated and its relationship to the patient's postoperative course underappreciated.[4] Even when aspiration is witnessed, the risk of complications associated with it varies considerably; for many patients there are no significant consequences.

A number of approaches have been recommended to reduce both the risk of aspiration and the physiologic consequences of aspiration should it occur.

The primary method for reducing the risk of aspiration is to ensure that the patient has an empty stomach before induction of anesthesia. Fasting is the recommended approach for reducing the quantity of gastric contents. Although no clear-cut data define the exact duration of fasting that is required, a number of recommendations have been proposed related to the duration of fasting and the type of foods that should be avoided. Based on a review of the evidence related to the risk of aspiration associated with increased gastric volumes and our current state of knowledge, practice guidelines have been developed to define the most appropriate duration of fasting for adults and children. The guidelines suggest a minimum fasting period of 2 hours after ingesting clear liquids. For adult patients, fasting for at least 6 hours after a light meal is recommended. Children taking breast milk or infant formulas should fast for 4 hours before elective surgical procedures for which anesthesia will be provided.[5,6] Unfortunately, even with fasting for these time periods or longer, patients can still have significant gastric volumes due to reduced gastric emptying as well as increased gastric secretions. As a result, although fasting is recommended and appropriate, the anesthesiologist must still be cognizant of the potential risk of aspiration even after a patient has been fasting for an extended period of time.

To reduce the volume and acidity of gastric secretions, a number of pharmacologic agents such as gastrointestinal stimulants, gastric acid secretion blockers, and antacids are commonly used by many clinicians. Although of theoretic value, there is, unfortunately, not much data to support their routine use. As a result, the use of any of these agents is not recommended, except in patients with a high likelihood of delayed gastric emptying, such as obese, pregnant, or diabetic patients.[7] For this select group of patients at higher risk of aspiration, if antacids are to be used, only nonparticulate agents should be

administered. The routine use of other agents, such as antiemetics or anticholinergics, has not been demonstrated to reduce the risk of pulmonary aspiration, although they may be of value in select patients at high risk of aspiration or in patients with known gastroesophageal reflux, including some elderly patients.[8,9]

Cricoid pressure has also been advocated as a way to reduce the risk of regurgitation and aspiration, particularly as part of the "rapid sequence induction" technique.[10,11] Although it is commonly used to reduce regurgitation and aspiration, there is not much objective data to support its value.[12,13] In addition, it is difficult to confirm proper application of the cricoid pressure, and, in some cases, the cricoid pressure interferes with airway management.[14]

Management Strategies

If a patient is identified as having aspirated, the primary therapeutic interventions are supportive. No specific therapies directed toward the aspiration itself are generally required unless there is clinical evidence to suggest airway obstruction due to particulate or foreign body aspiration. First, gas exchange must be assured. Supplemental oxygen should be provided to maintain adequate oxygenation. Routine bronchopulmonary hygiene, including suctioning of pulmonary secretions, and other supportive measures are the only additional approaches that have been demonstrated to be effective.[15] There are no data that support the empiric initiation of other therapies immediately after a witnessed or suspected aspiration.

In the event that aspiration is witnessed, careful assessment of the oropharynx should be performed. If necessary, the removal of debris from the oropharynx should be done with the use of a Yankauer suction catheter. If regurgitation or vomiting is ongoing, the patient should be placed in the head down lateral decubitus position to minimize the risk of further aspiration into the airway. Placement of a nasogastric tube may be required to remove additional gastric contents and prevent ongoing aspiration, although leaving a nasogastric tube in place may increase the risk of reflux.[16] Bronchodilator therapy with beta-agonists is indicated if bronchospasm is triggered by the aspiration. The bronchodilatory therapy will not only improve the wheezing but might also improve mucociliary function and facilitate clearance of secretions in the postoperative period.

For some patients with large-volume aspiration or those known to have aspirated particulate material or material with a low pH, additional interventions may be required. Bronchoalveolar lavage is not indicated in these situations as it can cause the aspirate to move more distally into the smaller airways rather than facilitate clearance of the aspirate.[15] Lavage does not reduce the likelihood of pneumonitis. Bronchoscopy can be used to facilitate removal of particulate aspirate, particularly if a foreign body is identified in the larger airways. If the patient develops further complications from the aspiration, including systemic inflammation and sepsis, additional therapeutic interventions may be necessary, including vasopressors and appropriate fluid resuscitation for optimization of intravascular volume.

For most patients who aspirate, antibiotic therapy is not required and should be withheld. Unless there is documented evidence of infection, the early administration of antibiotics may simply increase the risk of antibiotic-resistant infection. In general, antibiotics should be administered on the basis of documented clinical infection with a positive sputum Gram stain, positive cultures, or a focal persistent infiltrate associated with fever and an elevated white blood cell count. For the patient who requires continued ventilator support, bronchoalveolar lavage can be used to obtain a specimen for culture. In addition, later in the patient's postoperative course, if a pulmonary infiltrate persists or the sputum culture becomes positive, antibiotic coverage directed toward the offending organism should be initiated. Early administration of antibiotics may be appropriate in some select clinical situations. For example, if a patient has known bowel obstruction or the aspirated material is feculent, antibiotic therapy that provides adequate gram-negative bacterial coverage should be initiated.

EVIDENCE

Every anesthesiologist is concerned about aspiration in the perioperative period, but there is remarkably few data to support management strategies to reduce the risk of aspiration or treat it once it occurs. Although the risk of aspiration and its consequences, as well as clinical management strategies, have been evaluated in a wide variety of studies, little evidence exists to support our understanding of the risk factors, the actual incidence of aspiration, or the most effective ways to deal with it. Despite this lack of a large body of evidence to support clinical practice, some general principles have been defined, and their use has been justified based on reasonably sound data.

Incidence of Clinically Significant Aspiration

Although aspiration is of concern to every anesthesiologist, the incidence of aspiration in patients receiving anesthesia is difficult to define. It has been found to occur in 1 per 2000 to 3000 adult patients undergoing elective surgery and in 1 per 1200 to 2600 anesthetic procedures in children. During emergency procedures, the incidence may be three to four times higher than it is during elective procedures.[12,17,18] One of the difficulties in evaluating information obtained from published studies of the risk of aspiration is that the diagnosis is difficult to make and the frequency varies considerably by patient population and approaches to airway management. In some cases the aspiration may be silent and unrecognized. In addition, most patients who aspirate demonstrate no evidence of complications from the aspiration. Even those patients who have a witnessed aspiration often have minimal, if any, sequelae. As a result, the diagnosis may be missed because it is based primarily on the complications that result from the aspiration rather than on observation of aspiration itself.[4]

The incidence of aspiration reported in the literature is variable, influenced in large part by the definition of aspiration. One of the reasons for the lack of consensus about the definition of aspiration is that the clinical manifestations vary considerably, based in part on the volume of aspirate and in part on the characteristics of the aspirate itself. For example, the patient who loses the normal cough reflex during deep sedation or induction of anesthesia may aspirate small amounts of oral secretions with no obvious clinical manifestations and no clinical consequence. On the other hand, the patient who regurgitates gastric contents, such as a recently completed large meal, and aspirates the material into the lungs may have significant clinical manifestations, including laryngospasm, bronchospasm, gas trapping, gas exchange abnormalities (both acute and extended), pneumonitis, pneumonia, or pulmonary abscess formation.

Differentiating Aspiration Pneumonitis from Aspiration Pneumonia

Because of the overlapping clinical findings, the consequences of aspiration are difficult to characterize. One of the clinical challenges in the patient with documented pulmonary aspiration is to differentiate pneumonitis from pneumonia. The definitive differentiation is difficult to confirm because there are no obvious markers, and for some patients, inflammation associated with the aspiration causes pneumonitis, which may progress to pneumonia. In general, the diagnosis is made based on the clinical presentation and clinical signs and symptoms. Aspiration pneumonitis often gives rise to an infiltrate, but it is usually fleeting, lasting only a few hours. In fact, many patients with witnessed aspiration will have an infiltrate on chest radiography, but it will generally clear within hours of the aspiration without therapy. On the other hand, an aspirate that is acidic can cause chemical pneumonitis resulting in the exudation of fluid into the lung parenchyma. The risk of chemical pneumonitis is greatest if the pH of the aspirate is less than 2.5 or if the quantity of aspirate is large or particulate.[1,19,20] If blood is aspirated, there may be an infiltrate immediately after the aspiration, but it usually clears rapidly with minimal consequences.

The greatest concern in the patient who aspirates is the risk that the aspiration will progress to pneumonia. Although the clinical features of pneumonitis and pneumonia overlap, if the patient has a persistent fever that cannot be attributed to a wound infection or other cause or develops other clinical evidence of infection or sepsis, a pulmonary infection must be considered. An elevated white blood cell count, purulent sputum, and worsening clinical status are most likely associated with pneumonia after aspiration rather than inflammation (pneumonitis) alone.[19]

Risk Factors for Aspiration

The largest body of evidence related to the diagnosis and management of aspiration has concentrated on identification of patients at increased risk, particularly in the setting of anesthesia and surgery. Unfortunately, these studies do not rigidly or consistently define pulmonary aspiration, making the estimation of risk and analysis of the natural history of aspiration difficult.

Despite the difficulty in identifying specific risk factors, a number of factors have been associated with an increased likelihood of aspiration. Trauma patients[1] and any patient with impaired gastric emptying are at risk of aspiration when rendered unconscious. Many trauma patients have recently eaten, so their stomachs may be full; pain and discomfort will also delay gastric emptying. In addition, the trauma patient may have an altered level of consciousness due to the injury, compromising the ability to protect the airway before tracheal intubation. The same is true for the patient experiencing severe pain and those who have recently received narcotic analgesics that reduce gastric emptying. Other patients at risk of aspiration include those with pre-existing airway abnormalities, those with esophageal disease, motility disorders, and altered gastroesophageal sphincter tone.[8,9,1] The obese patient and the pregnant patient are also at increased risk of aspiration because of delayed gastric emptying and, in some cases, the lower pH of gastric contents.

In addition to the increased risk of aspiration in select patient populations, the likelihood of developing aspiration pneumonitis also varies by patient population. The primary problem for the clinician is to understand which patients are vulnerable to the more serious sequelae of aspiration, such as pneumonitis and pneumonia, versus those who aspirate without physiologic consequences. For instance, aspiration pneumonitis is a well-known complication after drug overdose, seizure, and cerebrovascular accident; it is also associated with general anesthesia. Aspiration has long been considered the most common cause of death in patients with dysphagia and a compromised coughing reflex, as may occur in neurologic disease. It has been estimated that 5% to 15% of community-acquired pneumonia is secondary to aspiration.[19] This complication is probably most common in elderly patients who reside in nursing homes.

In a study evaluating the significance of pulmonary aspiration during the perioperative period,[18] pulmonary aspiration was defined by the presence of bilious secretions or particulate matter in the tracheobronchial tree or new pulmonary infiltrates on postoperative chest radiography in patients without any clinical findings on preoperative examination. Clearly, this definition may mistakenly include patients with postoperative pulmonary edema, acute respiratory distress syndrome (ARDS), or pre-existing pneumonia that went undetected.

Some general conditions are associated with increased risk of aspiration. They include higher American Society of Anesthesiologists (ASA) physical status and patients undergoing emergency procedures. Many other conditions thought to be associated with aspiration were not found to be independent risk factors. Some of those include age, gender, obesity, ingestion of a meal within 3 hours, experience and type of anesthesia provider, and type of surgical procedure. It is also interesting that no pulmonary aspiration was detected in those

patients undergoing cesarean sections under general anesthesia. The most common predisposing conditions associated with aspiration for patients undergoing elective procedures are gastrointestinal obstruction, lack of coordination of swallowing,[19] depressed level of consciousness,[19] and having eaten a recent meal.[20]

Data from both animal and human studies suggest that a primary determinant in the development of aspiration pneumonitis is the pH of the aspirate. A pH of less than 2.5 in the aspirate is necessary to cause clinically significant aspiration pneumonitis.[20] The volume of aspirate also contributes to the likelihood of pneumonitis. A number of studies indicate that the critical volume is 25 mL or 0.4 mL/kg for causing pneumonitis.[21] Particulate antacids may increase the gastric pH but may also cause pulmonary problems if the particulate matter is aspirated. Nonparticulate antacids, often administered to reduce the pH of the gastric contents, on the other hand, may contribute to the risk of pneumonitis because they increase residual gastric volume.

The combined impact of the pH and volume on the risk of aspiration pneumonitis is not clearly defined. In at least one study evaluating volume and pH implications, 80% of rats survived aspiration of volumes exceeding 2.0 mL/kg as long as the pH was greater than 2.5.[22] Other studies support this conclusion, suggesting that the administration of a nonparticulate antacid is appropriate for the patient at increased risk of aspiration in spite of its effect on intragastric volume.

Anesthetic Induction Strategies in Patients at Risk

For those patients at risk of aspiration, including those with a full stomach or delayed gastric emptying (e.g., the diabetic patient or the obese patient), the airway must be secured with extreme caution. Although the data on the value of nonparticulate antacid are limited, it is probably prudent to administer it before induction of anesthesia. Cricoid pressure should be considered and is generally applied when the patient's normal protective reflexes are compromised or the patient is suspected of having a full stomach, although the value of this procedure has also not been proven.[14] These patients should also be placed in the head-up position, if clinically feasible, although positioning will be dictated by the overall clinical needs of the patient.

The best airway management technique to be used for the patient at risk of aspiration is not known. A cuffed endotracheal tube should be used for most patients at risk of aspiration, but the presence of a cuff alone may not protect the patient from aspiration of fluids around the cuff, particularly if the patient has increased gastric pressure or volume of secretions and is in the supine position. Nonetheless, the cuffed endotracheal tube will protect against aspiration of larger particulate matter.[23] There are now some case reports suggesting that endotracheal tubes with low volume, low pressure cuffs may reduce the risk of aspiration.[24] Other studies have suggested that endotracheal tubes with subglottic suction ports may allow better suctioning of secretions above the cuff of the endotracheal tube and thus may minimize the risk of aspiration while the patient is intubated[23,25,26] ProSeal laryngeal mask airways have also been shown to protect adult and pediatric patients from large-volume aspiration, although no studies have confirmed that these airways are as effective as cuffed endotracheal tubes at reducing the risk of aspiration.[27-29]

Documentation of Aspiration

Aspiration of clear liquids of high pH and limited quantity is generally tolerated with minimal sequelae. However, it is difficult to predict whether an individual patient will develop clinically significant pneumonitis, pneumonia, or ARDS after aspiration. The underlying clinical condition of the patient, the physiologic status of the patient at the time of the aspiration, and other factors will influence the subsequent course. If aspiration is suspected, the patient should be observed in a monitored setting for several hours after the aspiration so that appropriate management is ensured. A chest radiograph should be obtained and reviewed for evidence of aspiration or pulmonary infiltrate.

TREATMENT

Antibiotics and steroids should not be given empirically to the patient. Antibiotics, however, should be given if the patient's episode was associated with a high likelihood of gram-negative or anaerobic organisms, such as in the setting of known small bowel obstruction. Furthermore, if the patient's course continues to worsen or shows no sign of improvement after 2 to 3 days, then broad-spectrum antibiotics are indicated at least until a positive diagnosis is established by culture and sensitivity studies. There are no data to support the administration of steroids in the setting of aspiration. Recent studies in animal models suggest that alveolar macrophages play an essential role in the inflammatory response to the aspiration, particularly in cases of acid-induced lung injury. In this situation, the administration of an agent that depleted macrophages was highly effective at reducing neutrophil recruitment and vascular permeability in the lung.[30] Whether this therapy has application in the treatment of aspiration in human beings is unknown.

Sequelae of Aspiration Associated with Anesthesia

Most cases of aspiration resolve without specific treatment. However, in some specific situations aspiration can result in a number of clinically significant abnormalities. Aspiration can precipitate pneumonitis, give rise to pneumonia, or result in ARDS. Aspiration not only can lead to these serious sequelae but may also severely compromise oxygenation in the periprocedural period. Any aspirate in the upper airway, including particulate materials, can cause acute laryngospasm or bronchospasm. With supportive care, these consequences are generally easily managed. If the particulate material

enters the smaller airways, however, the patient can develop either aspiration pneumonitis or aspiration pneumonia. The same sequelae can result from aspiration of feculent material or acidic aspirate. Aspiration of gastric contents high in fat can result in severe lipid pneumonia. Aspiration pneumonitis is an inflammatory response in the airways. It was initially described in obstetric patients by Mendelson and is often referred to as Mendelson syndrome. Mendelson syndrome occurs when gastric contents chemically injure the bronchopulmonary tree. In contrast to aspiration pneumonitis, aspiration pneumonia is an infectious process caused by the introduction and proliferation of bacteria in the lungs. Distinguishing these two diagnoses continues to be a clinical challenge but is important because the differentiation has both prognostic and therapeutic ramifications.

In addition to developing pneumonia after aspiration, especially aspiration of particulate material, patients may also be at risk of pulmonary abscesses, most commonly in the setting of aspiration of anaerobic organisms. The patients at greatest risk for this complication are those with a depressed level of consciousness, swallowing dysfunction, or impaired cough reflex, and patients with a history of drug abuse. In these patients a cavity may be noted on chest radiography. When a lung abscess is identified, antibiotics may or may not be effective. The patient may also require a surgical or interventional radiologic procedure to drain the abscess.

CONTROVERSIES

Antibiotic Therapy

The initiation of empiric antibiotic therapy after aspiration is discouraged, although many clinicians find it difficult to resist starting broad-spectrum antibiotics in the patient who has aspirated while under their care. In general, antibiotics should be administered cautiously and only when there is clinical evidence to confirm infection or the patient's underlying condition is deteriorating in spite of intensive supportive care. Most studies that have attempted to evaluate the optimal use of and timing for administration of antibiotics suggest the initiation of antibiotics should only be considered when symptoms have persisted for about 3 days.[31] At that time, it becomes important to consider the clinical scenario so that the proper antibacterial coverage is chosen. Patients who have been in the hospital for several days will be at increased risk of gram-negative pneumonia, whereas most other patients are more likely at risk of anaerobic organisms found in healthy patients' oral flora.

Antibiotic therapy should be based on the results of blood and respiratory cultures and pleural fluid cultures when empyema or an abscess is suspected. If these results are unavailable or fail to isolate a specific species, then a broad-spectrum agent should be chosen pending results of subsequent cultures.

There is one clinical situation in which early administration of antibiotics may be required. For the patient who aspirates feculent gastric contents, particularly in the setting of small bowel obstruction, the risk of pulmonary infection is high. These patients may benefit from immediate administration of broad-spectrum antibiotics to prevent the development of serious necrotizing pneumonia. If antibiotics are initiated in this situation, serial sputum cultures (mini–bronchoalveolar lavage) and sensitivities should be obtained and antibiotics adjusted based on the results of the studies.

Steroids

Although corticosteroids have often been administered in the setting of aspiration, there is no strong evidence that any benefit exists. Two studies from the early 1980s[32,33] failed to show in animal models a benefit from corticosteroid therapy, particularly with regard to lung injury, pulmonary function, interstitial edema, and clinical outcomes. In a double-blind, placebo-controlled clinical trial, lung injury was found to resolve at a faster rate, as determined by chest radiographs, in patients who received corticosteroids.[34] Despite a more rapid resolution of infiltrates, no difference was noted in clinical outcomes. Given the lack of convincing data to support the use of corticosteroids in the setting of aspiration, they do not have a role in the management of patients who have aspirated.

Bronchoscopy and Bronchoalveolar Lavage

The use of bronchoscopy or lavage after aspiration is limited.[15] For patients known to have aspirated a foreign body, such as a tooth, denture, or gum, bronchoscopy may be the only way to remove the foreign body. In most other situations, simple saline lavage and suctioning is sufficient. Selective segmental lavage is not indicated because the irrigation may force aspirated materials into smaller airways that are more difficult for the patient to mobilize. Because normal mucociliary clearance and coughing are superior to selective suctioning, whenever possible, the patient's trachea should be extubated as soon as clinically appropriate to encourage normal bronchopulmonary hygiene. Only when the patient does not have a forceful cough or has a persistently depressed neurologic status is deep suctioning required.

AREAS OF UNCERTAINTY

As already noted, remarkably few data exist for determining how to reduce the risk of aspiration, particularly in those patients not known to be at high risk. Even for those patients with known gastroesophageal reflux or increased intragastric pressure, many of the maneuvers used to reduce the likelihood of aspiration are not evidence-based. They seem logical and, in most cases, have few if any sequelae. For example, the data related to time since last meal or drink are based on limited data about time to gastric emptying, most often in healthy patients. Even in patients with known risk, the majority

of the patients can be managed in ways that minimize aspiration. Whether any of these maneuvers alters the frequency of aspiration is difficult to determine because the true incidence of aspiration is not known. Cricoid pressure, which has been the mainstay of management for reduction of the risk of aspiration in high-risk patients, has not been documented to be effective and may complicate intubation.

The management options for the patient who aspirated are also limited, at least on the basis of current data. Therapy is primarily supportive, although other interventions have been used. Routine use of antibiotics or steroids is not recommended, but in some subset of patients who aspirate, early administration of either therapy might be appropriate. In addition, the use of hyperbaric oxygen has been suggested for the management of aspiration pneumonia, although its value cannot be confirmed.[35]

GUIDELINES

Aspiration is a known complication of anesthesia and surgery. For most patients, clinical management should be directed toward reducing the risk of aspiration. The risk reduction strategies include minimizing loss of airway protective reflexes whenever possible, reducing the quantity and raising the pH of the gastric contents, and providing supplemental protective approaches such as cricoid pressure during airway manipulations. For patients at high risk of aspiration, the administration of nonparticulate antacids may be appropriate (e.g., obese patients or parturients). For patients with known delayed gastric emptying, such as a diabetic patient, preoperative administration of a gastric stimulant (e.g., metaclopramide) may be indicated.

When a patient has a witnessed aspiration or the clinical course is suggestive of aspiration, a thorough clinical examination and chest radiograph should be obtained. The patient should remain in a monitored setting until clinically stable without evidence of gas exchange or other physiologic complications. Based on the findings of the evaluation, further management strategies can be determined. If the patient has wheezing or other evidence of increased airway resistance, bronchodilators should be administered. If the patient develops a pulmonary infiltrate, serial chest radiographs may be required for ongoing evaluation.

Routine administration of antibiotics or steroids should be avoided in the patient who aspirates. Care should be supportive, including administration of supplemental oxygen and monitoring of gas exchange and hemodynamics. Fluids should be administered to maintain normal intravascular volume. If the patient had known bowel obstruction or the aspirate was feculent, early administration of appropriate antibiotics may be required, although the antibiotic regimen should be guided by serial sputum cultures. Routine administration of antibiotics after aspiration is not indicated and may put the patient at risk of antibiotic-resistant infections. Steroid administration is not indicated.

AUTHOR'S RECOMMENDATIONS

Minimizing the Risk of Aspiration

- Elective patients should have nothing by mouth for at least 2 hours (clear liquids) or 6 hours (light meal) before initiation of anesthesia
- Administer nonparticulate antacid solution to high-risk patients
- Avoid positive pressure ventilation, whenever possible, during emergency airway management ("rapid sequence induction") and consider application of cricoid pressure, although neither approach has been documented to reduce the risk of aspiration

Diagnosing Aspiration

- Obtain serial chest radiographs based on the clinical course
- Obtain sputum by bronchoalveolar lavage for culture and sensitivity to diagnose pneumonia

Treating Aspiration

- Therapy is supportive
- Provide supplemental oxygen
- Provide fluids to optimize intravascular volume
- Provide routine bronchopulmonary hygiene
- Routine antibiotics are not appropriate; treat known infections based on clinical evidence of pneumonia and cultures
- Avoid steroids

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CHAPTER 49

Nonsteroidal Antiinflammatory Drugs, Antiplatelet Medications, and Spinal Axis Anesthesia

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INTRODUCTION

Many individuals use cyclooxygenase-1 and cyclooxygenase-2 inhibitors (COX-1 and COX-2 nonsteroidal antiinflammatory drugs [NSAIDs]) on a regular basis. This is particularly true of the elderly, who are more prone to having osteoarthritis and rheumatoid diseases. The elderly are also more likely to have had cardiac stent placements or coronary angioplasties performed and may be taking antiplatelet medications such as the thienopyridines (e.g., ticlopidine and clopidogrel) or the newer platelet antagonists, platelet glycoprotein (GP) IIb/IIIa agents (e.g., abciximab, eptifibatide, and tirofiban). All these agents alter platelet function and may increase the risk of spinal/epidural hematoma formation if spinal axis anesthesia is used without following proper precautions. All anesthesiologists should be familiar with these agents and how they work. More importantly, they should be familiar with the established guidelines set forth by the American Society of Regional Anesthesia and Pain Medicine (ASRA)[1] and the European Society of Anesthesiology (ESA).[2] These guidelines will help in the decision of when these agents should be stopped before surgery/anesthesia and when it is safe to remove spinal/epidural catheters so that all patients are provided the widest possible margin of safety.

OPTIONS

Neuraxial techniques for anesthesia have been gaining popularity because of the associated improvement in patient outcomes, such as morbidity and mortality, as well as those that are more patient-oriented, such as postoperative pain relief and early ambulation.[3-7] It has been suggested that it is the attenuation of the hypercoagulable response and the resulting reduction in the frequency of thromboembolism that is a major component of the decreased morbidity and mortality observed after neuraxial blockade.[1] Nevertheless, this effect remains insufficient to be the only means of thromboprophylaxis, and antiplatelet and anticoagulant medications continue to be used concomitantly in the prevention of thromboembolism. As more potent versions of these medications are introduced, concerns regarding the risk of neuraxial bleeding have become heightened and the guidelines for the selection of the most appropriate antithrombotic pharmacologic agents continues to evolve with regard to the duration of therapy and degree of anticoagulation that are both needed and safe.[8]

In 2007 it would have appeared that we had come full circle in the use of aspirin as the primary chemoprophylactic agent for the prevention of pulmonary embolism (PE) after hip pinning, total hip replacement surgery, and total knee replacement surgery. The material presented at the Third ASRA Consensus Conference (Vancouver, British Columbia, Canada, in April 2007) suggested that a growing body of literature showed that deep venous thrombosis (DVT) was not an accurate marker for the risk of embolic disease after total joint surgery because the incidence of PE had not declined proportionately with the decrease in the incidence of DVT that had resulted from the current use of the low-molecular-weight heparin (LMWH) regimens.[9] This claim is further highlighted by the observation that the clinical trials that assessed the efficacy of various regimens in determining the American College of Chest Physicians (ACCP) Guidelines on Antithrombotic and Thrombolytic Therapy rarely used clinical outcomes like fatal PE or symptomatic DVT as primary endpoints but instead relied on contrast venography and duplex sonography.[7] Subsequently, an actual reduction in clinically significant events has been difficult to demonstrate despite the successful reduction of asymptomatic thromboembolic events with standard use of antithrombotic therapy.[10] Furthermore, when LMWH is used as the primary DVT prophylactic agent, the risk that patients may develop a deep periprosthetic hematoma[9,11] or other surgical bleeding is increased.[12] If patients do develop a deep periprosthetic hematoma, there is a substantial risk that they will also develop a prosthetic infection and need additional surgery. More important, patients might require an amputation of the involved extremity. The use of aspirin in conjunction with pneumatic compression devices, on the other hand, allows one the option of providing or continuing epidural analgesia in the postoperative period. This, in turn, allows patients to ambulate with minimal discomfort in the immediate postoperative period and actively participate in physical therapy.[9,11] As a result of the aforementioned protocol, the incidence of PE is the same as that seen with LMWH therapy after total joint arthroplasty.[9,11] This observation

has been further demonstrated by an abstract portending a multicenter study conducted by Bozic et al[13] involving 93,840 patients undergoing total knee arthroplasty between 2003 and 2005. The results of the study revealed patients who received aspirin for thromboprophylaxis to have had a similar risk of thromboembolism compared with patients receiving LMWH and a decreased risk compared with those who received warfarin. The authors argue that the success of aspirin as thromboprophylaxis may have been a result of changing trends in patient characteristics and evolving surgical techniques. This position is further supported by the current ACCP guidelines, which state that both aspirin and LMWH can be used as thromboprophylaxis in patients undergoing major orthopedic surgery, with the benefit that aspirin does not need to be stopped during neuraxial anesthesia practices.[1,14] It is worth noting, however, that one member of the ACCP guidelines panel was so opposed to aspirin-only therapy for DVT prophylaxis in the setting of total hip or knee arthroplasty that he insisted his objections be noted in the final draft of their deliberations.[8]

In addition, an exhaustive literature survey and meta-analysis on spinal hematomas done by Kreppel and colleagues[15] showed that only 10% of all spinal hematomas were associated with the use of a spinal anesthetic procedure, and that 60% of these epidural hematomas were either associated with the presence of a coagulopathy or an anticoagulant had been administered to the patient. More important, none of these hematomas occurred in the presence of aspirin or NSAID therapy alone.[15] It would therefore appear that the timing of single-shot or catheter techniques in relation to the dosing of NSAIDs or aspirin does not increase the risk of spinal hematomas.

What is the evidence, however, that aspirin chemoprophylaxis reduces the risks of thromboembolic disease to an acceptable level after joint replacement surgery? A prospective study by Lotke and Lonner[9] used aspirin chemoprophylaxis, early ambulation, an increased use of regional anesthesia, and intermittent pneumatic compression to prevent fatal PE in 3473 consecutive patients undergoing total knee arthroplasty. Again, the authors used a reduction in the incidence of fatal PE, not DVT, to determine the effectiveness of their study protocol and compared their results with those of other studies in which more conventional chemoprophylactic agents, such as warfarin, fondaparinux, or LMWH, were used after total knee arthroplasty. The study period ran for a minimum of 6 weeks after each joint replacement. Lotke and Lonner[9] recorded a total of nine deaths during their study: two from PE, five from cardiac events, one from stroke, one from fat embolism; three cardiac-related events also occurred for which PE could not be ruled out as the primary cause of death. Therefore the best- and worst-case scenarios for PE were 0.06% and 0.14%, respectively. Thirteen patients required reoperation to evacuate deep wound hematomas (0.4%). With regard to the incidence of fatal PE, the results of this study compare quite favorably with other studies in which more conventional chemoprophylactic agents were used to prevent PE in patients having total knee replacement. However, the incidence of fatal PE was found to be approximately 0.1% in the other studies, irrespective of the chemoprophylactic used. Finally, the incidence of adverse postoperative bleeding events in the Lotke and Lonner[9] study was only 0.3%. This incidence is substantially lower than the rate of 2% to 5% reported in the literature with the more conventional chemoprophylactic regimens.

EVIDENCE

Cyclooxygenase-1 Nonsteroidal Antiinflammatory Drugs

Aspirin causes inhibition of platelet function through inhibition of platelet cyclooxygenase, an enzyme that is instrumental in the biosynthesis of thromboxane A_2 from arachidonic acid. Thromboxane A_2 is necessary for the formation of thromboxane, a prostaglandin that is a potent stimulator of platelet aggregation and adhesion.[16] Because the reaction between aspirin and platelet membrane cyclooxygenase is irreversible, inhibition of platelet function lasts for the life of the platelet (7 to 10 days).

The remaining COX-1 NSAIDs such as naproxen, ketorolac, diclofenac, piroxicam, ibuprofen, and others also act as prostaglandin synthesis inhibitors. All of them cause reversible competitive platelet inhibition, and platelet function usually returns to normal within 1 to 3 days after stopping the drug.[17]

Horlocker and colleagues[18-20] and Urmey and Rowlingson[17] all believe that there is a minimal risk of spinal hematoma formation when preoperative antiplatelet therapy has been administered with either aspirin or another COX-1 NSAID. These authorities believe that it is not necessary to stop these agents before surgery or to avoid spinal or epidural anesthesia in patients who have been using these medications in the preoperative period. Furthermore, they believe it is safe to remove epidural catheters from patients who have been administered aspirin or NSAIDs in the postoperative period.

Tryba[21] published an extensive review on spinal hematomas associated with regional anesthesia. Thirteen cases of hematoma were identified from the review of approximately 850,000 epidural anesthetics. Seven cases of spinal hematoma were identified from 650,000 spinal anesthetics. Statistical analysis of these data resulted in an estimated incidence of spinal hematoma of 1:150,000 for epidural anesthesia and an incidence of 1:220,000 for spinal blocks. These estimates represent the baseline risk of spinal hematoma formation with neuraxial anesthesia in the absence of antiplatelet agents.

Horlocker and colleagues[19] retrospectively reviewed 805 charts of patients who were receiving NSAIDs and who also were administered a spinal axis anesthetic. None of the patients developed a spinal hematoma in the postoperative period. In a more recent prospective study, Horlocker and colleagues[20] studied 924 patients who received 1000 spinal or epidural anesthetics. Of these patients, 386 (39%) were taking aspirin ($n = 193$) and the remaining 193 patients were taking another COX-1 NSAID. Moreover, 32 patients in this later group were taking more than one NSAID in the preoperative period. Blood was noted during needle or catheter placement

TABLE 49-1 **Horlocker Studies***

Date of Study	Type of Study	Number of Epidurals/Spinals	Number Taking NSAIDs	Number Taking Aspirin	Results
1990	Retrospective	924	301	N/A	No hematoma formations
1995	Prospective	1000	386	193	No hematoma formations
2002	Prospective	1214	383	158	No hematoma formations

NSAIDs, nonsteroidal antiinflammatory drugs.
*Presents the results of three studies by Horlocker and colleagues[18-20] that demonstrate no epidural hematoma formations in 3138 patients who received either a spinal or an epidural needle placement and who were also receiving aspirin therapy or another NSAID.

(minor hemorrhagic complications) in 223 of the patients (22%), including 73 who had frank blood in either their needle or catheter. None of the patients developed a spinal hematoma in the postoperative period. The authors concluded that preoperative antiplatelet therapy was not a significant risk factor for the development of neurologic dysfunction from spinal hematoma in patients who undergo spinal or epidural anesthesia while receiving these medications.[20]

In another study by Horlocker and colleagues[18] that involved 1035 patients who received 1214 epidural steroid injections, 383 of the 1035 patients (32%) were concurrently taking an NSAID. More specifically, 158 of these 383 patients were consuming aspirin and 104 of the 158 were using low-dose aspirin (325 mg/day or less). The authors conclude that epidural steroid injection is safe in patients receiving either aspirin or NSAIDs. Table 49-1 shows the combined results of the three Horlocker studies.[18-20]

Vandermeulen and colleagues,[22] in their review of the literature from 1906 to 1993, were able to find only three cases in which an NSAID was implicated in the formation of a postspinal/postepidural hematoma. One of the cases involved indomethacin; in the two other cases aspirin was implicated. One of these later two cases also involved the concurrent use of heparin. Two of the patients had epidural anesthesia, and the third had a spinal anesthetic. The authors conclude that the incidence of spinal hematoma after the placement of either spinal or epidural blockade in patients taking aspirin or other NSAIDs was very low. However, Vandermeulen was also an author on the German Society of Anesthesiology and Intensive Care Medicine consensus statement that suggests that a risk of hematoma is present when aspirin and NSAIDs are not stopped several days before the placement of a spinal or an epidural block.[23]

The evidence for a risk of hematoma formation if aspirin and other COX-1 NSAIDs are not stopped several days before the placement of spinal or epidural blockade is quite sparse and is limited to single-incident case reports. A report by Litz and colleagues[24] implicates the perioperative administration of ibuprofen as the offending agent that led to the formation of a hematoma after epidural catheter removal on the second postoperative day in a patient who had undergone a total knee replacement. However, the patient was also receiving LMWH.

The most alarming report is by Gerancher and colleagues.[25] Their patient had not undergone anticoagulation and had only received a single dose of ketorolac during surgery (30 mg intravenously) and then three doses in the postoperative period (15 mg intramuscularly every 6 hours). The patient's lumbar hematoma developed during the afternoon of the first postoperative day, and its presence was confirmed by magnetic resonance imaging (MRI). Even more alarming was the fact that it occurred as the result of a lumbar puncture with a small-gauge spinal needle. She had required three needle passes for her block to be placed. The first two were performed with a 27-gauge Quincke needle, and bone was encountered each time. The final pass was undertaken with a 25-gauge Quincke needle. No blood was aspirated or detected during any of the needle placements. Fortunately, the woman made a full recovery from her paraparesis without surgical decompression. Moreover, the concurrent use of ketorolac and LMWH has been implicated in three reports of spinal/epidural hematomas in conjunction with an axis anesthesia.[17] Two of these hematomas occurred immediately after the removal of an epidural catheter; therefore Litz and colleagues[24] warn that epidural catheter removal may be just as risky as catheter placement in regard to epidural hematoma formation in patients receiving anticoagulation or antiplatelet therapy.

A 1995 case report by Heye[26] presents a patient who was taking 250 mg/day aspirin and who developed an epidural hematoma after spinal trauma. Heye[26] suggested that, although aspirin did not cause the bleeding, it did have a major impact on the extent of the epidural bleeding. Finally, a more recent case report by Hyderally[27] describes a patient with ankylosing spondylitis who was undergoing total hip replacement and who was started on aspirin for postoperative thromboprophylaxis. This patient subsequently developed a thoracic epidural hematoma 36 hours postoperatively. More important, this thoracic-level epidural hematoma extended from T5 to T10, which was quite distant from the lumbar epidural catheter tip and was confirmed by an MRI to lie at L2/L3. Hyderally[27] concluded that the hematoma was not caused by the lumbar epidural catheter placement but that it occurred spontaneously, possibly as the result of concurrent aspirin therapy and the patient's primary disease of ankylosing spondylitis.

The scarcity of case reports related to neuraxial techniques and spinal hematoma in patients receiving antiplatelet medications is itself notable given the prevalence of NSAID use in the general American population, particularly in those with chronic pain–related illnesses. Thus, despite the aforementioned rare events, the ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation has twice concluded that use of NSAIDs alone does not significantly increase the risk of developing spinal hematomas.[1,28] Combination therapy with unfractionated heparin, LMWH, or oral anticoagulants has, however, been shown to increase the frequency of hemorrhagic complications.[29]

Areas of Uncertainty about Continuing Cyclooxygenase-1 Nonsteroidal Antiinflammatory Drugs before the Placement of an Axis Anesthetic

Although Urmey and Rowlingson[17] believe that there is a minimal risk of spinal hematoma formation when preoperative antiplatelet therapy has been administered with either aspirin or another COX-1 NSAID, they questioned the conclusions reached by the Horlocker study[20] because it was their belief that the study lacked adequate statistical power to conclude that there was no increased risk of spinal/epidural hematoma formation in patients taking a COX-1 NSAID. This may be particularly true for aspirin administration before the placement of an axis anesthetic.[17] They pointed out that, although no hematomas were detected in the study, fewer than 500 patients received both a spinal axis anesthetic and either aspirin or a COX-1 NSAID. Using Tryba's estimated incidence of spinal hematoma formation of 1:150,000 to 1:220,000,[21] one would need a study involving almost 200,000 patients to achieve adequate power, and then there would only be an 80% probability of detecting a tenfold increase in the frequency of hematomas in patients receiving both a neuraxial block and antiplatelet therapy.[17] Moreover, none of the patients in the Horlocker study[20] had received either the thienopyridines (ticlopidine and clopidogrel) or the newer platelet antagonists, platelet GP IIb/IIIa agents such as abciximab, eptifibatide, and tirofiban, in the preoperative period. Finally, the most recent Horlocker study[18] probably also lacks the statistical power to reach the conclusion that epidural steroid injections are safe in patients receiving aspirin and other COX-1 NSAIDs. Horlocker and colleagues[18] acknowledge that the rarity of spinal hematomas makes it impossible to make definitive conclusions on the safety of epidural steroid injection in patients who are also receiving NSAID therapy.

Another area of controversy is the use of bleeding time for determining whether it is safe to place a spinal or an epidural anesthetic in a patient who has been taking aspirin in the preoperative period. Hindman and Koka[30] do not believe that bleeding time is a reliable indicator of platelet function. Although the bleeding time may quickly normalize after aspirin ingestion, platelet function as measured by platelet response to adenosine diphosphate (ADP) or epinephrine may take up to a week to return to normal. Measurement of Ivy bleeding time before the placement of a spinal or an epidural anesthetic is not indicated and is of little value because there is no evidence to suggest that it can predict hemostatic compromise.[20,31]

Cyclooxygenase-2 Nonsteroidal Antiinflammatory Drugs

The COX-2 specific inhibitors (COX-2 NSAIDs) are essentially devoid of platelet-altering activity. The COX-2 inhibitor valdecoxib (Bextra) is 28,000-fold more selective against COX-2 than COX-1.[32] In early clinical trials valdecoxib did not affect platelet function.[33] The same is true for the older COX-2 agents celecoxib (Celebrex)[34] and rofecoxib (Vioxx).[35] However, the aforementioned information is now a moot point because celecoxib is the only remaining COX-2 inhibitor on the market today in North America.

Antiplatelet Drugs

Thienopyridines (Ticlopidine, Clopidogrel, and Prasugrel) Inhibit Platelet Function

Ticlopidine (Ticlid) is a long-lasting inhibitor of both primary and secondary phases of platelet aggregation induced by ADP, collagen, thrombin, arachidonic acid, prostaglandin endoperoxidase, and thromboxane A_2–like substances.[36,37] Ticlopidine's effect on platelet function is irreversible, and the drug's action lasts for the lifetime of the platelet.[38] However, prolonged bleeding time is normalized within 2 hours after the intravenous administration of methylprednisolone (20 mg) or the transfusion of platelets.[38] The drug is indicated for reducing the risk of thrombotic events in patients who have experienced stroke precursors and who are also intolerant to aspirin.[38] However, the aforementioned and subsequent discussions on the drug ticlopidine are probably a moot point because Apotex, the manufacturer of ticlopidine, stopped producing the drug on August 31, 2012.

Clopidogrel (Plavix) irreversibly inhibits platelet aggregation by selectively binding to adenylate cyclase–coupled ADP receptors on the platelet surface.[39] Furthermore, by blocking the ADP receptor, clopidogrel inhibits the binding of fibrinogen to the platelet GP IIb/IIIa receptor.[39] Clopidogrel has almost completely replaced ticlopidine because it has a wider therapeutic index, has a reduced side effect profile, and is more efficacious than ticlopidine at accepted clinical dosing parameters. It is important to note, however, that the antiplatelet effects of clopidogrel are not consistent in all patients and that up to 30% of patients have marked variability in the extent of platelet inhibition.[40] Furthermore, up to 15% of high-risk patients with acute coronary syndrome have further ischemic events despite adequate antiplatelet therapy with clopidogrel.[40] The reason for this variability seems to be due to the fact that clopidogrel is a prodrug and must be metabolized before it can bind to ADP receptors and inhibit platelet aggregation. The metabolic activation of clopidogrel

is catalyzed by CYP2C19, a genetically pleomorphic CYP-450 enzyme with a common single nucleotide polymorphism (SNP) that results in a truncated protein product with limited enzymatic activity.[41] An SNP is a variation in the genetic code that occurs when a single nucleotide in the genome differs between members of the same species at the same location or between paired chromosomes within the individual. Several studies have shown this genetic variation in the CYP 450 enzyme and the resulting reduction in enzymatic activity to be associated with decreased activation of the drug, resulting in lessened antiplatelet inhibition and an increased likelihood of cardiovascular events.[42,43] In addition, these observations have been supported by a genome-wide association study.[42] Consequently, several studies are under way to assess the effect of adjustments in dosing regimens in patients with CYP2C19 variant alleles; however, it is currently unclear whether genotyping to predict response to clopidogrel is clinically useful.[44,45]

Prasugrel (Effient) is the newest of the thienopyridines and has been demonstrated to inhibit platelet aggregation by a similar mechanism of irreversibly binding to ADP receptors; however, it does so to a greater extent, with more consistency, and at a more rapid pace.[46] Currently, the only labeled indication for prasugrel in the United States is for patients undergoing percutaneous coronary intervention in the wake of acute coronary syndrome.[47]

Ticlopidine prolongs template bleeding time.[38] It also displays nonlinear pharmacokinetics, and its clearance decreases markedly with repeated dosing. The half-life after a single 250 mg oral dose is 12.6 hours, but with repeated dosing at 250 mg twice daily, the elimination half-life rises to 4 to 5 days.[38] Ticlopidine has been implicated as the medication that caused a spinal hematoma in a 70-year-old woman who was having her toe amputated.[48] Ticlopidine was administered for 10 days before surgery, but it was stopped just before the surgery. She underwent several unsuccessful attempts at spinal block placement with a 23-gauge needle in the lumbar region, and she ultimately received a general anesthetic. On the sixth postoperative day the patient developed muscle weakness in both legs. On postoperative day 8 she had cervical myelography that showed an extramedullary block below the level of T10. She underwent an emergency laminectomy, and a hematoma was evacuated from the subarachnoid space. The clot extended from T10 to L5. She remained paralyzed after the laminectomy and died the next day.

Another case report by Maier and colleagues[49] in 2002 revealed another ticlopidine-related hemorrhagic complication; this time it was in the setting of lumbar sympathetic blockade. A 71-year-old man with progressive peripheral artery disease, taking ticlopidine for stroke prevention in the setting of carotid artery stenosis, underwent a lumbar sympathetic blockade for symptomatic relief. Unfortunately, his ticlopidine was continued during the intervention given the presumed absence of increased bleeding risks based on the patient's history and physical examination. Two days later, a widespread skin hematoma developed, and laboratory tests revealed a 2.2-g/dL drop in hemoglobin that prompted termination of ticlopidine therapy. The patient then underwent a second lumbar sympathetic block (6 days after the first one) and subsequently developed a large retroperitoneal hematoma that was associated with severe groin pain, a drop in blood pressure and hemoglobin level, and ultimately required the patient to undergo transfusion for hemodynamic stabilization. Of possible importance is the fact that during the second block, the 25-gauge block needle was discovered to be in an intravascular position. However, usually little clinical significance is attributed to the intravascular placement of a 25-gauge needle, even in heparinized patients, despite the difficulty of compressing the deep-set vessels potentially punctured by deep plexus blocks. The case report therefore prompted the authors to question the role of ticlopidine as a direct (or contributing) factor in the development of this retroperitoneal hematoma and to raise concern regarding the risk of anesthesia-related hemorrhagic complications in patients receiving ticlopidine therapy. The authors further urged the discontinuation of irreversible platelet inhibitors 7 days before any invasive techniques, given the absence of reliable and sensitive tests to ascertain the level of adequate platelet function in these patients.[50]

The elimination half-life of orally administered clopidogrel is only 7.7 hours after a single 75-mg dose,[39] but the irreversible platelet inhibition persists for several days after withdrawal of the drug and diminishes in proportion to platelet renewal.[51] Clopidogrel is 40 to 100 times more potent than ticlopidine,[52] and bleeding times are significantly prolonged at 1 hour after the administration of a single oral loading dose of 375 mg.[39]

Clopidogrel was implicated as one of the agents that may have led to the development of a cervical epidural hematoma in a patient who had received a cervical epidural steroid injection.[53] He was taking several antiplatelet medications just before block placement (i.e., diclofenac, clopidogrel, and aspirin). Quadriparesis developed 30 minutes after the performance of the cervical epidural steroid injection, and he did not regain lower extremity function after his C3/T3 hematoma was surgically evacuated. There is no case report in the literature that implicates clopidogrel alone as the causative agent in the production of a postneuraxial block spinal hematoma. The aforementioned epidural case report[53] highlights the fact that the effects of clopidogrel plus aspirin are additive and they may even be synergistic, depending on the method used to ascertain platelet function. This may explain why cardiac surgical patients who have received this drug combination appear to have excessive bleeding[54-56] and why it would seem prudent to refrain from placing neuraxial blocks and deep plexus blocks in patients taking this drug combination but who have not been free of the drugs for the 7-day period suggested by the ASRA guidelines.[1] Maier and colleagues[49] also report another catastrophic outcome when the ASRA guidelines were not followed to the letter for a patient who was receiving clopidogrel and underwent a lumbar spinal block. In this 2002 case report, a 79 year-old woman succumbed to complications after the placement of a lumbar spinal block; at autopsy she was found to have a massive

retroperitoneal hematoma. This adverse outcome may have occurred because the patient's clopidogrel was not discontinued until just 3 days before the procedure, and the anesthesia care team relied on the fact that all of her coagulation variables had normalized, including bleeding time. It is important to remember that the antiplatelet drugs do not alter the coagulation cascade, and testing for the activated partial thromboplastin time (aPTT), prothrombin times, and international normalized ratio (INR) are of no value. Furthermore, there is no value in obtaining a bleeding time. Bleeding times are highly variable, are very operator dependent, and do not reliably indicate whether platelets are functioning at an adequate level.

Prasugrel irreversibly inhibits 50% of platelets after a single oral dose and has a maximum effect 2 hours after administration. Platelet aggregation normalizes in 7 to 9 days after termination of therapy, and the drug label recommends discontinuing the drug "at least 7 days before any surgery." Despite the absence of any series involving performance of neuraxial blockade in the presence of prasugrel, the ESA has established guidelines along with a very strong warning for the placement of neuraxial blocks in patients receiving or who have received prasugrel.[2] The ESA guideline reads as follows: "In view of the higher incidence of bleeding compared to clopidogrel, neuraxial anesthesia should be strongly discouraged during prasugrel treatment, unless a (prasugrel free) time interval of 7-10 days can be observed." The ASRA has no guidelines for the placement of neuraxial blocks in patients who are receiving or have received prasugrel; however, Horlocker, the first author on all of the ASRA Anticoagulation Guidelines, authored a recent review article on regional anesthesia and antiplatelet therapy.[57] She was in total agreement with the ESA Guidelines and suggests a 7- to 10-day prasugrel free interval before undertaking the placement of a neuraxial block or any other invasive procedure.[57]

It is important to remember that many patients may come to the operating room or interventional suite already taking one of the aforementioned antiplatelet agents, given their use in the prevention of arterial thrombosis in multiple high-prevalence conditions such as ischemic heart disease, cerebrovascular disease, and peripheral artery disease. It is estimated that the number of patients taking antiplatelet agents requiring surgical or invasive procedures has reached 250,000 people annually, which has prompted the ACCP to set forth guidelines recommending the perioperative management of antithrombotic therapy in this setting.[8] The guidelines seek to balance the risk of thromboembolism against those of bleeding so that adverse clinical outcomes can be minimized. As such, patients taking antiplatelet medications are stratified according to risk. In patients with a coronary stent who require surgery, the ACCP recommends deferring surgery until 6 weeks after bare-metal stent placement and until 6 months after drug-eluting stent placement instead of undertaking surgery within these time frames.[8] If surgery cannot be delayed, however, the ACCP recommends continuing antiplatelet therapy preoperatively instead of stopping therapy 7 to 10 days before surgery.[8] It is worth noting that aspirin can be continued around the time of surgery and the ACCP does not require stopping therapy before surgery.[8]

Platelet Glycoprotein IIb/IIIa Antagonists

The identification of the platelet GP IIb/IIIa receptor, a fibrinogen receptor important for platelet aggregation, has led to the development of platelet receptor antagonists.[58] Activated GP IIb/IIIa receptors become receptive to fibrinogen, and when fibrinogen binds to the GP IIb/IIIa receptors located on two different platelets, it builds the crosslinks for platelet-to-platelet aggregation.[59] GP IIb/IIIa also mediates platelet adhesion and spreading.[58]

Abciximab is a monoclonal antibody that binds nonspecifically to the GP IIb/IIIa receptor.[58] The binding of abciximab to the platelet IIb/IIIa receptor is a rapid high-affinity interaction, and all the receptors are blocked within 15 minutes after the parenteral administration of a bolus dose of 0.25 mg. The biologic half-life of abciximab is approximately 12 to 24 hours, but 24 hours after administration, 50% to 60% of the platelet receptors are still blocked.[60] Abciximab can be detected on circulating platelets for more than 15 days, which indicates platelet-to-platelet transfer.[58] Abciximab cannot be effectively reversed with the transfusion of platelets because the new platelets are inactivated by the free-circulating monoclonal antibody or platelet-to-platelet transfer of the drug. Platelet function recovers over the course of 48 hours because of platelet turnover.[58] Abciximab prolongs activated clotting time (ACT) by 30 to 80 seconds, and the aPTT is also prolonged.[58] Comparative studies have shown that abciximab is superior to the other agents in preventing ischemic complications after percutaneous coronary interventions.[61] However, its potent inhibition of platelets also renders it likely to cause increased episodes of major bleeding.[62]

Eptifibatide is a small cyclic heptapetide.[58] The drug sits in the binding pocket between the IIb and IIIa arms of GP IIb/IIIa and prevents the binding of fibrinogen and thrombus formation.[63] Eptifibatide has a plasma half-life of 2.5 hours, with a rapid onset of action and a rapid reversibility of platelet inhibition.[58] Four hours after the termination of an eptifibatide infusion, platelet aggregation recovers to approximately 70% of normal and hemostasis normalizes.[64] The majority of the drug is eliminated by renal clearance.[58] Eptifibatide prolongs ACT by 40 to 50 seconds, but it has no effect on prothrombin time or aPTT.[58]

Tirofiban is a tyrosine derivative.[58] Tirofiban occupies the binding pocket on the GP IIb/IIIa receptor and competitively inhibits platelet aggregation mediated by fibrinogen and von Willebrand factor.[64] It is given via an intravenous infusion, and the plasma half-life is approximately 1.5 to 2.5 hours.[58] Greater than 70% of tirofiban is cleared by biliary elimination.[58] The remainder is eliminated by renal excretion, and the drug may be removed by hemodialysis.[58] The ACT is prolonged by 40 to 50 seconds.[64]

There are no known case reports of a spinal/epidural hematoma forming as the result of spinal axis blockade

TABLE 49-2 **Abciximab and Emergency Cardiac Surgery***

p < 0.02, Group 1 versus Group 2	*N*	Number Packs Platelets	Number Packs Packed Cells
Group 1: last dose abciximab <12 hr before surgery	6	20	6
Group 2: last dose abciximab >12 hr before surgery	5	0	0

*Results from a study by Gammie and colleagues[66] showing the need to delay emergent surgery for at least 12 hours after the administration of abciximab. The Gammie study does not attempt to ascertain the safety of placing a spinal or an epidural block in a patient who has received abciximab.

being performed in a patient who was simultaneously being treated with a GP IIb/IIIa antagonist. However, two studies show that patients who were using GP IIb/IIIa medications and required emergency cardiac surgery were at increased risk of having major bleeding compared with patients having elective surgery.[65,66] Eleven consecutive patients who were taking abciximab and required emergency cardiac surgery after failed angioplasty or stent placement were randomly assigned to two groups.[66] Group 1 patients ($n = 6$) had taken the last dose of abciximab 12 or less hours before surgery, and group 2 patients ($n = 5$) had taken it more than 12 hours before their surgery. Group 1 patients required 20 packs of platelets to control bleeding, whereas group 2 patients did not require any platelets ($p < 0.02$). Group 1 patients also required more packed erythrocyte transfusions (6 versus 0; $p < 0.02$). The results of the Gammie study[66] are outlined in Table 49-2.

GUIDELINES FOR SPINAL AXIS ANESTHESIA WITH ASPIRIN OR A CYCLOOXYGENASE-1 NONSTEROIDAL ANTIINFLAMMATORY DRUG

The ASRA provides the following guidelines for the anesthetic management of patients who are receiving aspirin or a COX-1 NSAID and in whom a spinal axis block is planned.[1]

American Society of Regional Anesthesiology Guidelines

1. NSAIDs appear to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia. The use of NSAIDs alone does not create a level of risk that will interfere with the performance of neuraxial blocks.
2. At this time, there do not seem to be specific concerns as to the timing of single-shot or catheter techniques in relationship to the dosing of NSAIDs, postoperative monitoring, or the timing of neuraxial catheter removal.
3. If, in the postoperative period, the concurrent use of other medications affecting clotting mechanisms (such as oral anticoagulants, unfractionated heparin, and LMWH) is anticipated in a patient receiving NSAIDs, performance of a neuraxial anesthetic technique is not recommended because of the increased risk of bleeding complications.

European Society of Anesthesiology Guidelines

The ESA has developed a set of guidelines for the performance of neuraxial anesthesia in patients who are receiving aspirin or another COX-1 NSAID.[2] The ESA guidelines have replaced the older German Society of Anesthesiology and Intensive Care Medicine and the Spanish Society of Anesthesia and Critical Care guidelines to provide "current and comprehensive guidelines for the continent as a whole."[2]

1. NSAIDs, including aspirin, when given in isolation, do not increase the risk of spinal epidural hematomas and are not a contraindication to neuraxial blockade.
2. Although the administration of aspirin alone does not appear to increase hematoma formation, a higher rate of complications has been seen in patients when heparins were administered concurrently. When aspirin is used alone, a cautionary approach to thromboprophylaxis is to start further venous thromboembolism postoperatively.

The authors of the ESA guidelines also draw attention to case series that have suggested that morbidity and mortality rates in patients with recently implanted coronary stents or unstable coronary syndromes are markedly increased if aspirin is stopped before a surgical procedure.[67-69] Subsequently, the authors emphasized that preoperative withdrawal of aspirin was unnecessary and, more alarmingly, was associated with a high risk of acute thrombosis.

It should be noted that very little difference exists between the ASRA[1] and ESA[2] guidelines, and the evidence-based material in the literature to support the conclusions and guidelines that have been reached by these two societies is scarce.[1,2] The practitioner's best judgment, based on all currently available information, should be used in the assessment of the risks involved in placing a spinal or an epidural block in a patient who is still taking or who has only recently stopped taking (the night before surgery) aspirin or a COX-1 NSAID.

Finally, a complete patient history and physical examination may be the most useful tools in guiding the decision about the risk–benefit ratio for the placement of a neuraxial block in a patient who has not curtailed aspirin or other NSAID therapy before surgery. The identification of alterations in health that might contribute to bleeding is crucial. These conditions include a history of easy bruisability or excessive bleeding, female gender, and increased age.[1]

GUIDELINES FOR SPINAL AXIS ANESTHESIA WITH A CYCLOOXYGENASE-2 NONSTEROIDAL ANTIINFLAMMATORY DRUG

The ASRA is the only group that provides guidelines for the anesthetic management of patients who are receiving a COX-2 NSAID.[1]

American Society of Regional Anesthesiology Guidelines

1. COX-2 inhibitors have minimal effect on platelet function and should be considered in patients who require antiinflammatory therapy in the presence of antithrombotic therapy.

GUIDELINES FOR SPINAL AXIS ANESTHESIA WITH A THIENOPYRIDINE

Both the ASRA and the ESA have guidelines concerning the use of thienopyridines in patients undergoing spinal axis anesthesia.[1,2] The ASRA guidelines remind practitioners that the actual risk of spinal hematoma formation with ticlopidine and clopidogrel is unknown and that patient management must be based on labeling precautions and surgical and interventional cardiology/radiology experience.

American Society of Regional Anesthesiology Guidelines

1. Ticlopidine should be discontinued 14 days before surgery.
2. It is recommended that clopidogrel be stopped 7 days before surgery.
3. Normalization of platelet function should be documented.

Of note, this normalization of platelet function is quite interesting because a comment contained in the body of the ASRA guidelines indicates that "there is no wholly accepted test, including bleeding time, that guides antiplatelet therapy."[1]

Benzon and colleagues[53] recommend that neuraxial blocks be postponed for 5 to 7 days in patients who are receiving several antiplatelet drugs. The manufacturer of ticlopidine suggests that ticlopidine be stopped 10 to 14 days before elective surgery.[38] The general recommendation is that clopidogrel should be stopped 7 days before surgery.[1]

European Society of Anesthesiology Guidelines

1. Ticlopidine should be discontinued for 10 days.
2. Clopidogrel should be discontinued for 7 days.
3. Prasugrel should be discontinued for 7 to 10 days.

If these conditions cannot be met, the ESA recommends against regional anesthesia and cites reports of spinal hematoma formation after neuraxial blockade during clopidogrel administration as supporting evidence for this advisory.

GUIDELINES FOR SPINAL AXIS ANESTHESIA WITH A GLYCOPROTEIN IIB/IIIA ANTAGONIST

The ASRA guidelines are based on the observation that platelet GP IIb/IIIa inhibitors exert a profound effect on platelet aggregation, even though the actual risk of spinal hematoma with these agents is unknown.[1] The guidelines are based on the known time from administration to recovery of normal platelet function.

American Society of Regional Anesthesiology Guidelines

The administration of all of the GP IIb/IIIa antagonists within 4 weeks of surgery is contraindicated; however, should urgent or emergent surgery be required, the following guidelines may prove to be helpful:

1. Abciximab should be discontinued 48 hours before surgery.
2. It is recommended that eptifibatide and tirofiban be stopped 4 to 8 hours before surgery.

The guidelines also warn that the increase in perioperative bleeding noted in patients undergoing cardiac and vascular surgery after having received a GP IIb/IIIa antagonist warrants concern about the risk of spinal hematoma if either spinal or epidural anesthesia is strongly indicated. Furthermore, Kam and Egan[58] indicate that literature concerning the safety of performing central neuraxial regional blockade (spinal or epidural anesthesia) in patients who have recently received a GP IIb/IIIa inhibitor is not available. Avoiding spinal anesthesia, epidural anesthesia, or a deep plexus block in these patients would appear to be wise.

European Society of Anesthesiology Guidelines

1. Neuraxial blockade is contraindicated.
2. If a catheter has to be removed after a GP IIb/IIIa inhibitor has been administered, the guidelines recommend waiting 48 hours after abciximab and 8 to 10 hours after tirofiban and that a platelet count be obtained to exclude thrombocytopenia before removing the catheter.

The ESA notes that the reason that neuraxial blockade is contraindicated is that GP IIb/IIIa inhibitors are used only in acute coronary syndromes, in combination with anticoagulants and aspirin, and cardiac surgery procedures are usually conducted as emergencies with continuing anticoagulation.[2]

Assessing platelet function with the use of platelet turbidometric aggregometry or platelet function analyzer PEA-100 may be useful in patients who have received a GP IIb/IIIa antagonist before anesthesia and surgery.[58] Unfortunately, neither of these tests is readily available.

AUTHORS' RECOMMENDATIONS

We agree that cyclooxygenase (COX)-2 inhibitors have a minimal effect on platelet function and that the available evidence in the literature supports the contention to continue COX-2 therapy during a neuraxial block or during the removal of either a spinal or an epidural catheter.

The development of a spinal/epidural hematoma is a rare event. Tryba[21] identified 13 cases of spinal hematoma after 850,000 epidural anesthetics and seven cases involving 650,000 spinal blocks. On the basis of these observations, he calculated the incidence of hematoma formation to be about 1 in 150,000 epidural blocks and 1 in 220,000 spinal anesthetics.[21] As such, no study, to date, has had a large enough patient population for anyone to state with any degree of certainty that no risk of hematoma formation exists when a patient continues to use COX-1 nonsteroidal antiinflammatory drugs (NSAIDs) before surgery.

Both the American Society of Regional Anesthesia and the European Society of Anesthesiology (ESA) believe that having patients without other risk factors proceed as scheduled for surgery even if they have continued to take aspirin or another COX-1 NSAID in the perioperative period will not increase their risk.[1,2] The societies' positions are supported by intuitive logic. Annually, millions of people worldwide undergo elective surgery and have continued to consume aspirin and other COX-1 NSAIDs, and the incidence of hematoma is almost nonexistent in this patient population.[20] More important, it would appear that we have come full circle in that many orthopedic surgeons now believe that the combination of aspirin, epidural anesthesia, and early ambulation may be the anticoagulation protocol of choice for total joint arthroplasty.[9,11] However, this position—the use of aspirin as the only prophylactic agent—is not supported by the American College of Chest Physicians 2012 guidelines.[8]

A substantial risk of hematoma formation exists for patients who have taken either ticlopidine or clopidogrel in the preoperative period. In brief, ticlopidine should be stopped 14 days before surgery, and patients should have a 7-day drug-free window from clopidogrel.[1] The ESA has similar guidelines but demands only a 10-day interruption before surgery for ticlopidine.[2]

Finally, a substantial risk of hematoma formation also exists in patients who have used a platelet glycoprotein IIb/IIIa agent before placement of a spinal/epidural block or catheter removal. Although there are no direct reports of this having occurred in any patient, this position was derived from the cardiac surgery literature.[65,66] In brief, abciximab should be discontinued 48 hours before surgery, and eptifibatide and tirofiban should be stopped 8 to 10 hours before surgery.[1]

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CHAPTER 50

DVT Prophylaxis with Heparin and Heparin-Like Drugs (UH, LMWH, Fondaparinux, and Rivaroxaban) Used in Combination with Neuraxial Anesthesia and Deep Plexus Blocks

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INTRODUCTION

Many patients undergoing surgery benefit from neuraxial anesthesia and analgesia, truncal blocks, and lower extremity nerve blocks with and without catheters. To this end, postoperative regional analgesia provides many advantages over parenteral opioids, especially for patients undergoing lower extremity orthopedic procedures; vascular, urologic, and gynecologic surgeries; and many cardiac and thoracic surgical procedures.[1-4] These benefits include improved pain relief, a decreased incidence of cardiopulmonary complications,[3] and reduced blood loss and the need for perioperative transfusions.[5,6] Numerous studies have documented the safety of neuraxial anesthesia and analgesia in the anticoagulated patient.[3,7-13] Spinal and continuous epidural infusion techniques provide effective operative and postoperative pain control, and frequently eliminate problems associated with general anesthesia.[1] However, there are some caveats to the use of neuraxial anesthesia, as well as deep plexus blocks, in that the blood vessels cannot be compressed by applying external pressure. Many surgical patients require preoperative deep vein thrombosis (DVT) prophylaxis, or they will receive DVT prophylaxis in the postoperative period. More importantly, some cardiac and vascular procedures may even require that the patient receive significant intraoperative anticoagulation.

There are valid concerns about the placement of neuraxial and, more recently, peripheral and deep plexus blocks in an anticoagulated patient.[14-17] The placement of neuraxial blocks can lead to the formation of spinal and epidural hematomas, and the incidence of this catastrophic complication is increased if the patient is receiving anticoagulation.[14,18] The safe management of patients who will be receiving a neuraxial block and perioperative anticoagulation therapy can be improved by coordinating the timing of needle placement and catheter removal with the administration of the anticoagulant.[19]

Familiarity with the pharmacology of the heparins, as well as other hemostasis-altering drugs; knowledge of the literature pertaining to patients receiving either neuraxial anesthesia or a deep plexus block while using these drugs; and the use of pertinent case reports can help guide the clinician in the management of these patients. The reasons that these patients receive anticoagulation are quite valid.[20,21] The reasons for preventing DVT/venous thromboembolism (VTE) and acute pulmonary embolism (PE) are obvious and critical to the provision of quality patient care.[21] In addition, vessel and graft patency are frequently dependent on adequate anticoagulation during both the intraoperative and postoperative periods. Finally, caution must be used when each patient's risk stratification is evaluated and when the use of a neuraxial anesthetic or a deep plexus block is considered in the presence of perioperative anticoagulation.

In this chapter we present a synopsis of the American Society of Regional Anesthesia and Pain Medicine (ASRA) Consensus Guidelines from 1998,[22,23] 2003,[24] and the most recent Consensus Guidelines from 2010 (third edition)[25] for the use of neuraxial anesthesia and deep plexus block techniques in patients receiving either unfractionated heparin (UH) or low-molecular-weight heparin (LMWH) in the perioperative period. We will also provide a brief overview on two new heparin-like agents, fondaparinux and rivaroxaban, and how these agents might be used in patients receiving a regional anesthetic. We will also present the current European thoughts and protocols (European Society of Anaesthesiology[26] and Belgian Association of Regional Anesthesia[27]) regarding these issues and discuss how they differ from the American guidelines. Finally, we will present two key articles from the most recent update (2012) by the American College of Chest Physicians (ACCP)[28] and recent input from the American Academy of Orthopedic Surgeons (AAOS) on the best prophylactic options for DVT in total hip replacement (THR) and total knee

replacement (TKR) patients (www.aaos.org/research/guidelines/VTE/VTE_full_guideline.pdf).

The use of direct thrombin inhibitors, vitamin K antagonists,[28a] and platelet inhibitors (see Chapter 49) are discussed elsewhere either in this text or in earlier editions of this text.

RATIONALE FOR THROMBOPROPHYLAXIS

The rationale for thromboprophylaxis stems from the high prevalence of VTE among postsurgical patients; the incidence can be as high as 80% in patients undergoing TKR who are not receiving anticoagulation therapy.[29] The clinically silent presentation of the disease in most patients and the morbidity and mortality frequently encountered when a VTE occurs make it imperative that all patients undergoing TKR, THR, hip fracture surgery (HFS), and certain abdominal and pelvic procedures receive DVT anticoagulation therapy.[29,30] PE produces few specific symptoms, and the presence of this devastating complication is often silent. Moreover, the clinical diagnosis of PE is very unreliable.[21-33] The first presentation of a VTE may be a catastrophic PE,[21,29] which requires that a preventive rather than a screening approach be taken to properly address the DVT/PE problem.[30] Routine screening of patients in the postoperative period for DVT and VTE has not been demonstrated to reduce the frequency of clinically significant outcomes such as VTE and PE[30] and has been shown to be cost-prohibitive when compared with routine prophylactic regimens.[31,32,34-39]

The risk of a patient developing an adverse event in the postoperative period such as myocardial infarction, DVT, or PE increases with age, and the elderly, particularly women older than 80 years, are at significant risk.[40] These data suggest that the risk of developing a VTE is substantial, be it a DVT or PE, without thromboprophylaxis. The potential severity of a VTE, as well as the difficulty and expense of screening for it postoperatively, warrants some type of thromboprophylaxis for all patients undergoing major lower extremity orthopedic surgery.[29,41] This chapter focuses on the relationships and benefits of neuraxial anesthesia or a deep plexus block in the patient requiring DVT prophylaxis via pharmacologic methods only.

HEMOSTATIC PROCESSES

An understanding of the mechanisms of the hemostatic cascade is important if one is to fully understand how anticoagulants work and the implications of their use in patients receiving regional anesthetics. The intrinsic, extrinsic, and final common pathways are featured in Figure 50-1. The extrinsic pathway is an alternative route for the activation of the clotting cascade. It provides a very rapid response to tissue injury, generating activated factor X almost instantaneously; on the other hand, the

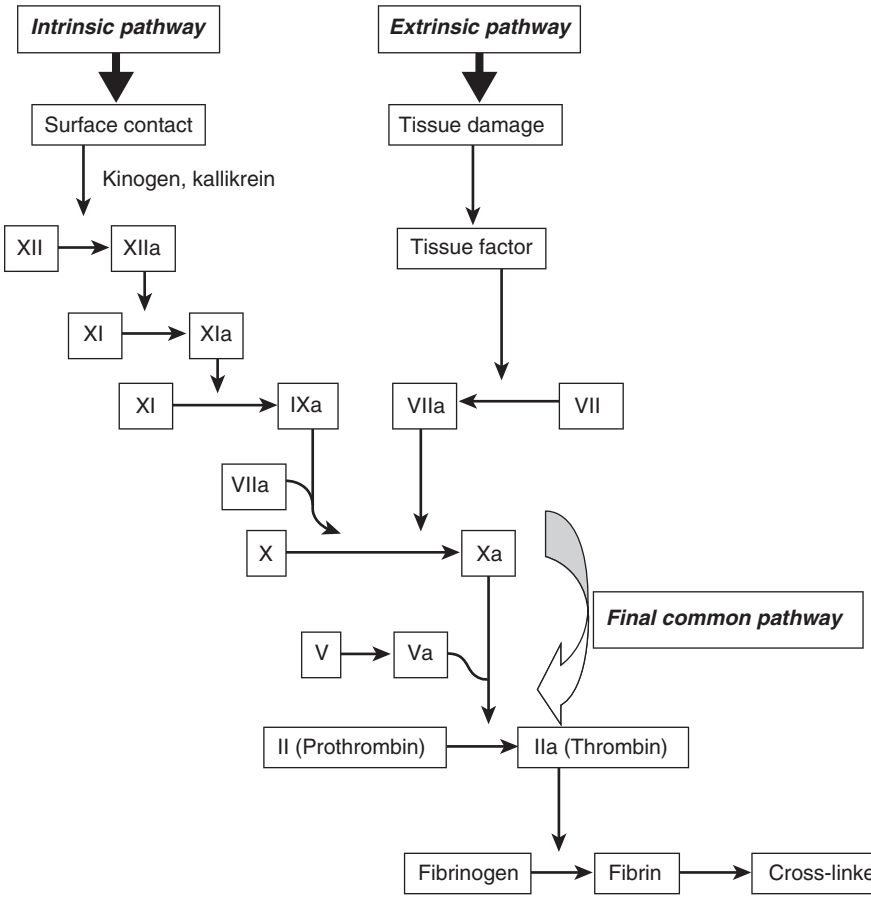

FIGURE 50-1 ■ Hemostatic Coagulation Cascade.

intrinsic pathway requires seconds or even minutes to activate factor X. The main function of the extrinsic pathway is to augment the activity of the intrinsic pathway.[40] The intrinsic and extrinsic systems converge at factor X to form the final common pathway, which is ultimately responsible for the production of thrombin (factor IIa).[40] The end result, as mentioned earlier, is the production of thrombin for the conversion of fibrinogen to fibrin. It is at the level of the conversion of factor X to Xa that all of the newer heparin and heparin-like drugs function (LMWH, fondaparinux, and rivaroxaban).

Interruption of the Coagulation Cascade

The heparins all work primarily by inhibiting the intrinsic limb of the coagulation pathway. A large portion of the clinical effects of both UH and LMWH occurs through enhancement of the action of antithrombin III (ATIII), an important endogenous inhibitor of coagulation that acts primarily by inactivating factor IIa and factor Xa.[42] The fundamental biologic difference between UH and LMWH stems from the relative potency of each drug to accelerate the basal rate of ATIII-mediated IIa and Xa inactivation.[43] UH enhances the inactivation of both IIa and Xa, whereas LMWH predominantly catalyzes factor Xa inactivation; fondaparinux and rivaroxaban are selective factor Xa inhibitors.

Monitoring of Anticoagulation

Monitoring of the level of therapeutic anticoagulation in patients receiving UH is achieved via the activated partial thromboplastin time (aPTT). In the aPTT test, a contact activator is used to stimulate the production of XIIa by providing a surface for the activation of high-molecular-weight kininogen, kallikrein, and factor XIIa. The contact activation is allowed to proceed at 37°C for a specified period of time. Calcium is then added to trigger further reactions, and the time (in seconds) required for clot formation is measured. Phospholipids are required to form complexes, which activate factor X and prothrombin. Normal values on the aPTT range from 24.3 to 35.0 seconds.[44]

The aPTT does not specifically measure anti-Xa activity, and little correlation exists between anti-Xa activity and aPTT.[45] Therefore aPTT is not generally used to monitor LMWH or anti–factor Xa therapy. Because of the very predictable plasma levels obtained when one administers either LMWH, fondaparinux, or rivaroxaban and the lack of correlation seen between the plasma levels of these drugs and aPTT and anti-Xa values, one should *not* attempt to monitor anticoagulant therapy with any of the aforementioned agents with either of these laboratory studies. However, in cases of renal insufficiency and obesity, monitoring may be justified.[46] In addition, the anti-Xa level assay is only available at major medical centers in North America, and again, it is of little value in determining whether it is safe to perform a neuraxial block or deep plexus block or to remove a catheter in a patient receiving LMWH or an anti–factor Xa drug.

Heparin Reversal with Protamine and Heparin-Induced Thrombocytopenia Syndrome

Unfractionated heparin is a highly negatively charged, water-soluble glycosamine with a variable molecular weight of about 15,000 daltons (range of 5000 to 30,000 daltons).[47a] This variation in molecular weight is a function of the number of attached polysaccharide chains. The major anticoagulant effect of UH is attributed to a unique pentasaccharide with a high-affinity binding to ATIII.[47b] This pentasaccharide subunit is the key component of fondaparinux and the reason why the action of LMWH differs from that of UH. Binding of this pentasaccharide to ATIII accelerates its ability to inactivate thrombin (factor IIa), as well as factors IXa, Xa, XIa, and XIIa. Unfractionated heparin catalyzes the inactivation of IIa by ATIII/heparin complex formation.[47b] This complex requires a chain length of at least 18 saccharide units and is the basis for the differences between LMWH and UH. Unlike UH, LMWH consists of primarily the pentasaccharide sequence and lacks the long polysaccharide unit required to bind to IIa and ATIII simultaneously. Thus LMWH has a Xa:IIa affinity ratio of approximately 3:1 and primarily inactivates Xa. The inactivation of Xa by ATIII/heparin does not require ternary complex formation and is achieved by binding of the enzyme to ATIII.[47c] The anticoagulant effect of UH depends on both the number of heparin molecules with the pentasaccharide chain (Xa inhibition) and the size of the molecules containing the pentasaccharide sequence (IIa inhibition).[22]

Both UH and LMWH are derived from animal sources. This explains the uncommon but serious occurrence of heparin-induced thrombocytopenia and thrombosis (HITT). The HITT syndrome is an IgG-mediated decrease in platelets to below 150,000 that usually occurs 5 days after initiating heparin therapy[47d] and may be complicated by pathologic thrombosis. Patients with a history of HITT syndrome should not receive LMWH because, as previously mentioned, it is also derived from animal sources and there is a high incidence of cross-reactivity

Serious bleeding associated with UH therapy may be controlled by the administration of protamine sulfate. Protamine is a strongly basic protein that binds to and neutralizes heparin.[47e] Most of the anticoagulant effects of UH are reversed by equimolar doses of protamine. Protamine is a positively charged protein derived from salmon sperm. When administered intravenously in the presence of heparin, the positively charged protamine interacts with the negatively charged portion of the heparin molecule and forms a stable complex. The long polysaccharide chains of UH appear to increase their attraction to protamine. The dose of protamine required to fully reverse heparin is 1 mg for each 100 units of circulating heparin. This dose is decreased if more than 15 minutes have elapsed since the last heparin administration.

Effectiveness of Low-Dose Subcutaneous Unfractionated Heparin Therapy

The administration of 5000 units of UH subcutaneously every 8 to 12 hours has been used extensively and effectively for the prevention of DVT. In a review of 11 trials, Geerts and colleagues[29] found that the overall risk of DVT in patients undergoing THR was 30% with low-dose UH compared with 54% in control subjects. The therapeutic basis for low-dose subcutaneous UH therapy is linked to the inhibition of activated factor X and the fact that the inhibition of small amounts of Xa prevents amplification of the coagulation cascade. Thus only small doses of UH are required for prophylaxis even though much larger doses are needed to treat thromboembolic disease. Maximum anticoagulation occurs 40 to 50 minutes after subcutaneous injection of UH and returns to baseline within 4 to 6 hours. The aPTT often remains in the normal range, but wide variances have occurred in individual patients.[47]

In their 1988 review of the results of randomized trials in urologic, orthopedic, and general surgery regarding fatal PE and venous thrombosis, Collins and colleagues[48] found that therapy with low-dose subcutaneous UH therapy, at 5000 units 2 hours before surgery and every 8 to 12 hours postoperatively, reduced the risk of DVT by 70% and fatal PE by 50%. However, if the efficacy of low-dose subcutaneous UH is compared with LMWH, UH is slightly less effective in the prevention of DVT and PE. Significant protein binding creates variability in the dose response to UH when compared with LMWH.[49]

EVIDENCE/GUIDELINES

Unfractionated Heparin

Spinal/Epidural Hematoma after Neuraxial Anesthesia

Bleeding is a recognized complication associated with the placement of a regional anesthetic block in the anticoagulated patient.[50] The most significant complication, however, is the development of a spinal axis hematoma.[51] The true incidence of neurologic complications caused from bleeding after spinal axis anesthesia is unknown; however, Tryba,[12] in his classic article, reported the estimated incidence to be less than 1 per 220,000 for spinal anesthesia and less than 1 per 150,000 for epidural anesthesia. A newer and more detailed study by Moen and colleagues[52] has shown that the predictions made by Tryba on the incidence of spinal and epidural hematomas were probably correct when all patients receiving spinal or epidural blocks are considered; however, if special subsets, such as elderly women undergoing TKR, are analyzed, the original calculations by Tryba grossly underestimate the incidence by as much as almost 100-fold.

In a review published in 1994 by Vandermeulen and colleagues,[14] the following possible risk factors were discussed for 61 previously reported spinal hematomas in patients receiving neuraxial anesthesia between 1906 and 1994:

- At the time of anesthetic administration, 42 of the 61 patients (68%) developing spinal hematoma had impaired coagulation. In 25 of 42 of the cases, some form of heparin therapy was present. An additional five of 42 patients had undergone a major vascular procedure in which heparin was likely used but not reported. The remaining 12 of 42 patients had a variety of medical conditions that could have produced an impairment in their ability to form a quality clot. These conditions included thrombocytopenia, hepatic dysfunction, and renal insufficiency, or they had been treated with another anticoagulant/antiplatelet agent at the time the bleeding occurred.
- The needle placement was reported as difficult in 15 of 61 patients (25%) and/or it was bloody in another 15 (25%) of the cases.
- Multiple punctures were reported in 12 of 61 (20%) of the cases.
- Pregnancy was noted in five of 61 (8%) of the cases.
- Anatomic abnormalities, such as spina bifida occulta and vascularized tumor, were noted in four of 61 (6.5%) of the cases.
- An epidural technique was used in 46 of 61 (75%) of the cases, and an epidural catheter was placed in 32 of 46 (70%). In 15 of 32 (47%) of the epidural catheter cases, the bleeding occurred immediately on removal of the catheter.
- A spinal technique was involved in 15 (25%) of the cases.

The Vandermeulen study[14] has two major shortcomings: it is a retrospective review of the literature and does not evaluate any primary data; of more importance, probably less than one in 10 adverse events that occur are ever reported in the literature.

More recently, Moen and colleagues[52] conducted a retrospective review of all central neuraxial blocks placed in Sweden between 1990 and 1999. The study encompassed two phases. First, a postal survey letter was sent to the chairperson of all anesthesia departments in which they were asked to provide the number of spinal and epidural blocks placed in their department during 1998. In addition, they were asked to provide the number of block-related complications that occurred in their department during the decade 1990-1999. The specific complications that the study addressed were epidural hematoma, epidural abscess, meningitis, and cauda equina syndrome. The researchers then went to the National Board of Health and Welfare (NBHW) and reviewed the quality assurance files associated with each complication. By Swedish law all serious complications must be reported to the NBHW. During the study period, Moen and colleagues[52] ascertained that 1,260,000 spinal blocks were performed and 450,000 epidural blocks were administered, including 200,000 labor epidural blocks. As a result of these blocks, 127 serious complications occurred, and 85 of 127 of these patients sustained permanent neurologic damage. Of the 127 complications, 33 were spinal axis hematomas, 32 were cauda equina syndrome, 29 were meningitis, 13 were epidural abscesses, and 20 were

miscellaneous. The results of the Moen study[52] mirror those of Tryba[12] in that the incidence of complications after epidural blockade was much more frequent than after spinal blockade. In addition, more complications than expected were found by Moen and colleagues.[52] The incidence of epidural hematoma in association with a labor epidural block was quite low (1:200,000), whereas those placed in women undergoing knee arthroplasty were very high (1:3600) and mirror the predictions made by Schroeder during the First ASRA Consensus Conference in 1998.[53] Perhaps the most alarming information reported by Moen and colleagues[52] is the fact that "one third of all spinal hematomas were seen in patients receiving thromboprophylaxis in association with a central neuraxial block (CNB) in accordance with the current guidelines and in the absence of any previously known risk factors." Consequently, adherence to the guidelines regarding LMWH and CNB may reduce but not completely abolish the risk of spinal hematoma after CNB. This latter fact is further reinforced by the case report by Sandhu and colleagues[54] in which they essentially followed the ASRA guidelines and still had an epidural hematoma occur in their patient 1 day after the removal of her epidural catheter. However, it must be noted that the patient in the Sandhu case report had two risk factors. The patient was elderly, age 79 years, and female. In brief, the Sandhu article[54] reports the placement of an epidural catheter on the third attempt, hours after the last 5000-unit dose of subcutaneous UH. The catheter was removed on the third postoperative day, 6 hours after the last 5000-unit dose of UH. The patient developed a symptomatic epidural hematoma the next day that required surgical evacuation. Her platelet count and aPTT were within normal limits at all times. Sandhu and colleagues[54] highlighted the need for all clinicians to be vigilant about the timing of epidural placement and removal, even in patients receiving standard-dose UH therapy, and they encouraged the routine and repeated monitoring of coagulation status.

The aforementioned two studies (the Moen and Sandhu studies) in which all guidelines were followed suggest that the incidence of these and similar catastrophic events are still very likely underreported. However, this impression may be tempered by a recent meta-analysis by Kreppel and colleagues.[55] Kreppel and colleagues analyzed 613 case studies of all neuraxial hematomas published between 1826 and 1996 and ascertained that, in about one third of the cases (29.7%), no etiologic factor could be identified as the cause of the bleeding. This idiopathic spontaneous hemorrhage group formed the largest group of patients who developed spinal/epidural hematomas. Spinal and epidural anesthetics placed in conjunction with anticoagulation therapy were actually the fifth most common cause of spinal/epidural hematomas, and spinal and epidural anesthetic procedures alone were the tenth most common etiologic factor. The second largest group comprised cases in which the patients were undergoing anticoagulation therapy (17%) in the absence of neuraxial blocks. Unlike Moen and colleagues,[52] Kreppel and associates[55] found elderly men between 55 and 70 years to be at the greatest risk of the development of spinal hemorrhage. In the Kreppel series,[55] 64% of the patients were men; however, all causes of spinal hemorrhages in patients in the Kreppel study were included, not just causes of hemorrhages in those undergoing total joint replacement under spinal/epidural anesthesia in conjunction with perioperative anticoagulation. In this latter scenario, elderly women are clearly at greatest risk.[52,53]

Spinal hematoma is a rare and catastrophic complication associated with both epidural and spinal anesthesia. It may occur with bleeding into either the epidural space or the subarachnoid space.[11,16,50] The prominent epidural venous plexus accounts for the majority of hematomas being formed in the epidural space. In addition, the radicular vessels along nerve roots can bleed either into the intrathecal or epidural space.[11]

Spinal hematoma is often occult, delaying both diagnosis and treatment.[16] The presenting symptom of spinal hematoma is not always radicular back pain. Vandermeulen and colleagues[14] found the presenting symptoms to be lower extremity weakness (46%), radicular back pain (38%), and paresthesia (14%). The diagnosis is frequently complicated and delayed because of residual paresthesia or anesthesia produced by the neuraxial block. The use of a short-acting local anesthetic agent for intraoperative anesthesia and then unilateral or motor block–sparing techniques for postoperative analgesia can avert such delays in diagnosis. There is likely a temporal relationship between the onset of paraplegia, surgical evacuation of hematoma, and recovery (Table 50-1).[14,56] Full recovery of neurologic function appears less likely if surgery is postponed or delayed for more than 8 to 12 hours.[14] Similar to the patients in the Vandermeulen series,[14] patients in the Kreppel series[55] who underwent rapid diagnosis and surgical evacuation obtained the most ideal recovery of neurologic function. In the Kreppel study,[55] 31 of 47 patients who received surgical treatment within 12 hours of the onset of their symptoms recovered completely (66%); more than half of the patients who did not obtain surgical decompression until 13 to 24 hours had elapsed did not recover any neurologic

TABLE 50-1 **Neurologic Outcome* in Patients with Spinal Hematoma after Neuraxial Blockade**

Interval between Onset of Paraplegia and Surgery	Good Recovery (*n* = 15)	Partial Recovery (*n* = 11)	Poor Recovery (*n* = 29)
Less than 8 hr (*n* = 13)	6	4	3
Between 8 and 24 hr (*n* = 8)	2	2	4
Greater than 24 hr (*n* = 11)	1	0	10
No surgical intervention (*n* = 13)	4	1	8
Unknown (*n* = 10)	2	4	4

*Neurologic outcome was reported for 55 of 61 cases of spinal hematoma after neuraxial block.

Modified from Vandermeulen EP, Van Aken H, Vermylen J. Anticoagulants and spinal-epidural anesthesia. Anesth Analg 1994;79:1165–77.

function. The exact treatment for a neuraxial hematoma, however, remains controversial. In the classic study by Moen and colleagues,[52] five of the six patients who recovered total neurologic function were conservatively managed; that is, they did not have surgical evacuation of their hematomas once they were diagnosed. However, among the 27 other patients with hematomas who did not recover neurologic function, 11 received a laminectomy and six were under consideration for a decompressive laminectomy that was not ultimately undertaken because of the delay from the time of symptom recognition until the time of diagnosis. In light of the mixed messages contained in these three studies,[14,52,55] if an epidural hematoma is suspected, promptly seek the advice of a consultant. Moreover, an emergent MRI and a neurosurgical consultation are imperative; the advice of consultants should be followed. Of note, it is possible for a select group of patients to recover totally from an epidural hematoma without surgery, and an epidural blood patch is, in fact, an epidural hematoma. On the other hand, the literature would suggest[14,55] that a decompressive laminectomy is the treatment of choice if one is faced with this catastrophic complication.

Safety of Neuraxial Anesthesia in Patients Receiving Low-Dose Subcutaneous Unfractionated Heparin

Multiple studies have demonstrated the relative safety of neuraxial anesthetic techniques in the presence of DVT prophylaxis with low-dose subcutaneous UH; in addition, there is little increased risk of spinal hematoma associated with this therapy.[8,9,13,57-59] Five series have been published involving more than 9000 patients receiving this therapy without any complications.[9-11,58,60] Allemann and colleagues[59] and Lowson and Goodchild[13] similarly reported no cases of spinal hematoma in 204 epidural blocks and 119 spinal blocks in patients who had received 5000 units of UH subcutaneously 2 hours before needle placement. The large amount of data suggests that subcutaneous heparin for DVT prophylaxis is both safe and efficacious in patients undergoing lower extremity orthopedic procedures and general, urologic, and gynecologic operations with a neuraxial block.

Currently, only three cases of spinal hematoma after neuraxial block in the presence of low-dose subcutaneous UH have been reported in the literature, two of which involved a continuous epidural anesthetic technique.[61-63] In one of these case reports, an epidural catheter was placed despite elevation of the patient's aPTT. In another, blood was aspirated from the catheter during placement. In the last case, spinal anesthesia was attempted multiple times.

ASRA 2010 Guidelines for the Use of Neuraxial Anesthesia and Low-Dose Subcutaneous Unfractionated Heparin

The material presented at the third annual meeting of the ASRA in Vancouver, British Columbia, Canada, in April 2007 appears to have served as the basis for most of the changes made to the earlier (1998[23] and 2002[24]) guidelines on the use of UH and LMWH in conjunction with neuraxial anesthesia and have acted as the platform for the drafting of the newest ASRA guidelines (2010).[25]

During subcutaneous (mini-dose) prophylaxis (5000 units, twice daily), no contraindication exists to the use of neuraxial techniques. The risk of neuraxial bleeding may be reduced by delaying the heparin injection until 1 to 2 hours after the block, and it may be increased in debilitated patients or after prolonged therapy. For the provision of the best possible patient care, it is imperative that every patient's chart is reviewed on a daily basis to determine that patients are not receiving concurrent medications such as LMWH, oral anticoagulants, or antiplatelet agents that could affect other components of the clotting cascade.[25] Because heparin-induced thrombocytopenia may occur, patients receiving heparin for more than 4 days should have a platelet count assessed before neuraxial block.[25]

- Avoid neuraxial techniques in patients with other coagulopathies.
- Heparin administration should be delayed for 1 hour after needle placement.
- Remove the catheter 1 hour before any subsequent heparin administration or 2 to 4 hours after the last heparin dose.
- Monitor the patient postoperatively to provide early detection of motor blockade, and consider the use of a minimal concentration of local anesthetic to enhance the early detection of a spinal hematoma.
- Although a bloody or difficult neuraxial needle placement may increase the risk of neuraxial bleeding, data do not support mandatory cancellation of a case. Clinical judgment is needed. If a decision is made to proceed, full discussion with the surgeon and careful postoperative monitoring are warranted.

Three Times Daily Dosed Subcutaneous Unfractionated Heparin. The concept of using thrice daily (subcutaneous low-dose) UH (tid-UH) appears to be driven by the most recent deliberations of the ACCP,[28,64] although few studies show efficacy or, more importantly, the superiority of this treatment plan compared with either twice-daily (bid-UH) or LMWH prophylaxis for TKR and THR.

A recent meta-analysis performed by King and colleagues[64] involving 7978 medical patients receiving either bid-UH (6314 patients) or tid-UH (1664 patients) for VTE/PE prophylaxis essentially showed no benefit to and an increased risk of bleeding with tid dosing ($p < 0.001$). The authors evaluated 12 studies in which either bid- or tid-UH efficacy rates, with regard to the prevention of VTE/PE, were compared with the rates found in a matched placebo group. Of note, the patients in the King study[64] were medical, not surgical, patients, but the incidence of major bleeding in the tid-UH prophylaxis group was still increased.

Surgeons at the University of Virginia[25] administered mini-dose subcutaneous tid-UH (5000 units) rather than bid-UH in keeping with the recent recommendations by the ACCP.[28] Between 2005 and 2007, 1920 patients received an epidural block. Of these patients, 768 (40%)

received tid-UH, and 16 of these patients had a hemorrhagic code found in their discharge record. However, none of the hemorrhages were identified as being "major." Moreover, an analysis of the aPTTs for the tid-UH group showed no significant variation from the normal range.

A case report by Jooste and colleagues[65] at the Children's Hospital of Pittsburgh would suggest that it is safe to place and remove a thoracic epidural catheter in a pediatric patient who had been receiving long-term LMWH therapy and then received bridge therapy with tid-UH by strictly adhering to the 2002 ASRA guidelines.[24] To comply with those guidelines,[24] Jooste and colleagues[65] stopped the child's enoxaparin (1.5 mg/kg every 12 hours) 5 days before surgery and substituted low-dose tid UH (5000 units subcutaneously). They then successfully placed a thoracic epidural catheter in accordance with the ASRA guidelines and continued tid-UH therapy into the postoperative period until the catheter was safely removed on postoperative day 7. However, the risk of spinal/epidural hematomas may be much less in children based on data gleaned from the study by Kreppel and colleagues.[55] More importantly, in the study by Jooste and colleagues,[65]daily platelet counts and the child's aPTT results were always in the normal range, the epidural catheter was removed 6 hours after the last heparin dose, and a neurologic examination was performed every 4 hours for the first 48 hours and then every 6 hours until 24 hours after the catheter was safely removed.

Unfortunately, the risk–benefit ratio has not been determined for tid-UH and DVT prophylaxis for TKR and THR in patients receiving neuraxial anesthesia or deep plexus blocks. Therefore ASRA provides the following recommendations and guidelines on the use of tid-UH and neuraxial techniques[25]:

- Because there is no apparent difference between bid-UH with the concurrent use of compression devices and tid-UH, it is advised that patients *not* receive tid-UH while epidural analgesia is maintained.
- Such patients should continue to be treated with both bid-UH and mechanical compression devices.[25]

Safety of Neuraxial Anesthesia in Patients Receiving Therapeutic or Full-Dose Unfractionated Heparin

Therapeutic or full-dose management modalities usually involve the injection of moderate amounts (5000 to 10,000 units) of intravenous (IV) UH intraoperatively. Injection during vascular cases may prevent thrombus formation during arterial cross-clamping. Alternatively, 20,000 to 30,000 units of UH may be injected during a cardiac procedure to facilitate cardiac bypass. In both these situations, high levels of UH are transient.

Several studies have demonstrated that spinal or epidural anesthesia followed by systemic UH administration is relatively safe.[8,22,66,67] Rao and El-Etr[8] reported on the outcomes of 3146 patients receiving continuous epidural anesthesia and 847 patients receiving continuous spinal anesthesia for lower extremity vascular procedures. UH was administered 50 to 60 minutes after catheter placement to achieve an activated clotting time (ACT) of twice the normal value. The UH was given every 6 hours throughout the period of anticoagulation therapy, and the catheters were removed the next day, 1 hour before the administration of the next maintenance dose of UH. None of the patients developed spinal hematoma. This UH therapy was closely monitored, and catheters were removed when UH levels were relatively low.

In 1998 Liu and Mulroy[22] reported on more than 1000 patients undergoing full intraoperative anticoagulation who had also received either a single-bolus spinal injection of opioids or an epidural opioid infusion without any incidence of spinal hematoma. The authors noted that communication with the surgeon regarding traumatic attempts and subsequent management of anticoagulation was critical. Similarly, in 1998 Sanchez and Nygard[66] reported on 558 patients undergoing cardiac surgery who had epidural catheters placed following strict guidelines. These guidelines mandated placement of the epidural catheters the day before surgery, use of a paramedian approach, obtaining an initial normal coagulation profile, carefully screening for preoperative drug use, and limiting catheter placement to two attempts. No incidence of spinal hematoma occurred in this study.

Baron and colleagues[67] published a retrospective review in 1987 that evaluated 912 patients who had received continuous epidural analgesia while undergoing major vascular reconstruction of a lower extremity. The patients all received transient, full anticoagulation with UH at a dose of 75 IU/kg, in addition to a maintenance dose of 1000 IU/hr. None of these patients developed neurologic evidence of spinal hematoma. In this review, 71% of the patients were male, the average age was 68.7 years, and the following hematologic studies were obtained preoperatively: hemoglobin level, platelet count, prothrombin time (PT), and aPTT. No reference was made to the timing of either catheter placement or removal.

The potential usefulness of thoracic epidural analgesia in patients undergoing cardiothoracic surgery has been shown in multiple studies. In 2000 Ho and colleagues[68] published a statistical analysis suggesting that, at most, one spinal hematoma secondary to epidural catheter placement would occur for every 1520 patients receiving epidural analgesia for coronary bypass surgery. This analysis was based on a zero incidence of spinal hematoma in more than 1500 reported uses of epidural analgesia in patients undergoing cardiac surgery. Thus studies purporting the safety of epidural anesthesia in the fully anticoagulated patient may be tainted by small sample sizes and type II statistical error.

It is important to recognize that other members of the care team may institute an inappropriate therapeutic intervention with catastrophic results. In a 2004 case report, a junior intensive care house officer administered an antithrombotic medication to a pediatric patient who had a functioning epidural catheter in place.[69] The patient had been ambulating before the administration of the alteplase. Almost immediately after the administration of the drug, the child developed severe back pain, and blood was noted in the epidural catheter. The house officer immediately removed the epidural

catheter and within minutes the patient developed lower extremity sensory and motor losses. The anesthesia care team was promptly notified, and a timely laminectomy and clot evacuation resulted in total recovery of neurologic function in the child 6 weeks later. This case report reinforces the need for all members of the care team involved in complex cases to be familiar with the guidelines for the management of epidural or other indwelling catheters. Moreover, this event occurred after the Rosen team had placed and managed slightly more than 1500 epidural catheters in infants and children undergoing total heparinization and cardiopulmonary bypass.

Davignon and colleagues[70] and Chaney[71] questioned the benefits of neuraxial blocks in patients undergoing cardiopulmonary bypass. The risks and benefits must always be carefully balanced.

In an article on the risks of neuraxial techniques and UH, Ruff and Dougherty[18] reported the occurrence of spinal hematomas in seven of 347 patients who had initially had signs of cerebral ischemia. After subarachnoid bleeding had been ruled out, each patient immediately underwent a diagnostic lumbar puncture with a 20-gauge needle, followed by the institution of IV UH therapy. Unfortunately, the amount of UH administered was not reported in the article. The authors concluded that traumatic needle placement, initiation of IV UH within 1 hour of lumbar puncture, and concomitant aspirin therapy were all risk factors that led to the development of the spinal hematomas.

The therapeutic benefits of UH are limited by an increased risk of bleeding, which is at least a partially dose-dependent phenomenon.[72] To optimize the balance between efficacy and bleeding complications, physicians have adopted two dosing practices. The first is estimation of UH plasma concentrations using frequent serial evaluations of the aPTT, a relatively inexpensive laboratory test. However, with repeated serial testing, cost may become an issue. The second is continuous IV administration of UH, in an attempt to allow multiple rapid dosage adjustments guided by aPTTs.[73]

ASRA 2010 Guidelines for Neuraxial Anesthesia and Full-Dose Unfractionated Heparin

Currently, insufficient data and experience are available to determine whether the risk of neuraxial hematoma is increased when neuraxial techniques are combined with the full anticoagulation of cardiac surgery. Postoperative monitoring of neurologic function and selection of neuraxial solutions that minimize sensory and motor block are recommended to facilitate detection of new or progressive neurodeficits.

Prolonged therapeutic anticoagulation appears to increase the risk of spinal hematomas, especially if combined with other anticoagulants or thrombolytics. Therefore neuraxial blocks should be avoided in this clinical setting.

- If systemic anticoagulation therapy is begun with an epidural catheter in place, it is recommended that catheter removal be delayed for 2 to 4 hours after therapy discontinuation and evaluation of coagulation status. The concurrent use of medications that affect other components of the clotting mechanisms may increase the risk of bleeding complications for patients receiving standard heparin. These medications include antiplatelet medications, LMWH, and oral anticoagulants.
- It is important to note that approximately half of the spinal hematomas that have involved epidural catheters have occurred on the removal of the catheter. Epidural catheter removal carries the same risk as catheter placement, and the same guidelines should be followed for both procedures.

European Guidelines for Neuraxial Blockade and Unfractionated Heparin

Tryba[74] found a low incidence of spinal hematomas in the large numbers of European patients receiving a spinal anesthetic and concurrent anticoagulation therapy. On the basis of their unique experiences and available experimental data, two European countries have recently promulgated new guidelines regarding the dosing of the heparins and heparin-like drugs in patients receiving neuraxial anesthetics. The European Society of Anaesthesiology (ESA)[26] and Belgian Association for Regional Anesthesia (BARA)[27] have both recently updated their guidelines, and they are now the standard by which other European nations manage and monitor the use of UH, LMWH, fondaparinux, and rivaroxaban in conjunction with neuraxial and deep plexus blocks. Only a few minor differences exist between the ESA and BARA guidelines.

Unfractionated Heparin in Low-Dose Regimen

- No increased risk of spinal hematoma has been observed with low-dose UH therapy, providing that a minimal interval between administration and puncture has been observed.[58,75,76]
- An interval of 4 to 6 hours between administration of UH and neuraxial block placement is recommended.[66,75]
- UH should be administered 1 or more hours after neuraxial block placement.[75]
- No laboratory tests are suggested for the first 4 postoperative days; platelet counts should be checked on day 5 because of the risk of heparin-induced thrombocytopenia.[58,75]

Unfractionated Heparin in Therapeutic or Full Doses

- Compared with low-dose prophylaxis with UH, therapeutic doses of IV UH are associated with an increased risk of spinal bleeding. Thus no neuraxial block or catheter removal should be performed in any patient receiving therapeutic anticoagulation.[14,74]
- If neuraxial block or catheter removal is required, UH administration must be stopped for 4 to 6 hours, and laboratory tests (ACT, aPTT, and platelet counts) should be evaluated and normalized before proceeding.[74]

- Because patients who receive intraoperative anticoagulation may benefit from a neuraxial block (e.g., patients undergoing vascular or cardiac surgery and patients with unstable angina),[2,77] IV UH (up to 5000 units) may not be considered an absolute contraindication, providing there is careful postoperative observation of the patient.[75]
- In the previous case, IV UH should be initiated no sooner than 1 hour after spinal puncture, the UH dose should be adjusted so that the aPTT does not exceed twice the normal value, and catheters should be removed no earlier than 2 to 4 hours after stopping the UH infusion.[74,75]
- If a bloody tap occurs during neuraxial puncture, it may be prudent to postpone surgery and heparinization for 6 to 8 hours per BARA[27] and 24 hours per ESA,[26] although no data exist to support either of these positions.
- Surgery should be postponed for 12 hours. Alternatively, catheters may be inserted the night before the surgery.[74]
- Administration of low-dose IV UH (total dose, 2000 units or less) has been shown to be effective in preventing thromboembolic complications during high-risk orthopedic surgery.[78] UH administration at this dosage does not result in a significant alteration of hemostasis and thus should not be considered as a contraindication to neuraxial blocks.[74]

Low-Molecular-Weight Heparin

Enoxaparin was the first commercially available LMWH. When compared with UH, LMWH does not usually prolong the aPTT to supranormal levels when prophylactic doses are used. A specific assay for anti-Xa activity may be used to monitor the biologic activity of LMWH; however, the monitoring of factor Xa levels is not recommended by ASRA.[24] This is because anti-Xa levels are not predictive of the development of hemorrhagic complications such as spinal hematomas. Finally, ACT is not useful for assessing anticoagulation with LMWH.[79]

A difference of opinion exists between the United States (America) and Europe with regard to DVT prophylaxis with LMWH when it is used in conjunction with a neuraxial anesthetic. The outcomes of a LMWH dose-response series by Planes and colleagues[80-83] have been used to establish the current European dosing protocols, and a review of the various guidelines from the ASRA, ESA, and BARA for all the agents is presented in Table 50-2.

Safety and Efficacy of Low-Molecular-Weight Heparin

The results of three successive prospective clinical trials by Planes and colleagues[81-83] attempting to define the once-daily dosing regimen protocol for enoxaparin in THR suggest that 40 mg dosed once daily is the superior combination for THR.[80]

Planes and colleagues[81] randomly assigned 228 patients to one of four groups. Group 1 (n = 50) received 60 mg enoxaparin once daily; group 2 (n = 28) received 30 mg enoxaparin twice daily; group 3 (n = 50) received 40 mg enoxaparin once daily; and group 4 (n = 100) received 20 mg enoxaparin twice daily. The groups were standardized to surgeon, operative approach, anesthesiologist, anesthetic, and postoperative physical prophylactic method. All therapies were initiated 12 hours before surgery. The number of red blood cell units transfused increased between doses of 40 and 60 mg (p = 0.006), and wound hematoma formation differed significantly between the groups. Group 2 (30 mg twice daily) had a wound hematoma occurrence rate of 22%; group 1 (60 mg once daily) had an occurrence of 12%; group 3 (40 mg once daily) had an occurrence of 6%; and group 4 (20 mg twice daily) had an occurrence of 2%. In addition, the incidence of both distal and proximal DVT ranged from 6% to 8% in all the groups. The proximal DVT rate in groups 1, 3, and 4 ranged from 4% to 6%. However, no proximal DVT formations occurred in group 2. The lack of proximal DVT formations coupled with the wound hematoma occurrence rate prompted the U.S. Food and Drug Administration (FDA) to initially accept only the 30 mg twice-daily dosing regimen for enoxaparin. It is likely that the aforementioned data on the incidence of wound hematomas probably also apply to the relative risk that a patient will have for the development of a spinal/epidural hematoma.

Planes and colleagues[82] studied two modes of administration for 40 mg enoxaparin: group A had two injections of 20 mg subcutaneously, and group B had one injection of 40 mg enoxaparin plus one injection of placebo, both administered subcutaneously. In all cases the first dose of enoxaparin was administered 12 hours before surgery. Subsequently, in group A, the patients received 20 mg in the evening of the first postoperative day (approximately 24 hours after the initial dose) and every 12 hours thereafter. In group B, the patients received 40 mg at 8:00 PM on the day of surgery (approximately 24 hours after the initial dose) and every evening thereafter. Patients with the following characteristics were excluded: age younger than 45 years, weight less than 45 kg, past history of VTE, those receiving spinal anesthesia, those undergoing revision of THR, those with recent trauma, thrombocytopenia, recent gastrointestinal bleeding, or ATIII deficiency, those undergoing recent platelet therapy or anticoagulant therapy, or those having a preoperative aPTT 10 seconds longer than control subjects. The number of red blood cell units transfused did not differ significantly between groups. Wound hematoma formation occurred at the same frequency in both groups (5%). The incidence of total DVT was 1.7% in group A (20 mg twice daily) and 10.5% in group B (40 mg once daily). The difference was found to be clinically insignificant (p = 0.11). No deaths or clinical signs and symptoms of PE were observed in either group.

Planes and colleagues[83] also performed a multicenter, double-blind, randomized, prospective study comparing enoxaparin with fixed doses of UH. A total of 237 consecutive patients undergoing elective hip surgery received one of the following DVT prophylaxis regimens: (1) 40 mg enoxaparin, once daily, with initiation of therapy

TABLE 50-2 **Summary of Recommended Time Intervals before and after Neuraxial Needle/Catheter Insertion and Withdrawal in the Face of Anticoagulation with Heparins and Factor Xa Inhibitors**

	American/ASRA 2010	European/ESA 2010	Belgian/BARA 2009
UH: Prophylactic Dose			
Drug to catheter insertion/removal	No contraindication to placement or removal of neuraxial blockade[a]	4-6 hr	4 hr
Catheter insertion/removal to drug administration		1 hr	(n/a)
Recommended laboratory tests	Plt[b]	Plt[b]	Plt[b]
UH: Therapeutic Dose			
Drug to catheter insertion/removal	2-4 hr	4-6 hr	4 hr
Catheter insertion/removal to drug administration	1 hr	1 hr	1 hr
Recommended laboratory tests	Assess coagulation status	aPTT/ACT/ Plt[b]	aPTT/ACT/ Plt[b]
UH: >100 units/kg/day (Full Intraoperative Anticoagulation)			
Drug to catheter insertion/removal	2-4 hr	4-6 hr	4 hr
Catheter insertion/removal to drug administration	1 hr[c]	1 hr[d]	1 hr[e]
Recommended laboratory tests	Assess coagulation status	aPTT/ACT/ Plt[b]	aPTT/ACT/ Plt[b]
LMWH: Prophylactic (≤40 mg/day)			
Drug to catheter insertion/removal	10-12 hr	12 hr	12 hr
Catheter insertion/removal to drug administration	2 hr	4 hr	2-4 hr
Recommended laboratory tests	Plt[b]	Plt[b]	Plt[b]
LMWH: Therapeutic (>40 mg/day)			
Drug to catheter insertion/removal	24 hr[f]	24 hr	24 hr
Catheter insertion/removal to drug administration	2 hr	4 hr	2-4 hr
Recommended laboratory tests	Plt[b]	Plt[b]	Plt[b]
Fondaparinux: 2.5 mg/day			
Drug to catheter insertion/removal	Perform neuraxial techniques only under conditions used in clinical trials: single-needle pass, atraumatic needle placement, avoid indwelling neuraxial catheters	36-42 hr	36 hr
Catheter insertion/removal to drug administration		6-12 hr	12 hr
Rivaroxaban			
Drug to catheter insertion/removal	No recommendations available	22-26 hr	18-20 hr[g]
Catheter insertion/removal to drug administration		4-6 hr	6 hr[g,h]

ACT, activated clotting time; *aPTT,* activated partial thromboplastin time; *ASRA,* American Society of Regional Anesthesia and Pain Medicine; *BARA,* Belgian Association for Regional Anesthesia; *ESA,* European Society of Anaesthesiology; *LMWH,* low-molecular-weight heparin; *Plt,* platelet count; *UH,* unfractionated heparin.

[a]Check platelet count if patient is taking UH or LMWH for more than 4 days because of risk of heparin-induced thrombocytopenia.

[b]The safety of neuraxial blockade in patients receiving doses greater than 10,000 U of UH daily or more than twice-daily dosing of UH has not been established.

[c]Although the occurrence of a bloody or traumatic neuraxial block may increase risk, there are no data to support mandatory cancellation of surgery. Direct communication with the surgeon is warranted.

[d]In the event of a bloody or traumatic neuraxial block, full intraoperative anticoagulation should be delayed for 6 to 12 hours.

[e]In the event of a bloody or traumatic neuraxial block, it may be safer to wait 24 hours before proceeding with surgery; however, there are no data to support this attitude.

[f]For postoperative administration of LMWH in therapeutic dosing schemes, indwelling catheters should be removed before initiation of LMWH.

[g]No formal guidelines. Recommendations are based on pharmacologic properties or manufacturer recommendation.

[h]In the event of a bloody or traumatic neuraxial block, wait 24 before administering next dose of rivaroxaban.

12 hours before surgery ($n = 124$) and (2) 5000 IU UH, every 8 hours (tid-UH), initiated 2 hours before surgery ($n = 113$). The same exclusion and standardization criteria that were used in the enoxaparin trial were used in the present trial.[83]

Red blood cell transfusion requirements were higher in the UH group ($p = 0.035$). Wound hematoma formation was 6.4% in the enoxaparin group and 5% in the UH group, but three patients in the UH group required reoperation, whereas none of the patients in the

enoxaparin group required surgical reintervention.[83] No deaths occurred in either group. Five patients developed PE, of whom two were in the enoxaparin group and three were in the UH group. The incidence of total DVT in the enoxaparin group was 12.5% compared with an incidence of 25% in the UH group ($p = 0.03$).

Although the Planes study[83] does not address the safety of leaving an indwelling epidural catheter in place in patients who are receiving tid-UH, it does show that the incidence of wound hematoma formation and the need for reoperation are similar to those seen in patients receiving 40 mg enoxaparin daily. As such, this study would suggest that it is probably safe to leave an epidural catheter in place in patients who are receiving tid-UH; however, the ASRA guidelines do not support this view.

Data extrapolated from the Planes study[80] demonstrate the relative safety and efficacy of 40 mg enoxaparin once daily, started the night before surgery. These data similarly show that the 40-mg daily regimen is superior to both the 60-mg daily and 30-mg twice-daily regimen in safety and that the efficacy of the higher doses is no better.

In a comprehensive review of the available literature, Geerts and colleagues[29] reported that LMWH is very effective for the prevention of DVT and suggested that LMWH is even more effective than UH for this indication. The results of 21 trials involving 9364 patients[29] demonstrated a DVT risk reduction rate of 76% when LMWH therapy was used and a 68% reduction when low-dose UH was used; these two therapeutic modalities were compared with control patients after general surgical procedures. In another series involving 30 trials and a total of 6216 patients,[29] a risk reduction of 78% was obtained with LMWH, 27% with low-dose UH, and 62% for adjusted-dose IV UH therapy when compared with control subjects after THR surgery.

In a double-blind randomized clinical trial, Turpie and colleagues[84] compared LMWH with placebo in patients undergoing elective hip surgery. Prophylactic treatment was begun postoperatively and continued for 14 days. In the placebo group ($n = 50$), 20 patients (51.3%) developed DVT. In the LMWH group ($n = 50$), four patients (10.8%) developed DVT. The observed hemorrhagic rate was 4% in each group.

In a 1997 *New England Journal of Medicine* article, Weitz[85] reported that LMWH significantly reduced the risk of DVT in patients undergoing THR and TKR, as well as in those sustaining multiple trauma injuries. He also reported that LMWH was found to be more effective than low-dose subcutaneous UH,[86] and it was equal to[87] or superior to[88] adjusted-dose IV UH.

Safety of Neuraxial Blockade and Low-Molecular-Weight Heparin

A large number of patients have safely received neuraxial anesthesia in combination with prophylactic LMWH therapy.[74,89,90] Tryba[74] reported that, in the European experience with LMWH, a dose of 40 mg or less once daily does not appear to increase the risk of spinal hematoma.

The administration of LMWH in patients undergoing neuraxial anesthesia was examined by Bergqvist and colleagues[89,90] in two reviews published in 1992 and 1993. In these reviews, they identified 19 articles involving 9013 patients who had safely received a combination of LMWH and neuraxial blockade.

Horlocker and Heit's 1997 review of the English language literature[7] identified 215 articles in which LMWH had been administered to surgical or obstetric patients. In 39 of the studies, representing 15,151 anesthetics, spinal or epidural anesthesia was used in combination with perioperative LMWH thromboprophylaxis. A single-dose spinal anesthetic was used in 7400 cases, a continuous spinal anesthetic was used in 20 cases, and an epidural anesthetic was used in 2957 cases. LMWH therapy was initiated preoperatively in almost 90% of the cases, typically with a regimen of 40 mg subcutaneously. No patient had a spinal hematoma.

Of the reports of spinal hematoma that have occurred in patients concurrently receiving DVT prophylaxis with LMWH and undergoing neuraxial blockade, the majority have been from the United States. A large number of spinal hematomas have occurred since LMWH was introduced to the United States in 1993. Within 1 year of the introduction of enoxaparin into clinical practice in the United States, two spinal hematomas were reported.[91] The initial dosing regimen involved the use of 30-mg twice-daily enoxaparin, and the first dose was administered as soon as possible after surgery. Unfortunately, more reports of epidural hematoma followed, and the manufacturer's prescribing information was changed in 1995 to recommend that the first dose be given 12 to 24 hours after surgery. By October 1995, 11 spinal hematomas had been reported to the MedWatch surveillance system. The drug label was again revised with an expanded Adverse Reactions and Warnings section.[91] Between 1993 and 1997 more than 30 cases of spinal hematomas were reported to the FDA's MedWatch surveillance system involving patients who had received LMWH therapy and a neuraxial block.[91] This prompted the FDA to issue a public health advisory in December 1997 asking physicians to carefully weigh the risks and benefits of neuraxial anesthesia in patients receiving LMWH therapy in the postoperative period.[91] Within the FDA advisory it was noted that 75% of the spinal hematomas had occurred in elderly women undergoing orthopedic surgical procedures.

According to the MedWatch surveillance system, between 1993 and 2002 more than 80 cases of spinal or epidural hematoma were reported in patients receiving neuraxial anesthesia with concurrent use of enoxaparin.[92] However, between 1998—the year in which the deliberations of the first ASRA consensus conference were published—and 2002, only 13 new cases of spinal hematomas after neuraxial blockade have been reported, either through the MedWatch system or as a case report.[24] The majority of these patients had postoperative indwelling epidural catheters (10 of 13) or received additional drugs affecting hemostasis, such as a nonsteroidal anti-inflammatory drug (NSAID).[24,92] In the interval between 2002 and 2010, only a handful of new spinal hematomas associated with neuraxial blockade were reported, but

the most alarming feature of many of these new reports is the fact that these hematomas occurred in patients in whom the existing ASRA guidelines were followed to the letter.[25]

The current FDA opinion is as follows:

- When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is used, patients receiving anticoagulation with LMWH or UH for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis.
- The risk of these events is increased by the use of indwelling epidural catheters for the provision of anesthesia/analgesia or by the concomitant use of drugs affecting hemostasis, such as NSAIDs, platelet inhibitors, and other anticoagulants.
- Patients should be frequently monitored for signs and symptoms of neurologic impairment. If neurologic compromise is noted, urgent treatment is necessary.
- Practitioners should carefully consider the potential benefits versus risks before performing a neuraxial intervention in patients' receiving anticoagulation for thromboprophylaxis.

ASRA 2010 Guidelines for Neuraxial Anesthesia and Low-Molecular-Weight Heparin

The new ASRA guidelines have been influenced by the European experience and now suggest that both of the following protocols have merit: the American protocol, in which 30 mg subcutaneous LMWH is administered twice daily, and the European protocol, in which only once-daily dosing with 40 mg enoxaparin is used. As such, both treatment plans are outlined in the current ASRA guidelines,[25] and both protocols are now approved by the FDA.[93]

Twice-Daily Dosing[25]

- The first subcutaneous dose of 30 mg enoxaparin is administered no earlier than 24 hours after surgery, and the next 30-mg dose is administered 12 hours later. This is the original dosage protocol approved by the FDA and may be associated with a higher risk of epidural hematoma than that found when the European protocol is used.
- **It is imperative that all indwelling spinal/epidural catheters be removed at least 2 hours before the administration of the first dose of enoxaparin.**
- Monitoring of the anti-Xa level is not recommended because it is not predictive of the risk of bleeding; therefore it is not helpful in the management of patients undergoing neuraxial blocks who have received LMWH.
- Antiplatelet or oral anticoagulant medications administered in combination with LMWH may increase the risk of spinal hematomas. Concomitant administration of medications that affect hemostasis, such as antiplatelet drugs, standard heparin, or dextran, represent an additional risk of development of hemorrhagic complications during the perioperative period. This includes spinal/epidural hematoma formation. Education of the entire patient care team is necessary to avoid potentiation of the anticoagulant effects.
- The presence of blood during needle and catheter placement does not necessitate postponement of surgery. However, initiation of LMWH therapy in this setting should be delayed for 24 hours after surgery. Traumatic needle or catheter placement may signify an increased risk of spinal hematoma, and it is recommended that this consideration be discussed with the surgeon.

Once-Daily Dosing[25]

- This dosing regimen approximates the European application (40 mg/day enoxaparin).
- The first postoperative LMWH dose should be administered 6 to 8 hours after surgery.
- The second postoperative dose should occur no sooner than 24 hours after the first dose.
- Indwelling neuraxial catheters may be safely maintained. However, the catheter should be removed a minimum of 10 to 12 hours after the last dose of LMWH. Subsequent LMWH dosing should occur at least 2 hours after catheter removal.

Preoperative Low-Molecular-Weight Heparin[25]

- Patients receiving preoperative LMWH can be assumed to have altered coagulation.
- A single-injection spinal anesthetic may be the safest neuraxial technique in patients receiving preoperative LMWH for thromboprophylaxis.
- In these patients, needle placement should occur at least 10 to 12 hours after the last LMWH dose.
- Patients receiving higher doses of LMWH, such as 1 to 1.5 mg/kg enoxaparin every 12 hours, 1.5 mg/kg enoxaparin daily, 120 U/kg dalteparin every 12 hours, 200 U/kg dalteparin daily, or 175 U/kg tinzaparin daily will require delays of at least 24 hours before block placement.
- Neuraxial techniques should be avoided in patients who have received a dose of LMWH 2 hours before surgery (general surgery patients) because needle placement would occur during peak anticoagulant activity.

European Guidelines for Neuraxial Blockade and Low-Molecular-Weight Heparin

The European experience surrounding the use of 40 mg or less of enoxaparin once daily clearly demonstrates that there is no increased risk of spinal hematoma formation, provided that a minimum interval of time is observed between the administration of LMWH and neuraxial puncture.[94] The current dosing regimen in Europe for enoxaparin (the most commonly used LMWH) is 40 mg subcutaneously once daily, and the initial dose is administered 10 to 12 hours before surgery.[26,27] In addition, the timing for the administration of the next subsequent dose after block or catheter placement remains 4 to 6 hours;[26,27] however, some European clinicians have also stated that if they plan to place an epidural catheter for surgical

anesthesia and postoperative analgesia, they administer the first dose of enoxaparin either12 or more hours before or after block placement. This usually translates into either the night before or the morning after surgery. From the standpoint of formation of an epidural hematoma, this course of therapy is distinctly different from and has proved to be much safer than the regimen used in the United States, in which 30 mg enoxaparin is administered subcutaneously twice daily for TKR and THR, and the first administration is 12 to 24 hours after surgery.[25] ESA guidelines recommend that, if LMWH is administered in a twice-daily schedule, one dose should be omitted to create a 24-hour interval before catheter removal. However, the major distinction between the European and American protocols is the fact that spinal/epidural catheters can be left in place if European guidelines are followed, whereas the ASRA guidelines call for their removal before the institution of anticoagulation therapy.[25] Of note, 75% of the neuraxial blocks performed in Europe are single-shot spinal blocks.[74]

- An interval of at least 10 to 12 hours should elapse after the administration of LMWH and placement of a neuraxial block.[26,27,74,75]
- The next dose of LMWH should be administered no sooner than 4 to 6 hours after needle or catheter placement; however, both ESA and BARA guidelines stress the importance of allowing a minimum time interval of 4 hours to elapse after the performance of a neuraxial technique (block placement or catheter insertion/removal) before the next dose of LMWH is administered.[26,27]
- In patients scheduled for neuraxial block, thromboembolism prophylaxis with LMWH should be initiated on the evening before surgery[26,27,75] and has an efficacy similar to that of a dosage regimen started on the morning of the surgery.[26,27,74,95,96]
- Catheter removal should occur at least 10 to 12 hours after the last LMWH administration. The next dose of LMWH should be delayed for 4 to 6 hours after catheter removal.[12,26,27,57]
- No laboratory tests are suggested for the first 4 postoperative days; however, a platelet count should be checked on day 5 because of the risk of heparin-induced thrombocytopenia.[26,27,75]

Fondaparinux

The basic science of and the clinical pharmacology for the drug fondaparinux (Arixtra) have been discussed at length previously.[97] Recently, however, Singelyn and colleagues[98] performed a study on the use of indwelling catheters after the institution of DVT prophylaxis with fondaparinux. In this very large prospective study, 5704 patients underwent either THR, TKR, or HFS in which they received a daily subcutaneous dose of fondaparinux (2.5 mg) for 3 to 5 weeks postoperatively. Patients with either a neuraxial catheter or a deep plexus catheter had the catheter removed 36 hours after their last dose of fondaparinux. Their next dose of fondaparinux was then administered 12 hours after the successful removal of their catheters. All patients were then followed up with a careful neurologic examination for 24 hours. The primary endpoints of this study were the presence of a symptomatic VTE or major bleeding up to 4 to 6 weeks after surgery.[98] Major bleeding was defined as fatal bleeding, bleeding into a critical organ or space (i.e., retroperitoneal, intracranial, spinal, intraocular, or pericardial), bleeding into the surgical site requiring reoperation, or bleeding into a nonsurgical site requiring the transfusion of two or more units of blood. Secondary outcomes of interest were death or other adverse events. VTE was defined as a symptomatic DVT (confirmed by ultrasound or venography) or a PE (confirmed by ventilation/perfusion scanning, pulmonary angiography, spiral computed tomography, or autopsy).

Patients were excluded from the EXPERT study[98] if difficulty was encountered during the placement of the spinal or epidural block (defined as three or more attempts or bleeding during the block placement). Other grounds for study exclusion were a plan to place a neuraxial or deep plexus catheter (defined as a lumbar plexus or parasacral sciatic) but the patient had not stopped aspirin 3 days before surgery or clopidogrel 7 days before surgery or if the plan was to withdraw their neuraxial or deep peripheral catheter the day after surgery.

The mean age of the study population was 66 years, and 24% of the patients were older than 75 years. Women outnumbered the men by a ratio of 2 : 1, and 30% of the patients were obese (BMI > 30).[98] Patients underwent THR (52%), TKR (40%), or HFS (6%). Surgeries were performed under regional anesthesia only (62%), general anesthesia (23%), or a combined regional/general anesthetic (15%).[98] Neuraxial catheters were placed in 1553 patients (27%), and deep peripheral catheters were placed in another 78 patients (1.4%). The majority (2183, 54%) of the regional anesthetics were single-shot spinal blocks.[98] The catheters were removed either 1 or 2 days after surgery (early removal group, 43%) or between postoperative days 3 and 6 (late removal group, 57%).

No difference in the VTE rate was seen for patients with or without a catheter or for patients who had their catheters removed early (0.6%) or late (1.0%).[98] Fatal bleeding occurred in five patients (0.1%), bleeding into a critical organ occurred in another 6 patients (0.1%), and bleeding at the surgical site requiring reoperation occurred in 26 patients (0.5%).[98] Finally, 23 patients (0.4%) died 4 to 6 weeks after surgery, as the result of either a probable or suspected PE.

In a recent meta-analysis,[99] the incidence of fatal PE was 0.18% after TKR and THR and 0.30% after HFS. In the EXPERT study,[98] the incidence of fatal PE was only 0.13%. More importantly, no epidural hematomas occurred in the 1553 patients who received neuraxial catheters, nor did any occur in the patients who received deep plexus catheters. While this landmark study[98] showed that fondaparinux could be safely administered to patients who still had either an epidural catheter or a deep plexus catheter in place, the ASRA guidelines working group chose to endorse the original guidelines that resulted from the outcomes of more than 7000 patients in which an atraumatic single-pass spinal block served as the only acceptable criterion for the subsequent administration of fondaparinux to study patients. The ASRA guidelines for fondaparinux are as follows[25]:

- Until further experience is available, performance of neuraxial techniques should occur under conditions used in clinical trials (i.e., single-needle pass, atraumatic needle placement, and avoidance of indwelling neuraxial catheters). If this is not feasible, an alternate method of prophylaxis should be considered.

Rivaroxaban

Rivaroxaban is an orally administered direct factor Xa inhibitor approved by the FDA in July 2011. Unlike the heparins and fondaparinox, which act to inhibit Xa via induction and increased production of antithromin III, rivaroxaban is a direct inhibitor. The large factor Xa molecule has four active binding sites where the rivaroxaban molecule binds reversibly and competitively to two sites to block activity. Ultimately, rivaroxaban is eliminated through renal excretion or by metabolism via the P450 enzyme system. Like all P450 substrates, drugs that affect p450 enzyme activity will affect rivaroxaban activity. Rivaroxaban has no direct effect on either thrombin or platelets.[100] The main advantage over existing anticoagulants is that it is easily absorbed through the gastrointestinal tract with 80% to 100% bioavailability, making it the first oral anticoagulant approved in the United States since warfarin.[101,102] Following ingestion, it has a rapid onset of 3 to 4 hours and a long half-life of 5 to 9 hours in healthy volunteers and 11 to 13 hours in elderly patients.[103] Rivaroxaban's pharmacodynamic effects persist for 24 hours, making once-daily dosing feasible.[103] The dose response curve is predictable across all age, ethnic, and gender groups, and monitoring with routine laboratory testing is not necessary. One third of the drug is excreted unchanged by renal elimination, and two thirds are metabolized by the liver, making patients with either renal or liver impairments less susceptible to prolonged anticoagulation and dosing variations.[101,102] The FDA approval for rivaroxaban is for DVT prophylaxis in adults undergoing either THR or TKR and in patients with nonvalvular atrial fibrillation.[104] (Because of expanding indications and general efficacy and superiority over existing anticoagulants, an increase in the use of rivaroxaban is inevitable, and familiarity with its properties is essential for all medical practitioners.)

The anticoagulation effects of rivaroxaban do not need to be monitored on a routine basis. The pharmacokinetics are very predictable, and the drug has a wide therapeutic index.[101,103] It would be helpful to have an assay for monitoring the anticoagulant effects of rivaroxaban for conditions such as emergency surgery, bleeding emergencies, complete hepatic or renal failure, or circumstances of drug overdose; however, to date, no such test has proved to be reliable,[105] and none of the currently available tests (PT, aPTT, and anti–factor X assay) are of any value in this setting. In addition, no agents are currently available to reverse the anticoagulation effects of rivaroxaban, and rivaroxaban is heavily protein bound and thus cannot be removed by dialysis.

It is now widely accepted that rivaroxaban has proved efficacious as a superior DVT prophylactic agent in patients undergoing lower extremity joint arthroplasty. The package insert and several clinical studies warn of the increased potential for bleeding in patients receiving rivaroxaban therapy.[104] Minor bleeding events such as wound hematomas and clinically insignificant surgical site bleeding occurred in patients taking rivaroxaban at a rate of 5.8%. Major bleeding events in clinical trials occurred at a rate of approximately 0.3% and included bleeding into critical organs (intraocular and gastrointestinal), bleeding leading to reoperation, and clinically overt extrasurgical site bleeding.[104,106]

One case of a spontaneous epidural hematoma occurring in a patient receiving rivaroxaban DVT prophylaxis has now been reported.[107] The patient, a 61-year-old woman, had recently undergone a proximal tibial osteotomy under general anesthesia and had been given rivaroxaban 8 hours postoperatively. No neuraxial or other nerve blocks had been performed. She developed severe thoracic pain 2 days after surgery and underwent emergent magnetic resonance imaging that showed a spinal epidural hematoma extending from C2 to T8. Her international normalized ratio (INR) at the time was 1.0, but her aPTT and platelet count were not reported. Her concurrent medications included tramadol and ibuprofen for analgesia, and it is possible that the addition of an NSAID could have contributed to the enhanced alteration of her coagulation profile. Four hours after the onset of her symptoms as the neurosurgical team was preparing for possible clot evacuation, the symptoms and deficits spontaneously resolved, and no surgical decompression was ever undertaken.

This case report[107] underscores the need for vigilance in looking for bleeding complications in patients receiving anticoagulant therapies with or without the use of regional anesthesia.

Neuraxial and Deep Plexus Blockade

At this time, no prospective studies have been published on rivaroxaban used concurrently with either neuraxial anesthesia or deep plexus blocks. In the RECORD trials, passing mention was made that a regional anesthetic was performed on more than half of the patients in the clinical trials without any additional details as to types of blocks performed, sizes and types of needles used, or whether catheters were inserted and maintained.[106,108-110] This lack of evidence makes it difficult to outline valid recommendations for the use of neuraxial blockade and deep plexus blocks in the presence of rivaroxaban. Current recommendations must be based on the known pharmacokinetic profile of rivaroxaban and previous experience with neuraxial blockade and other anticoagulant medications.

Rosencher and colleagues[111] recently proposed the following practical guidelines:

1. Removal or insertion of a neuraxial catheter or placement of a deep plexus block after the passage of at least two half-lives, which would result in less than 25% of active drug remaining, should prove to be safe.
2. After the removal of a catheter, wait a period equal to the amount of time needed for stable clot formation, which is 8 hours (minus the T_{max}

of the drug), before starting or restarting an anticoagulant.[111]

On the basis of this model, neuraxial catheters should not be placed or removed for at least 20 hours after the previous dose of rivaroxaban, and the next dose should be given no sooner than 6 hours later.[111]

ASRA 2010 Guidelines for Neuraxial and Deep Blocks and Rivaroxaban

- No official ASRA guidelines exist. Rivaroxaban had not yet been approved for use in the United States when the 2010 ASRA guidelines were published.[25]

European Guidelines for Neuraxial and Deep Blocks and Rivaroxaban

General European

- Allow a time interval of 22 to 26 hours to elapse from the last dose of rivaroxaban until catheter insertion or withdrawal is attempted.[26]
- After catheter manipulation, the next dose of rivaroxaban may be given in no less than 4 to 6 hours.[26]
- Extreme caution is warranted because of limited experience with rivaroxaban.[26]

Belgian

- Allow a time interval of 20 hours to elapse from the last dose of rivaroxaban before an attempt is made at catheter insertion or withdrawal.[27]
- After catheter manipulation, wait no less than 6 hours before administering the next dose of rivaroxaban.[27]

The differences in the recommendations between the different societies stems from the lack of data, experience, and studies in the use of rivaroxaban.[25-27] If the half-life of the drug is considered, then, in a healthy younger patient, a waiting time of two half-lives would be from 10 to 18 hours. However, in an older patient with either renal or hepatic impairment, the half-life may be prolonged to 13 hours, which would make a waiting period of 22 to 26 hours more prudent. The use of rivaroxaban must be individualized, and the patient's needs and risk factors must always be taken into consideration when the aforementioned guidelines are applied.

Guidelines for Deep Vein Thrombosis Prophylaxis from Other Major Societies

At the most recent ASRA annual meeting in San Diego, California (March 2012), Horlocker and colleagues indicated that the guidelines for antithrombotic therapy, including appropriate pharmacologic agent, degree of anticoagulation desired, and duration of therapy, continue to evolve. In addition, guidelines from other major societies were briefly outlined.

Guidelines from the American Academy of Orthopaedic Surgeons

These guidelines appear on line at www.aaos.org/guidelines and were recently updated in September 2011. The guidelines are more than 500 pages in length because they list all the articles reviewed to reach the evidence-based conclusions; however, a brief summary of the AAOS recommendations can be found at the same website, and these recommendations also appear in an abridged version in the most recent ASRA guidelines.[25] In the AAOS guidelines, patients are assigned to one of four risk categories based on a balance between their risk of bleeding and their development of a postoperative PE after hip or knee arthroplasty. In brief, the AAOS guidelines read:

- Patients undergoing elective hip and knee arthroplasty should discontinue all antiplatelet medications (e.g., aspirin and clopidogrel).
- Patients who are not at elevated risk beyond the surgery itself for the development of venous thromboembolism (VE) or bleeding should receive pharmacologic agents and/or mechanical compressive devices. However, current evidence is unclear about which prophylactic option is optimal. Therefore the AAOS is unable to recommend any specific prophylactic option.
- In the absence of reliable evidence about how long one should use these prophylactic strategies, it is the opinion of the AAOS working group that patients and physicians should discuss the duration of prophylaxis.
- Patients who have had a previous DVT should receive both pharmacologic prophylaxis and mechanical compression devices.
- Patients known to have a bleeding disorder such as hemophilia or active liver disease should only use mechanical compression devices for the prevention of a VE.
- It is the opinion of the AAOS working group that all patients undergoing TKR or THR should begin early ambulation.
- Finally, the use of spinal or epidural anesthesia should be used to help limit blood loss, even though current evidence does not suggest that neuraxial anesthesia affects the occurrence of VE.

The aforementioned abbreviated AAOS guidelines were also accompanied by an abstract (Abstract 073) from the 2008 annual meeting of the AAOS found at www.aaos.org/news/aaosnow/apr08/clinical1.asp. In this news article the key elements of the abstract presented by Bozic and colleagues entitled "Is there a role for aspirin in venous thromboembolism prophylaxis following total knee replacement?" are discussed. In this abstract, the Bozic team compared the results of 93,840 patients who underwent knee replacement surgery at 300 hospitals between October 2003 and September 2005. They compared the risk factors for blood clot formation, mortality, surgical site bleeding, and infection in patients who received aspirin and in those who were given "guideline-approved therapies." These researchers found that patients taking aspirin had fewer preoperative risk factors for blood clot formation; in addition, their odds of having a postoperative clot when compared with patients receiving either warfarin or injectable therapies was also lower. No differences were found between treatment groups with regard to bleeding risk or mortality. Unfortunately, the numerators for each of the treatment

groups (i.e., aspirin, warfarin, or injectable therapies) are not provided.

Guidelines from the American College of Chest Physicians

The ACCP recently updated its evidence-based guidelines in February 2012 after the deliberations of the Ninth Conference on Antithrombotic and Thrombolytic Therapy.[112] For the most part, the guidelines of the ACCP are derived from the presence or absence of asymptomatic thrombus formation, which are detected by ultrasonography or contrast venography and not clinical outcomes such as a reduction in the incidence of fatal PE, symptomatic DVT formation, or surgical bleeding, and herein lies the problem. In brief, many orthopedic surgeons do not believe that chest physicians, who do not perform surgery, should set the anticoagulation guidelines for surgeons.[25,113] The orthopedic surgeons point out that there has been no correlation between the reduction in the incidence of DVT and the incidence of fatal PE. The incidence of fatal PE remains 0.1% after joint surgery, irrespective of the DVT rate.[113]

Fortunately, the new ACCP guidelines are much more definitive than those provided by the AAOS and give us several new insights and more direction. The new ACCP guidelines for the use of one of the heparins or heparin-like drugs in hip and knee replacement surgery are as follows:[28,112]

- In patients undergoing TKR or THR, the ACCP recommends the use of one of the following therapeutic modalities for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis: LMWH, fondaparinux, apixaban, dabigatran, UH, dose-adjusted warfarin, aspirin, or an intermittent pneumatic compression device (IPCD).
  - With regard to the use of an IPCD, the ACCP recommends that only portable battery-powered IPCDs be used that are capable of recording and reporting proper wear time on a daily basis for both inpatients and outpatients. Moreover, efforts should be made to achieve 18 hours of daily compliance.
  - **One ACCP panel member strongly opposed the use of aspirin as the only prophylactic measure used to prevent DVT/PE after either THR or TKR.**
- For patients undergoing THR, TKR, or HFS receiving LMWH, the ACCP recommends that thromboprophylaxis begin either 12 hours or more preoperatively or 12 or more hours after surgery.
- The ACCP recommends LMWH over all other treatment modalities for the prevention of DVT/PE in both TKR and THR surgery.
- **For patients undergoing major orthopedic surgery (TKR, THR, and HFS), the ACCP recommends extending thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days.**
  - It is important to note that most fatal PEs associated with TKR and THR surgeries occur after hospital discharge and the simultaneous curtailment of DVT prophylaxis.
- In patients undergoing major orthopedic surgery, the ACCP recommends the use of dual prophylaxis with both an antithrombotic agent and an IPCD during hospitalization.
- In patients at an increased risk of bleeding undergoing major orthopedic surgery, the ACCP suggests that only an IPCD be used and that pharmacologic interventions be avoided.
- Finally, in patients who are either uncooperative or who refuse injections or the use of an IPCD, the ACCP recommends the use of an oral agent such as dabigatran, apixaban, rivaroxaban, or adjusted-dose warfarin, if one of the newer oral agents is not available, rather than other forms of prophylaxis.

AUTHORS' RECOMMENDATIONS

There is very little question that patients undergoing surgical procedures that place them at a high risk of developing a postoperative thromboembolic complication will benefit from prophylactic anticoagulation. Choosing the best anticoagulant agent and dosing regimen for a particular patient undergoing a surgical procedure should be guided by the available literature and the individual patient. Differences exist in the costs, convenience, safety, and efficacy of the available agents; however, patient safety has the highest priority when an agent and dosing schedule are chosen. Nothing is as expensive as a bad outcome.

The practitioner must carefully consider each patient individually and weigh the risks of the procedure against the benefit of a neuraxial technique. However, based on the current literature, it would appear that spinal anesthesia is associated with a lower risk of spinal/epidural hematoma,[12,14,61,63] and 40 mg enoxaparin once daily, with the first administration the evening before surgery, affords one the same efficacy of deep vein thrombosis prophylaxis as higher dose regimens (30 mg twice daily), with less risk of surgical hematoma formation.[80] Although never prospectively studied, this reduced rate of surgical hematoma formation likely also translates into a reduced risk of spinal/epidural hematoma formation. It is also important to consider the risks of a spinal/epidural hematoma when an epidural catheter is removed. Epidural catheter removal in the anticoagulated patient carries the same risk of hematoma formation as does catheter insertion.[14,25]

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CHAPTER 51

Is Regional Anesthesia Appropriate for Outpatient Surgery?

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INTRODUCTION

With the developments of the last three decades, outpatient surgery now constitutes more than 60% of surgery performed in most medical centers in the United States. It has initiated major revisions in the approach to anesthetic management and has been supported by the development of new drugs and techniques. Outpatient anesthesia requires more rapid recovery and a faster return to full mental function than standard inpatient procedures. It also requires minimum nausea, vomiting, and postoperative pain that might otherwise delay hospital discharge or precipitate unplanned overnight admission. The emphasis on home discharge has also elevated the patient's perception of "satisfactory" anesthesia, which now includes a greater emphasis on alertness, a sense of well-being, and adequate pain relief at home without disabling side effects.[1] Fortunately, new general anesthetic agents meet many of these requirements, especially rapid induction and emergence, which will theoretically improve the turnover in ambulatory surgery units.

Local anesthesia for the performance of surgery is ideal. Local anesthetics cause no loss of consciousness and provide excellent residual postoperative analgesia. This combination makes local anesthetic agents attractive options for outpatient surgery, where rapid discharge with minimal nausea and sedation is important to health care providers and patients. Regional anesthesia has been shown in some series to provide the same advantages,[2] but meta-analysis of published series fails to show accelerated discharge despite better analgesia and nausea control.[3] Neuraxial (spinal and epidural) techniques have also been advocated because of their rapid onset of dense anesthesia, but they also do not improve discharge and, like peripheral nerve blocks, require additional time for performance.[3] Neuraxial approaches also require resolution of the block before a patient can walk, and they obviously require an alternative method of postoperative analgesia. There is also the issue of the potential for postspinal headaches and, more recently, transient neurologic symptoms (TNS) after spinal anesthesia.[4]

Thus, although there are several advantages to regional techniques, it is legitimate to question whether regional anesthetic techniques are appropriate in the outpatient setting.

OPTIONS

Major options available in outpatient anesthesia are local, general, and regional techniques. For the sake of focus, this chapter will not include a discussion of local infiltration anesthesia techniques because these have universally been shown to be ideal techniques in outpatient anesthesia. This includes the use of local anesthesia for retrobulbar, peribulbar, or topical anesthesia for cataract surgery, which has been associated with a low risk of morbidity and with rapid discharge and high satisfaction in the elderly high-risk patient group undergoing this operation. Local techniques are also excellent for other superficial surgeries, such as hernia repair, breast biopsy, and perianal procedures.

General anesthesia is the most frequently used alternative, primarily because of the newer drugs available. The introduction of rapid-induction and fast-emergence general anesthetic agents (i.e., sevoflurane, desflurane, and propofol) in the last 30 years has produced dramatic improvement in the early emergence from general anesthesia.[5] These advantages are balanced by side effects. The absence of analgesia in the postoperative period necessitates the addition of opioids and their attendant mental obtundation and nausea. The inhalational agents themselves continue to be associated with a 20% to 50% risk of postoperative nausea and vomiting,[6] although this can be minimized by generous use of prophylactic medication.[7] Propofol appears to be associated with a lower frequency of this complication but requires greater resources to administer and is no less expensive than the volatile drugs.

The regional techniques offer a third alternative, also with advantages and drawbacks. The two major categories are peripheral nerve blockade (PNB) and neuraxial blockade (NAB). Continuous peripheral nerve catheters (CPNB) have emerged as a third application.[8] There are multiple reports of PNB, including intravenous regional anesthesia of the upper and lower extremities, as well as specific nerve blocks of the brachial and lumbar plexus (summarized in the recent meta-analysis[3]). They require a somewhat longer time to perform and a longer time for initiation of adequate anesthesia than either general anesthesia or the neuraxial techniques. NAB includes the use of spinal as well as epidural and caudal injection. Caudal anesthesia is primarily limited to pediatric practice, where it is usually performed as an adjunct to a

general anesthetic in this patient population. Spinal anesthesia should be the most effective example of regional techniques in the outpatient setting because of its simplicity of performance and rapidity of onset but may be limited by prolonged discharge times.

EVIDENCE

Most of the reports of regional techniques for outpatients are from enthusiastic supporters and usually do not include a comparative general anesthesia group. These reports are positive in their descriptions of analgesia, discharge times, and patient satisfaction. Although randomized blinded comparative studies are more desirable, it is impossible to perform a "blinded" study comparing the two because even the most naive of observers would be able to distinguish the presence of a local anesthetic block from a general anesthetic. It is also difficult to successfully randomly assign patients to different techniques for many procedures and many patient populations. Nevertheless, the literature search and meta-analysis already mentioned reviewed 15 studies comparing general anesthesia with NAB (Table 51-1) and seven comparing PNB with general anesthesia (Table 51-2).[3] These studies support the use of regional techniques when compared with general anesthesia in terms of superior analgesia and reduced nausea but raise concerns about the time involved and the impact on significant outcomes such as discharge time (Table 51-3).

Seven studies of NAB and six trials of peripheral nerve catheters that measured induction time showed an increase by 8 to 9 minutes in induction time associated with regional techniques. Two of the studies showed that blocks performed in an induction room outside the operating room during the room turnover process could allow for the total anesthesia time to be competitive with general anesthesia.[9,10] Two other studies looking at the use of block rooms showed actual reductions in induction time.[11,12] The use of rapid-acting drugs, such as 2-chloroprocaine, and the presence of experienced anesthesiologists also appear to reduce the additional time required for regional techniques.[13,14] Nevertheless, the overall data indicate that a greater time is required for the performance of blocks and the onset of satisfactory analgesia.

TABLE 51-1 **Central Neuraxial Block versus General Anesthesia for Ambulatory Surgery**

Outcome	Number of Trials	Neuraxial (Mean)	General (Mean)	Odds Ratio or WMD (95% CI)
Induction time (min)	7	17.8	7.8	8.1 (4.1 to 12.1)†
PACU time (min)	10	56.1	51.9	0.42 (–7.1 to 7.9)
VAS in PACU	7	12.7	24.4	–9 (–15.5 to –2.6)*
Nausea	12	5%	14.7%	0.40 (0.15 to 1.06)
Phase 1 bypass	4	30.8%	13.5%	5.4 (0.6 to 53.6)
Need for analgesia	11	31%	56%	0.32 (0.18 to 0.57)†
ASU discharge time (min)	14	190	153	34.6 (13 to 56.1)*
Patient satisfaction	11	81%	78%	1.5 (0.8 to 23.1)

ASU, ambulatory surgical unit; *CI*, confidence interval; *PACU,* postanesthesia care unit; *VAS,* visual analog scale; *WMD*, weighted mean difference.
*$p < 0.01$.
†$p < 0.001$.
Adapted from Liu SS, Strodtbeck WM, Richman JM, Wu CL. A comparison of regional versus general anesthesia for ambulatory anesthesia: a meta-analysis of randomized controlled trials. Anesth Analg 2005;101:1634–42.

TABLE 51-2 **Peripheral Nerve Block versus General Anesthesia for Ambulatory Surgery**

Outcome	Number of Trials	Nerve Block (Mean)	General (Mean)	Odds Ratio or WMD (95% CI)
Induction time (min)	6	19.6	8.8	8.1 (2.6 to 13.7)*
PACU time (min)	6	45.2	72	–24.3 (–36.3 to –12)*
VAS in PACU	7	9.6	35.8	–24.5 (–35.7 to –13.3)*
Nausea	6	6.8%	30%	0.17 (0.08 to 0.33)*
Phase 1 bypass	6	81%	315	14.3 (7.5 to 27.4)*
Need for analgesia	6	6.2%	42.3%	0.11 (0.03 to 0.43)*
ASU discharge time (min)	6	133.3	159.1	–29.7 (–75.3 to 15.8)
Patient satisfaction	4	88%	72%	4.7 (1.8 to 12)*

ASU, ambulatory surgical unit; *CI*, confidence interval; *PACU,* postanesthesia care unit; *VAS,* visual analog scale; *WMD*, weighted mean difference.
*$p = <0.01$.
Adapted from Liu SS, Strodtbeck WM, Richman JM, Wu CL. A comparison of regional versus general anesthesia for ambulatory anesthesia: a meta-analysis of randomized controlled trials. Anesth Analg 2005;101:1634–42.

TABLE 51-3 **Summary of Regional versus General Anesthesia for Outpatients**

	Neuraxial Block	Peripheral Nerve Block
Induction time	Increased	Increased
PACU time	Same	Reduced
PACU VAS	Reduced	Reduced
Nausea	Same	Decreased
Phase 1 bypass	Same	Increased
Need for analgesics	Reduced	Reduced
ASU discharge time	Prolonged	Same
Patient satisfaction	Same	Greater

ASU, ambulatory surgical unit; *PACU,* postanesthesia care unit; *VAS,* visual analog scale.

Ten studies of NAB showed no decrease in postanesthesia care unit (PACU) time, or in the rate of PACU bypass, probably related to the persistent immobility associated with neuraxial anesthesia in the early recovery phase. In contrast, PNB allowed for earlier discharge from phase 1 PACU, as well as a higher percentage of eligibility to bypass phase 1 at the end of surgery.

Both NAB and PNB were associated with significantly lower visual analog scale (VAS) scores in the PACU, as well as a significantly reduced requirement for postoperative analgesics in the PACU. Despite better pain relief, as noted previously, no difference was seen in the PACU time with NAB.

A 40% reduction in nausea was associated with NAB, but this was not statistically different from the general anesthesia group. PNB did provide a significant fivefold decrease in nausea.

Despite the significant advantages of low pain scores and less analgesic requirements and nausea with PNB, no difference was seen in the total time for discharge from the ambulatory surgical unit (ASU). NAB actually required a longer discharge time than general anesthesia in the 14 trials that reported discharge times, with an average prolongation of 35 minutes. Although part of this prolonged discharge may have been related to the use of a longer acting spinal anesthetic (bupivacaine was used in six trials, although in low doses), additional requirements frequently associated with NAB in an ASU (for ambulation and voiding) may have contributed to the longer times. Only one study used procaine, and none used 2-chloroprocaine, which has been reported to be associated with faster resolution and discharge times than lidocaine in three studies that did not include a general anesthesia comparison.[15-17]

General anesthesia is more reliable than regional techniques. In those studies that report results, success rates of 90% to 95% appear to be common, especially with PNBs. Spinal and epidural anesthesia have a high reliability, but none of the techniques equals the 100% efficacy of general anesthesia.

All the comparisons of pharmacoeconomics show that regional techniques are at least no more expensive than general anesthesia, and in most cases they are less expensive than general anesthetic techniques.[18,19]

Satisfaction with central NAB was high (81%) but not significantly different from general anesthesia. With PNB, there was a significant increase in patient satisfaction compared with general anesthesia (88% versus 72%).

In the majority of the published series, the complications were equally proportioned between general and regional anesthesia. Minor complications of backache and postdural puncture headache were higher in the regional technique groups, whereas postoperative nausea and vomiting and sore throats were more frequent in the general anesthesia group. The incidence of overnight admission was higher after general anesthesia in the two series that reported this as an outcome after shoulder surgery. In both reports the admission rate was related to increased pain in the general anesthesia groups.

CONTROVERSIES AND EMERGING DEVELOPMENTS

Induction Rooms

In a recent small study of efficiency and regional anesthesia,[20] the authors noted that the use of an anesthesia care team, an induction room, and a "swing operating room" (two operating rooms for one team) decreased turnover time, increased the number of cases one surgeon could perform in a day and decreased overall hospital time compared with one anesthesiologist performing general anesthesia for day surgery hand cases. Although this model used an induction room and two operating rooms, thus increasing the need for additional space, the authors reported a greater than $400 savings per patient due to decreased PACU stay alone. The authors excluded any patients who were at high risk of block failure.

Peripheral Nerve Infusions

The latest development in the application of regional techniques in the outpatient setting has been the use of continuous local anesthetic infusions through peripheral nerve catheters in patients who are discharged home from an outpatient unit.[8] The development of new catheter systems and especially new lightweight reliable portable infusion pumps has been instrumental in this change.[21] The use of these new technologies does not fit into the same paradigm as the previously discussed comparison of regional techniques with general anesthesia for the performance of intraoperative anesthesia but, nevertheless, represents a significant change and potential advantage for outpatient surgery. This new technology may reframe the question of regional anesthesia for outpatients: rather than an exclusive choice of general anesthesia or regional anesthesia, growing data suggest that a combination of either regional or general for the surgery with a CNPB for postoperative analgesia may be the optimal "package" for attaining the goals of ambulatory

surgery. In a review of 11 published studies of the use of continuous catheters, Ilfeld and Enneking[22] found significant improvement in pain control after discharge in the patients who were treated with local anesthetic infusions compared with placebo in four trials. In all the published series, there was a decreased use of oral analgesic medications when peripheral nerve catheters were provided. This was associated with a reduction in several adverse side effects such as nausea and sleep disturbance. Others have found a faster return to normal activity[23] and greater patient satisfaction. Specific examples include continuous interscalene blocks to decrease the time to discharge after total shoulder arthroplasty,[24] continuous infraclavicular nerve block to benefit patients with elbow surgery,[25] and continuous femoral nerve blocks to decrease the time to discharge for patients after anterior cruciate ligament repairs.[12] Few of these series have measured the extent of additional time that is required for the placement of the catheters, which would be expected to exceed the performance of a simple single-injection PNB. For patients with continuous femoral nerve blocks, postoperative weakness may prevent full ambulation until catheter removal. Although this creates a significant risk of patient falling,[26] extensive experience has shown that patients can be discharged safely to home with continuous catheters.[27] This level of care does require a dedicated team to provide home follow-up and immediately available resources for patients but has generally been met with gratitude by surgeons who see better at-home analgesia and fewer needs for their interventions after discharge. The significant advantages that have been demonstrated with these techniques suggest that the benefits outweigh the risks and argue that this is the most appropriate use of regional anesthesia in the outpatient setting.

The use of continuous catheters has also prompted attempts to be even more aggressive in performing procedures that previously required a hospital stay, such as joint replacement, on an outpatient basis. Ilfeld and colleagues have reported preliminary experiences with CPNB therapy for elbow,[25] hip,[28,29] and knee[30] replacement that suggest that these procedures can be performed on an ambulatory basis (or, at most, with an overnight stay) because of the superior analgesia provided by CPNB. Further research is needed to support these advanced applications of outpatient procedures.

AREAS OF UNCERTAINTY

The major discussion appears to be about the perception of an increased time to perform regional techniques and the lower level of reliability of regional anesthesia, which counterbalance the higher degree of alertness, the potential for more rapid discharge, and the improved postoperative analgesia both in the PACU and after discharge home. Thus the controversy is not necessarily whether regional anesthesia is appropriate in the outpatient setting but whether it is a cost-effective, reasonable alternative in a specific clinical setting.

In addition to that global controversy, more specific controversies appear to be related to the use of spinal anesthesia in the outpatient setting. The issue of postspinal headaches remains a reality, although the use of new needles has appeared to reduce the incidence to less than 1% in adult outpatients. Another controversy associated with subarachnoid anesthesia is the phenomenon of TNS that has been associated most particularly with the use of lidocaine.[4] This is unfortunate because lidocaine historically is the drug associated with the most rapid resolution of blockade and readiness for discharge. Reduction of the dose or concentration does not appear to alleviate the frequency of the syndrome. Preliminary data suggest that the preservative-free 2-chloroprocaine may be a competitive alternative,[15-17] but further data are needed on the safety and reduced incidence of TNS with this drug. A recent retrospective review of one institution's results with more than 4000 2-chloroprocaine spinal anesthetic procedures revealed no complications and a shorter discharge time than with lidocaine for the same procedure.[31] This retrospective review reported no instances of TNS with 2-chloroprocaine spinal anesthetics in the 503 patients reviewed. In the meantime, it appears that patients undergoing arthroscopy or lithotomy-position operations on an outpatient basis have a 15% to 40% risk of the TNS syndrome if lidocaine is used for spinal anesthesia. However, spinal anesthesia is the most reliable and rapid in onset of the regional anesthetic techniques, and it should be the ideal technique for other uses in the outpatient setting.

Another issue with spinal anesthesia is the concern about return of voiding function. Previous data had shown a high incidence of urinary retention with long-acting spinal blocks, but recent data suggest that urinary retention after a short-acting spinal anesthetic in low-risk patients (those with no history of retention and not undergoing hernia or urologic surgery) is not any more frequent than with general anesthesia.[32]

GUIDELINES

There are no formal guidelines on the use of regional anesthesia in the outpatient setting. Some general guidelines are based on the literature. Certain adjustments must be made to the techniques and the drugs to ensure an appropriate result.

1. Excessive sedation for the performance of blocks must be avoided if the advantage of a high degree of alertness and rapid discharge is to be maintained.
2. Rapid onset and highly reliable techniques will help resolve some of the issues of efficiency and cost-effectiveness. Spinal anesthesia and intravenous regional anesthesia are perhaps the most appropriate, given these considerations. Ultrasound guidance may prove useful in shortening performance time of PNB and CPNB, but further data are needed.
3. PNBs appear to provide the greatest advantages in the outpatient setting in terms of discharge times, postoperative analgesia, PACU bypass, and reduction of nausea but are also associated with a slower onset than general anesthesia. The

performance of these blocks in a separate induction area is therefore optimal.

4. The choice of drugs for PNBs has not been addressed by any of the comparative studies, but it remains an issue. Long-acting aminoamides may provide 12 to 24 hours of postoperative analgesia; CPNB has been used for as long as 72 hours. The benefits of these techniques must be weighed against the risk of injury to a numb extremity after discharge, and thus appropriate guidelines should include clear written instructions for all patients regarding the protection of extremities that remain anesthetized after discharge. This also includes the risk of falls with lower extremity blocks.
5. The use of continuous peripheral nerve infusions is associated with significant improvement in postoperative analgesia, reduction of postdischarge complications, and patient satisfaction. The additional time required may well be offset by the advantages for more painful outpatient procedures.
6. Spinal anesthesia is best performed with small-gauge, rounded bevel needles to reduce the incidence of postspinal headaches. Its use should be limited to patients who can return to the emergency department easily for evaluation and management of postdural puncture headache.
7. The problem of TNS has not yet been resolved. It appears to be lowest with the use of bupivacaine, although prolonged discharge may be associated with the use of this drug. Preliminary data suggest that 2-chloroprocaine may have a low incidence,[31] but further information regarding the safety of the preservative-free solution is needed.
8. Discharge times after spinal anesthesia also require careful selection of drug and dose. It appears that the addition of epinephrine to subarachnoid local anesthetics increases the potential for urinary retention and for prolonged discharge times. The use of fentanyl may be a better choice for intensifying local anesthetic effect without prolonging discharge due to urinary retention.
9. Urinary retention after a short-acting spinal anesthetic in low-risk patients is not any more frequent than with general anesthesia,[32] and these patients can be discharged without mandatory voiding.
10. The duration of spinal anesthesia is proportional to the total milligram dose of the local anesthetic involved, and thus high-dose techniques are generally best avoided. Data suggest that preservative-free 2-chloroprocaine provides the shortest duration, potentially competitive with general anesthesia. Further data are needed on its safety and association with TNS.[33]
11. Epidural anesthesia appears to be appropriate in the outpatient setting, although it should be limited to the use of short-acting drugs such as chloroprocaine and lidocaine. It does require a longer time for performance and onset than spinal anesthesia.

AUTHORS' RECOMMENDATIONS

On the basis of the data, we believe that regional anesthesia does have an appropriate role in the outpatient setting if appropriate techniques, drugs, and doses are selected.

- Local anesthesia is clearly ideal and should be used whenever possible as the sole anesthetic regimen or at least should be included for postoperative analgesia after any technique.
- Peripheral nerve blockade is highly effective in providing postoperative analgesia and rapid discharge and should be used whenever possible for upper or lower extremity surgical procedures. It is also applicable for some of the truncal operations such as hernia repair.
- Performance of a block in a separate induction room may reduce the additional time otherwise required for regional anesthesia. Additionally, the use of an anesthetic team—with the anesthesiologist performing a regional anesthetic technique and an anesthesia care team member in the operating room for monitoring during surgery—will decrease turnover times and increase case capacity.
- The use of continuous catheter techniques provides maximum benefit, whether combined with a general or a regional technique for the surgery itself. The additional time required for the block is counterbalanced by the impressively superior postoperative analgesia over the next several days and the potential for more rapid discharge. The reduced opioid use, nausea, and sleep disturbance contribute to significant patient satisfaction.
- If neuraxial blockade is chosen, spinal anesthesia has the advantages of rapid onset and high reliability. Unfortunately, at the current time, there appears to be a persistent risk of transient neurologic symptoms (TNS) with the drugs and doses that are commonly used. A low dose of bupivacaine (less than 6 mg) will provide a low risk of TNS with the potential for a short discharge time; however, a high degree of variability exists and surgical anesthesia to the lower extremity and rectal area may be limited. The use of 2-chloroprocaine may provide a low risk of TNS with an even more reliable and desirable shorter discharge time, but this has yet to be proved.
- An epidural anesthetic procedure provides a more rapid discharge than with most of the current spinal techniques and has the added advantage of flexibility in duration and extent of blockade if a catheter is placed.

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CHAPTER 52

What Is the Best Technique for Hip Surgery?

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INTRODUCTION

Anesthesia and analgesia for hip surgery present a great challenge, especially considering the patient demographics of those undergoing the surgery: usually elderly patients with significant comorbidities such as cardiac disease, pulmonary disease, or renal insufficiency, among others. All of these conditions could adversely affect the surgical outcome. Therefore effective management of perioperative anesthesia and analgesia is essential in improving functional recovery, decreasing morbidity and mortality rates, and improving long-term surgical outcomes.

Hip surgery is traditionally performed under general anesthesia (GA) or spinal epidural anesthesia (SEA). Regional anesthesia is an emerging approach, and several case reports have discussed the use of psoas compartment block (PCB) to provide surgical anesthesia and analgesia for hip surgery.[1] The choice of surgical anesthesia does not effect surgical outcomes in elective hip surgery. However, a regional anesthesia technique might decrease perioperative complications for trauma patients undergoing hip surgery. Future prospective studies are pending.

The three emerging techniques for postoperative analgesia management after hip surgery are as follows: (1) lumbar plexus block (LPB)/PCB, (2) femoral nerve block (FNB)/fascia iliaca block (FIB)/3-in-1 nerve block (3NB), and (3) high-volume local infiltration analgesia (LIA).

Although all these approaches sound promising, it is important to define the basis of the anesthesia and analgesia goal. Anesthesia and analgesia for hip surgery could be covered mostly by targeting of the lumbar plexus T12-L4 area. However, the T12 to L1 dermatome could be involved to a certain extent, which might not be covered sufficiently by LPB. Because the articular branch that innervates the anteromedial capsule of the hip joint originates from the obturator nerve, it would not be covered by a classic FNB. Similarly, branches of the sciatic nerve innervate the posteromedial capsule and thus require coverage beyond an LPB.

EVIDENCE AND CONTROVERSIES

Lumbar Plexus Block/Psoas Compartment Block

The LPB has the definitive advantage of providing profound coverage of T12 to L4 for hip surgery. It was first described by Winnie and colleagues[2] in 1974 as LPB, then as PCB in 1976 by Chayen and colleagues.[3] Many more modifications have been proposed over the years. Although anesthesiologists have not been able to agree on the exact anatomic space that is being targeted, thus proposing various names for the nerve block, the fundamental goal is to block the lumbar plexus. Hereupon, all similar nerve blocks will be referred to as LPB in this section. No differences exist in clinical efficacy among the different approaches, but side effects tend to be fewer with nerve blocks performed at the L4 level and with a more lateral approach.

The first study on the efficacy of LPB in hip surgery was published in 2000 by Stevens and colleagues, who recruited 60 patients into their study.[4] They concluded that the LPB group had greater analgesia, especially during the first 6 hours postoperatively. Their study also showed that LPB modestly decreased perioperative blood loss up to 48 hours postoperatively. A similar result was reported by Biboulet and colleagues[5]: single-shot LPB was effective for purposes of analgesia for up to 4 hours, and no difference was seen in functional outcomes.

Several research studies on continuous LPB further supported its efficacy in hip surgery. Continuous LPB reduces narcotic consumption and related side effects and improves patient satisfaction.[6-8] It seems that continuous LPB is not inferior to FNB,[9,10] and LPB is equally effective for postoperative analgesia compared with continuous epidural analgesia.[11] Omar and colleagues[12] compared single-shot LPB with single-shot caudal block in pediatric patients undergoing hip surgery and found that single-shot LPB was superior to caudal block in the duration of analgesia postoperatively. Even though all evidence indicated that LPB was effective in analgesia for hip surgery, continuous LPB failed to show long-term outcome benefits 12 months after hip arthroplasty.[13]

Femoral Nerve Block/Fascia Iliaca Block/3-in-1 Nerve Block

FNB alone is not sufficient for hip surgery simply because it does not provide sufficient coverage for the obturator nerve, lateral femoral cutaneous nerve, and sciatic nerve distribution. Detailed review of all articles on nerve blocks of the femoral nerve for hip surgery showed that all studies were intended to block the femoral nerve, obturator nerve, and lateral femoral cutaneous nerve. Although the names of the nerve blocks were reported

differently, all intentions were to inject under the fascia iliaca or to diffuse local anesthetic retrograde within the femoral nerve sheath to target the lumbar plexus.

Goitia Arrola and colleagues[14] reported that single-injection FIB was initially effective in controlling postoperative pain after total hip replacement; however, the effect was short-lived. Uhrbrand and colleagues[15] concluded that 3NB injection was also beneficial for postoperative analgesia but that this result might not be clinically relevant because of its limited benefit. Beaudoin and colleagues[16] studied ultrasound-guided FNB in the emergency department in elderly patients with hip fractures. The authors concluded that injection under the fascia iliaca with intentional cephalic spreading significantly reduced pain over their observation period. A similar conclusion was drawn by Stevens and colleagues,[17] who also noted a narcotic sparing effect up to 24 hours postoperatively.

Winnie and colleagues[18] first described 3NB as the anterior approach to the LPB. They specifically highlighted the importance of targeting the three main branches of the lower extremity, femoral nerve, obturator nerve, and lateral femoral cutaneous nerve. Ilfeld and colleagues[10] compared a continuous FNB with a posterior LPB in postoperative analgesia after total hip arthroplasty and concluded that both approaches were equally effective. The continuous catheter was placed with continuous nerve stimulation, thus making the approach similar to an anterior approach with LPB.

Singelyn and Gouverneur[19] compared intravenous patient-controlled analgesia (IV PCA), epidural analgesia, and continuous 3NB. Although all approaches were effective in controlling postoperative pain, the authors noted significantly less side effects, such as nausea, vomiting, and pruritis, in the 3NB group. Although these studies confirm that regional analgesia can provide a certain level of benefit for patient care, Biboulet and colleagues[5] found IV PCA to be safe and effective after comparing IV PCA, FNB, and PCB.

FNB/3NB is easy to perform and has showed promising analgesic effects, but the evidence is less convincing. For hip surgery, dermatome coverage may be quite challenging because it involves both the lumbar plexus and sacral plexus. One interesting article published by de Leeuw and colleagues[20] illustrated the concept of using high-volume expansion to cover both the lumbar plexus and the sciatic nerve with one injection technique. This technique covers L2-S2 but may not cover L1, which was a common site of pain among patients in the study. The authors' results were very encouraging. However, the concentration and amount of local anesthetic used might be unacceptable to some anesthesiologists. Currently, ongoing clinical trials are investigating the application of FIB in hip surgery.[21]

Local Infiltration Analgesia

LIA for hip surgery was first reported by Bianconi and colleagues in 2003.[22] The concept is very appealing because of its simplicity and safety. It has gained popularity over the last several years mostly among orthopedic surgeons. The local anesthetic mixture contains various medications and concentrations based on institutional or departmental protocol. In general, it contains local anesthetics, epinephrine, narcotics, ketorolac, antibiotics, and steroids.

Several studies have supported the effectiveness of LIA. However, most of these studies have limitations. Andersen and colleagues[23] reported that LIA was effective in controlling postoperative pain; however, their study was poorly designed and lacked control subjects. Andersen and colleagues[24] reported that LIA was effective in decreasing pain and opioid consumption postoperatively; however, no nonsteroidal antiinflammatory drugs (NSAIDs) were given to the control group. Three other studies[25-27] support the efficacy of LIA in hip surgery patients, but all have similar study design limitations. Scott and colleagues[25] reported that periarticular injection of local anesthetics decreases perioperative narcotic consumption and length of hospitalization. However, the study was a retrospective, nonrandomized, controlled chart review.

The validity of LIA was finally addressed in 2011 with two double-blind randomized controlled studies.[28,29] Both studies concluded that there were no difference between intraoperative LIA and saline. It is important to note that both studies adopted multimodal pain management algorithms as the basis for perioperative pain management. However, an interesting article from Switzerland in 2012 suggested that continuous epicapsular LIA was effective in decreasing morphine consumption and in improving postoperative analgesia.[30]

More studies are required to determine whether LIA is effective for hip surgery, but it seems that LIA is an acceptable alternative approach for postoperative pain control. However, its merit is limited by coexisting multimodal postoperative pain management algorithms, especially when NSAIDs are added to the algorithm.

Intravenous Patient-Controlled Analgesia and Epidural Analgesia

Both PCA and epidural analgesia have been widely used clinically for analgesia management. Both approaches can provide analgesia for hip surgery, but both have distinct advantages and disadvantages. IV PCA is easy to set up and is effective in general. However, the opioid does not reliably provide sufficient analgesia, and the dosage is difficult to predict, especially among patients who are already dependent on narcotics because of long-term use, which is a fairly common situation among patients undergoing total hip replacement. In addition, opioids can cause excessive sedation, respiratory depression, nausea and vomiting, constipation, and pruritis.[19,31,32]

Epidural analgesia is a very reliable technique that provides superior pain relief after total hip replacement.[33,34] However, it is associated with certain risks, such as spinal hematoma, transient neurologic symptoms, and caudal equina syndrome.[35-37] The risks may be further increased if clinical use of anticoagulation therapy becomes more prevalent.[38] In addition, epidural analgesia is also associated with more hypotension, urinary retention, and motor block.[39] These side effects could impair the physical therapy and rehabilitation process.

GUIDELINES

No universal guidelines exist for management of anesthesia and analgesia in hip surgery. Involving anesthesiologists, orthopedic surgeons, and other perioperative service teams to establish institutional consensus is recommended.

AUTHOR'S RECOMMENDATIONS

Multimodal (intravenous [IV], intramuscular [IM], and by mouth [PO]) postoperative pain management should be adopted for analgesia management in patients undergoing hip surgery. Regional anesthesia is beneficial for analgesia management, especially in patients with significant coexisting medical conditions.

I would advocate regional anesthesia in patients with chronic pain taking high-dose narcotics, in patients with a history of intolerance of narcotics with significant side effects, and in patients with coexisting pulmonary hypertension.

- Continuous lumbar plexus block (LPB) is the recommended choice.
- Fascia iliaca block or 3-in-1 nerve block is an alternative approach if LPB is contraindicated because of technical or anticoagulation issues.
- Local infiltration analgesia is not advised if a multimodal IV/IM/PO postoperative pain management regimen is being used, especially if nonsteroidal anti-inflammatory drugs could be administrated as needed.
- Epidural analgesia is a reasonable choice, especially if epidural anesthesia is accepted as the primary surgical anesthesia. The postoperative anticoagulation regimen needs to be adjusted accordingly.

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CHAPTER 53

Does Intraoperative Regional Anesthesia Decrease Perioperative Blood Loss?

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INTRODUCTION

The attempt to minimize exposure to allogeneic blood products remains a goal of perioperative care despite improvements in the safety of the blood supply. The risks of viral infection, bacterial contamination, hemolytic reactions, and transfusion-associated lung injury (TRALI) have been reviewed elsewhere.[1] Evidence suggests that allogeneic blood transfusion may have immunosuppressive effects, possibly leading to increased cancer recurrence, increased susceptibility to wound infections, and even an increased mortality rate.[1] Thus perioperative transfusion of blood products may be associated with an increase in perioperative morbidity and mortality rates.

Although many strategies decrease intraoperative blood loss, the use of regional anesthetic techniques has been suggested to diminish intraoperative blood loss and blood transfusions.[2] In addition to decreasing perioperative morbidity and mortality rates, neuraxial blockade has been shown to diminish the risk of postoperative deep venous thrombosis and pulmonary embolism.[3,4]

OPTIONS AND THERAPIES

Many strategies have been suggested to decrease perioperative exposure to allogeneic blood products. These can generally be divided into three categories: (1) pharmaceuticals (e.g., erythropoietin, epsilon-aminocaproic acid, aprotonin, and blood substitutes); (2) techniques (e.g., minimally invasive and other surgical techniques, autologous donation, short-term normovolemic hemodilution, and deliberate hypotension); and (3) devices (e.g., intraoperative blood salvage). Many of these are discussed elsewhere. However, in comparison with these options, neuraxial regional techniques (e.g., spinal and epidural anesthesia) offer a particularly attractive alternative for reduction of perioperative hemorrhage because they are inherent to the anesthetic itself; they require no modification of surgical technique or additional pharmacologic manipulation. The majority of randomized data supports the use of neuraxial regional anesthetic techniques in decreasing blood loss and the need for blood transfusion; however, there is a lack of large-scale randomized data examining the effect of peripheral regional anesthesia on perioperative blood loss. Recently, three meta-analyses have been published evaluating the effects of neuraxial techniques on surgical blood loss and blood transfusion requirements.[5-7] Data from at least two of these studies confirm the benefits of neuraxial anesthesia in reducing blood loss,[5,6] although the combination of general anesthesia with epidural analgesia seems to negate the benefits of decreased blood loss.[5]

EVIDENCE

Since 1966, at least 139 studies comparing regional with general anesthesia have included either perioperative blood loss or transfusion requirement as an outcome measure. Of the two meta-analyses published in 2006, one identified 66 randomized controlled trials that compared neuraxial anesthesia with general anesthesia with a quantification of intraoperative blood loss[5] and the other identified 24 trials.[6] The large difference in trials included by the two meta-analyses may be explained by a much broader search (667 articles reviewed for inclusion[5] versus 103 articles[6]) or possibly by unpublished exclusion or inclusion criteria that differed between the two studies. A 2009 meta-analysis of 28 randomized controlled trials comparing general anesthesia with regional anesthesia or analgesia for patients undergoing total knee arthroplasty found no difference in intraoperative blood loss but did note an improvement in the outcomes of postoperative pain and opioid-related adverse effects, a reduced hospital stay, and improved rehabilitation in the regional anesthesia and analgesia groups.[7] A PubMed search through March 16, 2012, using the search criteria used by Richman and colleagues,[5] identified 11 additional studies that would meet inclusion criteria if the analysis were repeated (Table 53-1).[8-18] A comparison of blood loss by location of surgery from the meta-analysis by Richman and colleagues[5] is shown in Table 53-2, and a comparison of blood loss from trials limited to direct comparisons of various techniques is shown in Table 53-3.

Some of the variability in the effect of regional anesthesia on blood loss may reflect differing mechanisms of hemorrhage during different surgical procedures. The largest body of literature on this subject has focused on surgery of the hip. Since 1966, at least 29 randomized controlled trials have measured differences in blood loss

TABLE 53-1 **Recent Studies: Estimated Blood Loss**

Author (Year)	Surgery	*N* = Total Subsets	EBL*	Transfusion†‡	Comments
Attari[8] (2011)	Spine	*N* = 72			
	Lumbar disk	SA = 35 GA = 37	210 ± 40 350 ± 35	Not reported	RCT SA versus GA for lumbar disk surgery comparing intraoperative and postoperative outcomes. Reported decreased EBL, improved hemodynamics.
Heidari[9] (2011)	Ortho	*N* = 387			
	Elective hip fracture repair	NA = 190 GA = 197	458 ± 335 697 ± 424	Not reported	RCT GA versus NA (either SA or GA) for elective hip fracture surgery. Outcomes followed EBL and Hb for 5 days. Concluded decreased EBL, postoperative pain, and hospital stay.
Tikuisis[10] (2009)	Urology	*N* = 54			
	RRP	EA+GA = 27 GA = 27	740 ± 210 1150 ± 290	0.19 units 0.52 units	RCT GA+EA versus GA for RRP surgery. Outcome EBL and transfusion. Reported induced HoTN with EA/GA; decreased EBL and transfusion.
Sadrolsadat[11] (2009)	Spine	*N* = 100			
	Lumbar disk	SA = 50 GA = 50	464 ± 69 438 ± 66 *p* = 0.054	No transfusions	RCT SA versus GA in lumbar disk surgery. EBL was not a statically significant difference in either group. No transfusions were required.
O'Connor[12] (2006)	Urology	*N* = 102			
	RRP	EA+GA = 51 GA = 51	955 ± 517 1477 ± 823	4%‡ 3 units 18%‡ 24 units	RCT EA+GA with deliberate HoTN versus GA. Primary outcome: percent age of patients transfused with allogeneic blood. Reported EA+GA had less EBL; less transfusion than GA group.
Eroglu[13] (2005)	Ortho	*N* = 57			
	THA	EA = 20 GA = 37	305 (210-550 mL) 515 mL (380-780 mL)	1.15 units 2.45 units	RCT HoTN EA versus HoTN GA (TIVA) in THA. Primary outcomes were EBL, Hb concentration, and transfusion in both groups. Reported HoTN in both groups and less EBL in EA versus GA group.
Yoshimoto[14] (2005)	Spine	*N* = 40			
	Lumbar spine fusion	EA = 20 GA = 20	546 g 631 g	Not reported	RCT EA versus GA; primary outcome EBL, intraoperative HoTN, and postoperative analgesia. Reported less EBL in EA group.
Borghi[15] (2005)	Ortho	*N* = 210			
	THA	EA = 70 EA+GA = 70 GA = 70	435 ± 233 449 ± 207 515 ± 219 **p* not reported	No transfusions	RCT EA+GA versus EA. Primary outcome intraoperative and postoperative blood loss. The EA+GA group had lowest EBL compared with all groups.
Ozyuvaci[16] (2005)	Urology	*N* = 50			
	Radical cystectomy	EA+GA = 25 GA = 25	875 ± 191 1248 ± 343	230 ±107 mL 420 ± 145 mL	RCT EA+GA versus GA. Primary outcomes EBL, transfusion MAP, and PCA use. EA+GA was lower in all outcomes.
Salonia[17] (2004)	Urology	*N* = 72			
	RRP	SA = 38 GA = 34	984 ± 91 1247 ± 96	398 ± 49 mL 318 ± 53 mL	RCT SA versus GA in RRP surgery. Reported decreased EBL, postoperative pain, and faster recovery in SA versus GA group.

Continued on following page

TABLE 53-1 **Recent Studies: Estimated Blood Loss** (Continued)

Author (Year)	Surgery	*N* = Total Subsets	EBL*	Transfusion†‡	Comments
Hong[18] (2003)	OB Cesarean section	*N* = 25 EA = 13 GA = 12	1418 ± 996 1622 ± 775 not statistically significant	0.38 ± 0.9 units 1.08 ± 1.6 units	RCT EA versus GA in elective C-section for placenta previa. Primary outcomes: maternal hemodynamics, EBL, transfusion, neonatal outcome. EBL was not statistically significant between the two groups.

EA, epidural anesthesia; *EA+GA,* combined epidural-general anesthesia; *EBL,* estimated blood loss; *GA,* general anesthesia; *Hb,* hemoglobin; *HoTN,* hypotension; *MAP,* mean arterial pressure; *NA,* neuraxial anesthesia; *OB,* obstetric; *PCA,* patient-controlled analgesia; *RCT,* randomized controlled trial; *RRP,* radical retropubic prostatectomy; *SA,* spinal anesthesia; *THA,* total hip arthroplasty; *TIVA,* total intravenous anesthesia.
*All data are expressed in milliliters.
†All data are expressed as blood units unless noted as milliliters.
‡Data are expressed as percentage of patients receiving transfusions. *p* values are less than 0.05 unless reported.
Table created from results of updated literature search using the National Library of Medicine's PubMed database since the publication of the following reference through March 16, 2012: Richman JM, Rowlingson AJ, Maine DN, Courpas GE, Weller JF, Wu CL. Does neuraxial anesthesia reduce intraoperative blood loss? A meta-analysis. J Clin Anesth 2006;18(6):427–35.

TABLE 53-2 **Estimated Blood Loss: Comparison among Anesthetic Techniques and Type of Surgery**

Surgery	Anesthesia	Mean Difference*	95% CI	*p* Value
Abdominal		**Spinal versus**		
	Epidural	–440	–698/–181	<0.001
	GA	–962	–1169/–756	<0.001
	EA–GA	–1344	–1561/–1128	<0.001
		Epidural versus		
	GA	–523	–721/–324	<0.001
	EA–GA	–905	–1113/–696	<0.001
		General versus		
	EA–GA	–382	–521/–243	<0.001
Pelvic		**Spinal versus**		
	Epidural	–315	–375/–255	<0.001
	GA	–235	–280/–191	<0.001
	EA–GA	–150	–227/–72	<0.001
		Epidural versus		
	GA	79	23/135	0.001
	EA–GA	165	81/249	<0.001
		General versus		
	EA–GA	85	12/160	0.011
Lower Extremity		**Spinal versus**		
	Epidural	–1	–62/61	1.0
	GA	–65	–111/–20	0.001
	EA–GA	–114	–194/–34	0.001
		Epidural versus		
	GA	–65	–120/–9	0.014
	EA–GA	–114	–200/–27	0.003
		General versus		
	EA–GA	–49	–125/27	0.529

CI, confidence interval; *EA*, epidural anesthesia; *EA–GA*, combined epidural–general anesthesia; *GA*, general anesthesia.
*All data expressed in milliliters. (–), indicates the mean difference favors the primary anesthetic. For instance, the first comparison (abdominal; spinal versus epidural) would have favored the use of spinal anesthesia in decreasing blood loss by a mean of 440 mL.
From Richman JM, Rowlingson AJ, Maine DN, Courpas GE, Weller JF, Wu CL. Does neuraxial anesthesia reduce intraoperative blood loss? A meta-analysis. J Clin Anesth 2006;18(6):427–35.

TABLE 53-3 Comparison of Estimated Blood Loss from Trials with Direct Comparison of GA versus SA, GA versus EA, or GA versus EA–GA

	N (Articles)	Mean EBL	SD	95% CI	*p* Value
EA	368 (17)	559	372	521-597	
GA	399 (17)	748	444	704-791	<0.001
SA	729 (14)	297	197	283-312	
GA	757 (14)	401	211	386-416	<0.001
EA–GA	399 (20)	1322	822	1241-1403	
GA	401 (20)	1244	811	1164-1323	0.175

CI, confidence interval; *EA*, epidural anesthesia; *EA–GA*, combined general anesthesia and epidural anesthesia; *EBL*, estimated blood loss (mean blood loss measured in milliliters); *GA*, general anesthesia; *N*, total number of patients in group; *SA*, spinal anesthesia; *SD*, standard deviation.

From Richman JM, Rowlingson AJ, Maine DN, Courpas GE, Weller JF, Wu CL. Does neuraxial anesthesia reduce intraoperative blood loss? A meta-analysis. J Clin Anesth 2006;18(6):427–35.

based on anesthetic technique with patients undergoing total hip arthroplasty or hip fracture repair. These studies have consistently reported significant decreases in blood loss with neuraxial versus general anesthesia and combined neuraxial and general anesthesia versus general anesthesia alone. In 2000 Stevens and colleagues[19] published the first data associating peripheral nerve blockade with a reduction in blood loss, although in this study the difference did not reach significance when those patients with evidence of epidural spreading of their lumbar plexus blocks were eliminated from the analysis. The trial by Singelyn and colleagues[20] compared postoperative intravenous patient-controlled analgesia, continuous femoral nerve block, and continuous epidural analgesia and found no statistically significant difference in blood loss or transfusion in any of the three groups.[20] The association between regional anesthesia and reduced blood loss during hip fracture repair compared with total hip arthroplasty operation has been much weaker. A 1992 meta-analysis of 13 randomized controlled trials comparing regional with general anesthesia for surgical repair of femoral neck fractures found no difference in estimated operative blood loss (the use of general anesthesia was associated with a mean of +18 mL of blood loss; 95% confidence interval, –99 to 116 mL).[21] Since 1992, at least one other investigation has revealed no difference in blood loss among patients operated on under continuous spinal, single-dose spinal, or general anesthesia with positive pressure ventilation.[22] This is supported in part by the meta-analysis by Guay,[6] in which a statistically significant difference in blood transfusion was seen for total hip replacement but not for hip fracture. Interestingly, blood loss was not decreased significantly for total hip arthroplasty, whereas it was for hip fracture.[6] Overall, total blood loss was much greater in total hip arthroplasty, possibly accounting for an increased need for transfusion.

Prostate surgery has also been evaluated extensively in outcomes research comparing regional and general anesthesia. Numerous studies have been performed on patients undergoing transurethral resection of the prostate (TURP); some investigators have found a decrease in blood loss attributable to neuraxial anesthesia,[23-25] whereas others have been unable to discern a statistically significant difference.[26-29] Because essentially all of the blood lost during TURP is aspirated into suction canisters by the resectoscope, this procedure allows for a relatively easy and extremely accurate estimate of hemorrhaging. Several factors aside from anesthetic technique have been implicated as causes of increased blood loss during TURP, including infection and weight of the prostate resected.[29] Eleven prospective studies evaluated blood loss in a randomized fashion for open prostatectomy with almost universal results of neuraxial techniques resulting in decreased blood loss.[10,12,17,30-38]

Fewer data are available on other general surgical patients. In a randomized study of the effects of epidural anesthesia on splanchnic blood flow during colorectal surgery, Mallinder and colleagues[39] noted a nonsignificant trend toward decreased blood loss among patients receiving epidural blockade in comparison with a total intravenous anesthetic control group. Bredtmann and colleagues[40] found similar results in a study of 116 colonic surgery patients randomly assigned to receive general anesthesia followed by systemic opioids or combined general–epidural anesthesia followed by continuous epidural infusion of bupivacaine postoperatively. The authors found no significant difference in blood loss, despite a trend toward increased need for blood replacement among the regional anesthesia patients.[28] These findings are consistent with earlier retrospective reviews of patients undergoing gastrointestinal surgery, which failed to demonstrate a difference in blood loss between patients treated with regional versus general anesthesia.[41,42] Blood loss for many gastrointestinal procedures is relatively small when compared with hip arthroplasty or radical prostatectomy, which may account for inconsistency in individual clinical trials in demonstrating reduced blood loss. One possible explanation for the lack of decreased blood loss noted for general surgical patients is the confounding factor of combined general–epidural anesthesia, resulting in equivalent operative blood loss to general anesthesia alone in that surgical population. The meta-analysis by Richman and colleagues[5] demonstrates decreased blood loss for abdominal operations with spinal or epidural anesthesia compared with general anesthesia but no difference in blood loss with a combined technique. It is not clear why the combination of general anesthesia with epidural analgesia negates the benefits of decreased blood loss. The mechanism may be related to the use of spontaneous versus controlled ventilation, in that controlled ventilation might result in slightly higher venous pressure and blood loss compared with spontaneous ventilation[43] or other undetermined factors. In one study on total hip arthroplasty combined epidural–general anesthesia with spontaneous ventilation did result in a greater decrease in blood loss than did epidural

anesthesia alone or general anesthesia alone.[15] A similar result was present in a study involving a radical prostatectomy: the group with combined epidural–general anesthesia with spontaneous ventilation had a decrease in blood loss compared with the group receiving general anesthesia alone.[38] Two more radical prostatectomy studies found decreased blood loss in the combined epidural–general anesthesia versus the general anesthesia group with positive pressure ventilation and induced hypotension.[10,12] The mechanism here may be related to the induced hypotension and the lowered use of inhaled agents.

As in that for gastrointestinal surgery, the data for vascular surgery are limited and equivocal. Randomized trials of combined epidural–general anesthesia versus general anesthesia alone for patients undergoing repair of abdominal aortic aneurysms (AAAs) failed to discern a difference in blood loss or transfusion requirements.[44,45] A more recent retrospective review of endoluminal AAA repairs found similar results.[46] There is, however, at least one study demonstrating lower blood loss during vascular surgery with subarachnoid anesthesia. In 1986, Cook and colleagues[47] randomly assigned 101 patients undergoing lower extremity peripheral vascular surgery to receive either general or spinal anesthesia and found that blood loss was significantly lower in the spinal (560 ± 340 mL) than in the general anesthesia group (792 ± 440 mL). The spinal group also experienced significantly greater hypotension in this study.

A variety of other mechanisms have been proposed to explain the beneficial effects of regional anesthesia on perioperative hemorrhaging. The most frequently cited explanation has been that neuraxial blockade predictably lowers arterial blood pressure, which, in turn, has been associated with decreased blood loss. However, in an elegant study of regional versus general anesthesia for total hip arthroplasty, Modig[48] demonstrated that the effects of regional anesthesia on peripheral venous pressure may be more relevant. Modig randomly assigned 38 patients undergoing total hip arthroplasty to one of three anesthetics: (1) epidural anesthesia alone, (2) general anesthesia with spontaneous ventilation, or (3) general anesthesia with positive pressure mechanical ventilation. As expected, the epidural group experienced lower mean arterial blood pressure and less blood loss than either general anesthesia group. However, there was no significant correlation between arterial blood pressure and blood loss. Meanwhile, regression analysis revealed significant relationships between peripheral venous pressure (measured in the operative wound) and intraoperative blood loss for all three groups ($r = 0.92$ to 0.94).[48] Modig postulates that arterial bleeding contributes less to intraoperative hemorrhaging than does venous bleeding because it is easier to control surgically.

AREAS OF UNCERTAINTY

Any legitimate study of the effects of anesthetic technique on surgical blood loss must a priori describe and use a validated, accurate technique of measuring the amount of blood actually lost. Unfortunately, much of the data available on anesthetic technique and blood loss is reported as a secondary outcome variable; however, subgroup analysis from a recent meta-analysis of intraoperative neuraxial regional versus general anesthesia trials demonstrated that the use of neuraxial regional anesthesia decreased perioperative transfusion requirements by 50%.[3] Decreased blood loss and transfusion requirements have been confirmed by both the recent meta-analyses, although the analysis by Richman and colleagues[5] showed decreased transfusion only with spinal anesthesia and the decrease in transfusion noted in Guay's study[6] was negated if the effect of total hip arthroplasty was removed. Nevertheless, the methods used to calculate blood loss are often suspect. Other authors have chosen not to measure blood loss at all but used transfusion requirement as a surrogate endpoint.[41] Although transfusion requirements may represent a clinically relevant marker for the efficacy of a technique to minimize blood loss, it is subject to individual variation in the criteria used for determining the need for transfusion.

Several techniques for accurately measuring intraoperative and postoperative blood loss have been established, but none has gained uniform acceptance. The most commonly used technique is the "gravimetric" method, which consists of adding the volume estimated from the weight of surgical sponges to that in suction canisters. More sophisticated photometric methods have been developed for transurethral surgery, during which essentially all the lost blood is conveniently collected through the suction port of the operative resectoscope.[49,50]

The most consistent methodologic problem in studies of regional versus general anesthesia and blood loss has been standardization of mean arterial pressure and central venous pressure. Deliberate arterial hypotension has been shown to reduce blood loss in a variety of settings, including total hip arthroplasty.[51-53] Meanwhile, deliberate central venous hypotension has been demonstrated to diminish blood loss during hepatic resection.[54] Another study, however, disputes the effects of profound hypotension (45 to 55 mm Hg) on blood loss, although this may have been the result of imprecision in the measurement technique (as in all studies) or a plateau in the benefit of deliberate hypotension in decreasing blood loss.[55] Because major conduction blockade is well-known for its ability to induce arterial and venous hypotension, any study of the effects of regional versus general anesthesia on blood loss should ideally include a description of hemodynamic responses to anesthesia.

The ability of regional anesthesia to decrease perioperative blood loss would not be predicted based on the known hematologic effects of local anesthetics. Studies attempting to elucidate the mechanisms behind the decreased risk of thromboembolic events after regional compared with general anesthesia have shown that local anesthetics exert numerous anticoagulant effects. These include (1) enhanced fibrinolytic activity produced via prevention of postoperative increases in plasminogen activator inhibitor-1, (2) more rapid return of antithrombin III levels from increased to normal values, (3) attenuation of postoperative increases in platelet aggregation, and (4) epidurally administered local anesthetics reaching plasma concentration sufficient to

impair platelet aggregation and reducing blood viscosity directly.[56] Despite the suggestion that intraoperative regional anesthesia will decrease perioperative blood loss and blood transfusion requirements, the presence of methodologic issues in the randomized studies examining the effect of regional anesthesia on blood loss makes it difficult to draw clear conclusions. The data from the recently published meta-analyses confirm the expected benefits of decreased blood loss and transfusion for neuraxial anesthesia when not combined with general anesthesia; however, the exact mechanism for this is still unclear. If reduced blood loss is primarily related to the effect of spontaneous rather than positive pressure ventilation, it may ultimately prove that there is no definitive link between decreased blood loss and neuraxial anesthesia.

GUIDELINES

No practice guidelines exist regarding the use of regional anesthesia in an attempt to decrease perioperative blood loss.

AUTHORS' RECOMMENDATIONS

- On the basis of the available evidence, neuraxial blockade induces both arterial and venous hypotension below the level of blockade. This relative hypotension appears to result in diminished blood loss during surgery, although whether this results in an actual decreased administration of transfused blood is uncertain.
- The beneficial effects of neuraxial anesthesia on hemorrhaging may be lost when positive pressure ventilation is used, unless induced hypotension is also used. Therefore if a combined regional–general anesthesia technique is used, spontaneous ventilation should be maintained when possible and if there are no additional risks to the patient (with use of spontaneous ventilation) versus controlled ventilation.
- No current high-quality evidence exists to support an association between peripheral nerve blockade and reduction in blood loss.

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CHAPTER 54

What Is the Optimal Management of Postdural Puncture Headache?

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INTRODUCTION

Despite advances in equipment and regional anesthetic techniques, postdural puncture headache (PDPH) remains a persistent problem. In many cases, the headache is mild in intensity and brief in duration, without significant sequelae; however, this is not always the case. PDPH is occasionally severe enough to leave patients bedridden and often delays hospital discharge. PDPH can be prolonged, with reports of symptoms lasting months or even years.[1] There is evidence that unintentional dural puncture with a Tuohy needle can lead to the development of chronic headache.[2] Untreated PDPH can lead to the development of persistent cranial nerve palsies and even subdural hematoma.[3,4] Finally, despite the perception among physicians that PDPH is merely a nuisance, it is a surprisingly frequent, and sometimes a distressingly costly, source of litigation.[5]

A wide range of both conservative and invasive treatments for PDPH has been described in the literature, sometimes with scant scientific support. The rationale for the more common treatments of PDPH in this review are based on our current understanding of the pathophysiology of PDPH. Because there are so few well-controlled studies of the treatment of PDPH, however, many of the treatment recommendations will be based on case reports, observational studies, and personal experience. A century after August Bier first described PDPH, the optimal management of PDPH is a question that remains unanswered.[6]

PATHOPHYSIOLOGY

This chapter deals primarily with the treatment of PDPH; however, it should not be forgotten that our main goal should be the prevention of PDPH. As in many other areas of medicine, prevention is far preferable to treatment. There are numerous risk factors for PDPH that cannot be modified, but the two most important can be: needle shape and size. The use of small pencil-point needles for spinal anesthesia (25- or 27-gauge Whitacre, Sprotte, Gertie Marx, or Atraucan needles) will reduce the incidence of headache after dural puncture to 1% or less, even in high-risk populations.[7] If a cutting needle (e.g., Quincke) is used, insertion of the needle with the bevel parallel to the longitudinal axis of the body will significantly decrease the risk of headache.[8] When epidural anesthesia is performed, the option of using such small needles is not possible; we must, instead, rely on meticulous technique. The use of the combined spinal–epidural technique may reduce the risk of accidental dural puncture; the incidence of headache requiring autologous epidural blood patch (EBP) has been reported to be no higher with this technique than with traditional epidural anesthesia.[9]

An understanding of the pathophysiology of PDPH is essential when considering its treatment. There are two competing yet somewhat complementary theories. The first is predicated on the belief that the continued leak of cerebrospinal fluid (CSF) from a dural puncture leads to a loss of fluid from the intracranial compartment. The loss of the cushioning effect of CSF allows the brain to sag within the skull, which places traction on the pain-sensitive meninges, an effect that becomes most apparent in the upright position. This suggests that the treatment of PDPH should be based on minimizing the leak of CSF, increasing CSF production, or translocating CSF from the spinal to the intracranial compartment.

The second theory postulates that the loss of CSF causes intracranial hypotension, which leads to compensatory cerebral vasodilation. This suggests that PDPH is similar to migraine headache, a theory supported both by the similarly increased incidence of migraine and PDPH in women and by MRI studies that demonstrate enhanced cerebral blood flow in PDPH.[10] This theory suggests not only that PDPH will be relieved by restoration of intracranial CSF volume but also that cerebral vasoconstrictors might provide symptomatic relief.

OPTIONS

The treatment of PDPH is traditionally divided into conservative and, for want of a better term, aggressive treatment (Box 54-1).

EVIDENCE

Bed Rest

Bed rest will provide symptomatic relief of PDPH. However, a review of the literature demonstrated that bed rest after dural puncture did not reduce the risk of developing a headache; in fact, the trend was toward increased headache in patients placed at rest.[11] There was no evidence that prolonging the duration of bed rest

BOX 54-1 Treatment Options for Postdural Puncture Headache

Conservative Treatment
- Bed rest
- Hydration
- Prone position
- Abdominal binder
- Caffeine (oral or parenteral)
- Triptans
- Adrenocorticotropic hormone/corticosteroids

Aggressive Treatment
- Intrathecal saline injection
- Intrathecal catheter
- Epidural saline
- Epidural morphine
- Epidural blood patch
- Prophylactic epidural blood patch
- Epidural dextran

after dural puncture decreased the likelihood of headache. Early ambulation after dural puncture should be encouraged; patients with an established headache should ambulate as much as they are able to.

Hydration

Despite the widespread enthusiasm for aggressive hydration after dural puncture, only one study of fluid supplementation after dural puncture has been performed[12]; there was no evidence of any decrease in the incidence of PDPH.

Prone Position

The prone position can relieve headache in some patients with PDPH, but no published studies support this common practice. Presumably, increased intra-abdominal pressure translocates CSF from the lumbar spine to the intracranial compartment. The prone position may be worthwhile in patients whose surgical incision does not preclude this posture.

Abdominal Binder

A single study suggested that an abdominal binder prevents the development of spinal headache.[13] It may provide symptomatic relief by the same mechanism as prone positioning. Again, this may not be feasible in patients with an abdominal incision.

Caffeine (Oral or Parenteral)

A study of 41 patients with headache unresponsive to conservative measures demonstrated that 500 mg intravenous caffeine led to permanent resolution of symptoms in 70% of subjects.[14] The small size of the study and the lack of a control group cast doubt on the routine use of this therapy. Because intravenous caffeine is unavailable in many hospitals, the use of oral caffeine has been proposed as a substitute. Oral caffeine, 300 mg, produced a more significant decrease in headache intensity than placebo[15]; the effect was short-lived, however, and no reduction was seen in the percentage of patients requiring an EBP.

Sumatriptan

The serotonin agonist sumatriptan is a cerebral vasoconstrictor that is used to treat migraine. One study reported relief of PDPH in four of six patients treated with 6 mg subcutaneous sumatriptan.[16] A subsequent study did not replicate these results, and this treatment should be considered unproved.[17]

Corticosteroids/Adrenocorticotropic Hormone

A number of case reports have suggested a therapeutic role for corticosteroids or adrenocorticotropic hormone (ACTH). A single randomized study demonstrated that high-dose hydrocortisone reduced the severity of spinal headache compared with placebo.[18] A randomized study could not demonstrate any benefit to the administration of ACTH.[19]

Intrathecal Saline

Injection of 10 mL of preservative-free saline via the Tuohy needle after accidental dural puncture decreased the need for EBP from 43% to 5%. Injection of normal saline through an intrathecal catheter placed after accidental dural puncture appeared to decrease the incidence of headache, but the number of patients in this group was too small to achieve statistical significance. When both groups were combined, the incidence of headache after injection of saline through either a catheter or a needle decreased from 62% to 25%.[20]

Intrathecal Catheter

After accidental dural puncture during attempted epidural placement, a catheter can be placed in the subarachnoid space to provide continuous spinal anesthesia. Some studies have suggested that this technique will reduce the incidence of subsequent spinal headache.[21] This result has not been consistently demonstrated, however, perhaps because of differing durations of subarachnoid catheterization in different studies.[22] In fact, one study did show improved results when the catheter remained in place for 24 hours after delivery.[23] If a spinal catheter is placed, it is critical that the sterility of the catheter be maintained. It is also imperative that all anesthetic providers be aware of the subarachnoid location of the catheter so that injection of large (epidural) doses of local anesthetic does not occur.

Epidural Saline

Continuous epidural infusions of normal saline have been reported to prevent or relieve the symptoms of

PDPH after accidental dural puncture during epidural placement.[24] Unfortunately, discontinuation of the infusion usually leads to recurrence of the headache. This technique may be useful in patients who refuse an EBP, providing symptomatic relief until the dural puncture spontaneously heals.

Epidural Morphine

A single randomized controlled trial demonstrated that 3 mg epidural morphine administered at the conclusion of anesthesia and the following day decreased the incidence of PDPH from 48% to 12%.[25]

Epidural Blood Patch

The EBP has been proposed as the gold standard for the treatment of PDPH: early reports suggested a success rate (permanent and complete relief of headache) of as high as 95%. Unfortunately, the great majority of these studies were not prospective, and a large meta-analysis suggested that evidence for the efficacy of EBP is lacking.[26] Additionally, some reports suggested that the success rate of EBP may actually be as low as 65%.[27] However, a more recent randomized controlled trial showed that after 7 days, the incidence of headache in patients receiving EBP was reduced to 16% compared with 86% in control subjects; patients in the EBP group with residual headache characterized the severity as mild.[28] EBP is least likely to be successful in patients with larger dural punctures, and these are the very patients in whom headache is most likely to be severe and persistent. In those patients with recurrence of headache after EBP, a repeated procedure is usually successful. Failure of a second EBP should encourage a search for other possible causes of the headache.

The technical aspects of a blood patch increase the likelihood of its success. The spinal interspace chosen for the blood patch should be as close as possible to the initial puncture site, but if the volume of injected blood is sufficient, the spreading of blood in the epidural space is usually extensive enough to reach the dural puncture site from any lumbar interspace. If significant back pain does not develop during injection, a volume of 15 to 20 mL of blood is optimal. The success rate of EBP is improved if the patient is allowed to remain supine for at least 1 hour and possibly as long as 2 hours.[29] The patient should be advised to avoid heavy lifting or straining for at least 48 hours because a forceful Valsalva maneuver may dislodge the patch, which may lead to recurrence of the headache.

The decision to perform an EBP may be influenced by other considerations. The procedure is obviously contraindicated in patients thought to have bacteremia, but a low-grade fever is probably not a contraindication, especially if antibiotic therapy has been initiated. Despite early concerns that central nervous system involvement would be accelerated in human immunodeficiency virus (HIV)-infected patients receiving a blood patch, there is no evidence that this is the case, and EBP is not contraindicated in these patients.[30] Finally, for Jehovah's Witness patients who refuse EBP for religious reasons, the use of epidural dextran may be an effective alternative, although published experience with this technique is limited, and the patient should be fully informed about the speculative nature of this therapy.

Prophylactic Epidural Blood Patch

EBP administered via an epidural catheter placed subsequent to accidental dural puncture has been reported to decrease the incidence of PDPH by as much as half, from 70% to 30%.[31] More recent work suggests that the usefulness of prophylactic EBP has been significantly overstated,[32] although some evidence has shown that prophylactic EBP may decrease the duration of the headache even if it does not prevent it.[33,34] Because not all patients will develop PDPH after dural puncture, a substantial number of those who receive a prophylactic EBP will be treated for a complication that may never have developed even in the absence of the treatment. It is therefore essential that patients be fully informed of the potential complications of EBP and that every effort is made to prevent those complications, particularly infection.

Epidural Dextran

In those patients who cannot receive EBP because of a fever or who refuse EBP because of religious reasons, epidural dextran has been used with some success.[35] This modality has never been studied in prospective fashion, and concerns about the potential for neurotoxicity and the risk of allergic reaction remain. Epidural dextran infusions must be considered nonstandard therapy at the present time.

AREAS OF UNCERTAINTY

Pharmacologic Management

In view of the mixed results of such interventions as caffeine, sumatriptan, and ACTH, yet acknowledging the benign nature of these treatments, is there any value to a trial of these agents, or should EBP be offered early in the course of PDPH?

Intrathecal Catheter Placement after Accidental Dural Puncture

Evidence for the prophylactic value of this technique is sufficiently heterogeneous, and the potential risks of intrathecal catheterization (e.g., drug overdose or misadministration and infection) are great enough that utilization of this technique after accidental dural puncture, or the placement of an epidural catheter at a different level, can both be justified.

Neuroimaging

Considerable overlap exists between the symptomatology of PDPH and intracranial venous thrombosis. In the setting of a failed initial EBP, it is not clear whether

neuroimaging studies should be obtained before repeated EBP.[36]

GUIDELINES

The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology has concluded that the use of an atraumatic spinal needle decreases the incidence of PDPH in adult patients, as does the use of smaller-sized needles.[37]

The American Society of Anesthesiologists Practice Guidelines for Obstetric Anesthesia recommend that pencil-point spinal needles should be used instead of cutting-bevel needles so that the risk of PDPH is decreased.[38]

AUTHOR'S RECOMMENDATIONS

It should be clear from the preceding discussion that postdural puncture headache (PDPH) can be debilitating, that it can cause serious morbidity, and that it may, in fact, result in significant litigation. In view of the multiple consequences of PDPH, the anesthesiologist should make every effort to minimize the risk of headache by optimizing those factors that can be controlled, namely, needle size and shape. Despite our best efforts, however, these headaches will continue to occur, and we will continue to be called on to manage them. Unfortunately, despite many years of research, the optimal treatment for PDPH is still not clear. What follows, then, is one suggested management approach, based on the literature as well as on personal experience.

In patients who develop PDPH, ambulation should not be restricted because bed rest has no demonstrated effect on the duration of the headache. Patients should therefore ambulate as much as they can tolerate. Although forced hydration is unlikely to augment cerebrospinal fluid production to any significant degree, dehydration will worsen the headache, and intravenous fluids should be provided to patients who are unable to maintain adequate oral intake. Oral analgesics should be made available; for a severe headache, narcotic analgesics may be required and should be provided on a round-the-clock basis.

In patients who decline or who cannot receive an epidural blood patch (EBP), pharmacologic therapy should be considered. The only therapy that appears to be consistently effective is caffeine; if the intravenous preparation is available, one or two doses of 500 mg caffeine benzoate should be administered. Otherwise, 300 mg of oral caffeine can be administered every 6 hours. Until more supportive evidence is available, the routine use of sumatriptan cannot be recommended.

My practice is to wait at least 24 hours after the onset of symptoms before considering a blood patch because some headaches may resolve by that time, and I would prefer to avoid the possible complications of EBP in headaches that resolve that quickly. Exceptions, however, include patients with a debilitating headache due to accidental dural puncture with a large epidural needle, in whom the likelihood of rapid spontaneous resolution is small. In this case, I will perform a blood patch soon after the development of symptoms. Bear in mind, however, that EBP performed within 24 hours of dural puncture has a lower success rate; whether this is because headaches treated within 24 hours are more severe and thus more likely to lead to a failed EBP procedure or whether there is an intrinsic increased failure rate with early EBP is unclear.

In the setting of a known accidental dural puncture during epidural placement, the likelihood of headache is so high that prophylactic measures should be considered. Because the evidence that placing an intrathecal catheter through a dural puncture decreases the incidence of headache is inconsistent, the decision to use a continuous spinal anesthetic should be made on the basis of other considerations, such as difficult airway or morbid obesity, in addition to the possible effect on the development of headache. If this is done, it is critically important for all caregivers to be notified of the intrathecal location of the catheter, to prevent the administration of what would be an appropriate epidural dose into the subarachnoid space. If a catheter is placed in the epidural space subsequent to a dural puncture, an infusion of epidural saline (20 to 30 mL/hr) will frequently prevent a headache from developing; however, a headache usually develops after the infusion is stopped. Finally, an immediate blood patch performed via an epidural catheter may prevent the development of a headache. Of course, as many as 50% of patients with a dural puncture from even a 17-gauge Tuohy needle will not develop a headache, and these patients therefore would be treated unnecessarily. For this reason, I reserve immediate EBP for those patients in whom I suspect a repeated epidural procedure would be technically difficult. I also reserve immediate EBP for those patients whose epidural catheters were treated in strict sterile fashion after the initial dural puncture because the consequences of injecting blood through a contaminated catheter are potentially catastrophic.

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CHAPTER 55

Should Ultrasound Guidance Be the Standard of Practice for Peripheral Nerve Blockade?

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INTRODUCTION

Ultrasound (US)-guided peripheral nerve blockade is gaining popularity among anesthesiologists. US guidance transformed peripheral nerve blocks from blind procedures relying on anatomic landmarks and indirect methods to localize different nerves to procedures in which the anesthesia provider is able to visualize the target nerve or nerves and the surrounding structures, introduce the block needle toward the target, and observe the local anesthetic being injected and surrounding the nerve in real time. The interest in US-guided regional anesthesia (USGRA) generated an increasing number of randomized controlled trials (RCTs) addressing the question of whether US leads to better patient outcomes compared with traditional techniques. The outcome variables relevant to the individual blocks were time to performance of nerve blocks, number of attempts, patient discomfort during performance of the nerve blocks, local anesthetic volume, predictable quality of the sensory and motor block, safety profile, learning curve, and the success of the blocks.[1]

Despite the excitement about US, skeptics argue that the lack of an evidence-based foundation makes it difficult to adopt US-guided peripheral nerve blocks as a standard of care. Historically, anesthesiologists performed peripheral nerve blocks by eliciting paresthesia on needle contact with a nerve. By adding nerve-stimulating devices, we have been able to more precisely locate peripheral nerves based on muscle twitch patterns in response to peripheral nerve stimulation. The improved technology of US now allows us to visualize the target peripheral nerves and surrounding structures in real time as we perform these blocks.

Basic Physics: Sound waves are high-energy waves generated by passing an alternating electric current through piezoelectric crystals. The sound waves will travel through different body tissues and will be reflected off the tissue interface and returned to the transducer. The transducer transforms the echo (mechanical energy) into an electric signal, which is processed and displayed as an image on the screen.[2,3] Different tissues have different affinities for sound waves. Sound waves will be reflected, absorbed, or scattered at different tissue interfaces to variable degrees. Acoustic impedance is the resistance of a tissue to the passage of US. The higher the degree of impedance mismatch between adjacent tissues, the greater the amount of reflection of the sound waves. A transducer that sends a high-frequency signal will generate higher resolution images with well-defined details, with the sacrifice of decreased penetration (depth). Newer US machines, however, can produce higher resolution with relatively deeper penetrations.[4]

TECHNIQUE

The transducer frequencies used for peripheral nerve blocks range from 3 MHz to 15 MHz. The appropriate probe is chosen based on the depth of the nerve to be blocked and the resolution required. Superficial structures are best visualized with the use of a high-frequency linear probe. To visualize deep neural structures, we recommend using a curved array probe.[5] A preblock scan should be performed to identify the nerve and, perhaps more important, the surrounding structures such as bone, muscle, and vascular structures. To optimize the view, the anesthesiologist adjusts the transducer by sliding it along the skin, rotating it, and tilting it. Almost all peripheral nerves to be blocked are visualized in the short axis view.[6] After sterile preparation of the skin with an alcohol-based solution, the US probes is covered with a sterile sleeve with a conducting US gel inside the sleeve. The block needle is advanced to the target nerve or nerves without making direct contact. The needle is either kept in the US plane and seen in its entirety during the block or advanced to its target out of the US plane and only the tip is visualized. The most common error committed by novices during training on USGRA is losing sight of the needle tip or losing site of the whole needle as it advances toward the target. With the needle, nerve, and surrounding structures in view, a catheter can be placed for continuous perineural infusion or local anesthetic can be injected through the needle to surround the nerve. The local anesthetic should be seen completely surrounding the nerve[7]; however, if the nerve is directly injected, it will appear swollen.[8,9]

EVIDENCE

Overall, data support the use of US guidance as a safe adjunct to nerve stimulation techniques or as a complete replacement for nerve stimulation. The most difficult question to answer is whether US guidance improves success rates and decreases the number of complications.

Studies have used various criteria to demonstrate higher success rates and shorter onset time for US guidance compared with conventional techniques. Orebaugh and colleagues[10] conducted a retrospective chart review of more than 5000 cases and concluded that US might offer the potential advantage of decreasing adverse outcomes. In addition, RCTs have demonstrated several benefits of US over nerve stimulation or other landmark techniques.

Procedure Attempts, Times, and Comfort

Time to perform the block, number of attempts, and patient comfort during the procedure are important quality measures when evaluating peripheral nerve blocks. When compared with traditional nerve localization techniques, US was associated with less time to perform the block and fewer needle passes needed to perform the block.[11-18] Definition of time to perform the block was not consistent among all the RCTs. Although these US techniques are approximately 2 to 6 minutes faster than landmark or nerve stimulation techniques, they do not account for prescanning and preparation of the US machine and probe, which could lengthen the procedural time. Three RCTs involving ankle blocks favored a landmark approach.[19-21] Fewer needle passes have been reported for US-guided sciatic nerve blocks.[22] These findings indicate that patient comfort is likely improved because the needle is in contact with the patient for a shorter period of time. In fact, children expressed lower pain scores during block performance with US compared with nerve stimulation.[23] The use of US was also associated with a significantly lower incidence of paresthesia compared with landmark techniques during performance of brachial plexus blocks.[24] In patients with fractures of the extremities, painful muscle contractions that occur with nerve stimulation can be avoided with a US-guided nerve block.[25]

Block Onset Time

Block onset time is defined as the time interval from completion of injection of the local anesthetic and removal of the needle to a complete sensory block.[1] In several randomized trials, onset times were shorter for US-guided blocks than for blocks placed with conventional techniques by approximately 2 to 12 minutes.[11-15,26-31] More specifically, shorter onset times have been documented for brachial plexus blocks in children and for femoral (3-in-1) blocks in adults.[23,24,32] Casati and colleagues[33] demonstrated a faster onset of sensory axillary brachial plexus block but found no difference in onset of motor block or in overall preparation time for surgery. Similarly, sensory block onset was faster for supraclavicular brachial plexus blocks, but the rate of motor block onset was unchanged.[34] Onset times were also faster for interscalene and axillary brachial plexus blocks with US compared with nerve stimulation.[24] In other RCTs,[11,22,25,31] there was no statistical difference between US and landmark techniques. The close proximity of the needle tip to the target nerve and surrounding the target nerve or nerves with local anesthetic may explain the shorter onset times. The clinical significance of the shorter onset time and the shorter time to perform the block can be argued.[35] The value of decreasing this time is variable, depending on the setting of each individual practice.

Local Anesthetic Volume

US may also provide the means to reduce the dose of local anesthetic necessary to achieve endpoints in a nerve block. For example, a lower volume of local anesthetic was required to encircle sciatic nerves (one-half volume) and femoral nerves (one-third volume) in children with the use of US guidance compared with the set dose used for nerve stimulation. The US-guided group achieved successful blocks that also lasted longer than the nerve stimulation group.[36] For ilioinguinal–iliohypogastric nerve blocks, children needed less local anesthetic with US than with the conventional "facial click" techniques (0.19 mL/kg versus 0.3 mL/kg). The US group of children also had better quality blocks on the basis of a physical examination of sensory and motor block distribution.[37] A US-guided group that received 20 mL of local anesthetic for a femoral nerve block experienced a higher quality block than a nerve stimulation group that received 30 mL of local anesthetic.[38] Casati and colleagues[33] used the up-and-down staircase method to determine the amount of anesthetic required to achieve a sensory and a motor femoral nerve block. The minimum effective volume of 0.5% ropivacaine was 15 mL in the US-guided group and 26 mL in the nerve stimulation group.[39] US guidance likely reduces local anesthetic dosing because reliable visualization of the local anesthetic spreading around a nerve is possible to confirm the block. A lower total dose of local anesthetic may be a means of reducing the incidence of systemic local anesthetic toxicity.

Block Quality and Success

Most RCTs define the quality of a block as a complete sensory block in the area supplied by the target nerve or nerves. Criteria to define success rates for nerve blocks vary depending on the purpose of a block. Success of blocks placed for postoperative analgesia may be measured by opioid consumption or distribution of sensory analgesia. If the purpose of the block is surgical anesthesia, block quality may be assessed through the need for supplemental analgesia or the conversion rate to general anesthesia. Smaller intraoperative and postoperative analgesic doses were required in children receiving ilioinguinal–iliohypogastric nerve blocks with US placement than with conventional facial click technique.[37]

Clinical studies favor US over conventional techniques for improved block quality as assessed by physical examination measurements. Several randomized studies have

demonstrated reduced sensitivity to painful stimuli after US-guided femoral (3:1) blocks in adults and infraclavicular brachial plexus blocks in children.[23,32,38] US-guided interscalene and axillary brachial plexus blocks also produced more complete sensory and motor blocks.[24] A higher incidence of complete sciatic nerve block and better tolerance of a tourniquet have been found with US-guided blocks than with nerve stimulation.[22] Success rates are also higher in US-guided axillary brachial plexus blocks than with the transarterial approach.[14] Half of the failures in the transarterial approach result from an inability to locate the axillary artery, and the remainder are caused by inadequate intraoperative analgesia. In a quality study, Chan and colleagues[13] randomly assigned three groups to receive axillary brachial plexus blocks with the use of US guidance, nerve stimulation, or dual techniques (US and nerve stimulation). US guidance with or without nerve stimulation was superior to nerve stimulation alone, and adding a nerve stimulator to the US technique did not provide any additional benefit. However, another study involving supraclavicular brachial plexus blocks did not report improved success or a reduced conversion rate to general anesthesia with US guidance and nerve stimulation techniques compared with nerve stimulation alone.[40] In a recent meta-analysis, a significant increase was seen in the overall success rate for blocks performed with the use of a US-guided technique versus all non-US techniques.[41] These results are similar to those found in other systematic reviews and meta-analyses. A meta-analysis of 13 RCTs found that peripheral nerve blocks performed with US guidance were more likely to be successful.[42] Another systematic review of 16 RCTs found that the use of US for upper and lower extremity nerve blocks was associated with a better quality of block.[43]

Avoiding Adverse Outcomes

US has the potential to avoid complications of mechanical nerve injury, intravascular injection, and adverse effects. However, adverse outcomes with USGRA are still reported.[44-46] Of note, the ability of US to prevent potential complications is very operator dependent. Sites et al[47] showed that failure to visualize the needle during advancement occurred in up to 43% of the procedures performed by novice trainees. US resulted in a statistically significant decrease in the rate of paresthesia during block placement[12,24,48] and unintended vascular puncture when compared with traditional nerve localization techniques.[13,17,27,49] Liu and colleagues[26] did not show a statistically significant difference in adverse neurologic outcomes between US-guided interscalene blocks and the landmark technique. US may reduce the incidence of intraneural injection of local anesthetic. Most experts agree that intraneural injection is associated with postoperative neurologic dysfunction and should be avoided. Before US technology, the only indicators for intraneural needle placement were very painful paresthesia, high injection pressures, or very low nerve stimulation current necessary to achieve a twitch. In an ultrasonographic study in pigs, Chan and colleagues[9] produced clear image differences between a perineural injection and a direct injection of a nerve in the axillary brachial plexus. According to these images, an intraneural injection is easily detected with US. The histologic examination of the nerves injected revealed infiltration of the injectate within the epineurium or perineurium. On the other hand, Bigeleisen[50] found that intraneural injection of low volumes of local anesthetic during US-guided axillary blocks did not cause neurologic dysfunction. The relationship between neurologic dysfunction and intraneural injection is still unclear, but US imaging can show when a nerve is being injected and may help to avoid injecting high volumes of local anesthetic directly into a nerve. The absence of neurologic complications reported in a recent small series,[50,51] however, should not be mistakenly interpreted to justify the indiscriminate practice of intraneural injection in all peripheral nerve blockade models (Table 55-1).[52]

CONTROVERSIES

Adopting US as the standard of care for performance of peripheral nerve blocks still has a long way to go. The learning curve for USGRA is steeper than conventional techniques. Learning how to perform US-guided peripheral nerve blocks is a two-step process. The first step is learning the sonoanatomy and interpretation of the two-dimensional US images as they relate to the three-dimensional anatomy. The second step is mastering hand-eye coordination and driving the needle into the target nerve or nerves and keeping it in the plane of the US. This later step can be especially frustrating for the novice and for practicing anesthesiologists who want to incorporate US into their regional anesthesia practice. The significant cost of obtaining US technology and time invested in training are other reasons that may dissuade small group practices from adopting US.

The referenced studies support US guidance in regional anesthesia. However, the advantages that USGRA can offer are operator dependent to a large extent. Training in US has become a controversial topic. Some experts believe that training and subsequent certification will improve the practice of regional anesthesia and avoid errors and complications. Others argue that training and certification programs limit the use of US and that even US in the hands of the novice can offer some benefits to patients over nerve stimulation alone.

Although US guidance has become fairly common in large academic centers, many worry that graduating anesthesiology residents are no longer proficient in the conventional techniques of regional anesthesia, which they may well need if they take jobs in smaller community practices that do not have the benefit of US technology.

GUIDELINES

In 2005, regional anesthesia fellowship program directors and other advocates of regional anesthesia were invited to participate in a collaborative project to establish a standardized curriculum for regional anesthesia fellowships. Guidelines were created based on the existing

TABLE 55-1 **Summary of the Randomized Clinical Trials Comparing Ultrasound Guided– with Nerve Stimulator–Based Peripheral Nerve Blocks**

Study (Year)	Site (n)	Study Design	Intervention	Control	Outcomes
Thomas et al (2011)[53]	Interscalene brachial plexus (41)	Prospective RCT	Ultrasound guided	Nerve stimulation	Faster onset; improved performance in training environment
Geiser et al (2011)[54]	Infraclavicular brachial plexus (56)	Prospective RCT, single-blinded	Ultrasound guided	Nerve stimulation	Significantly higher success rates and shorter times of onset
Zencirci (2011)[55]	Axillar brachial plexus (60)	Prospective RCT	Ultrasound guided	Nerve stimulation	The motor blockade was more intense in US group
Orebaugh et al (2009)[10]	Peripheral noncatheter nerves (2146 versus 3290)	Retrospective chart review	Ultrasound guided	Nerve stimulation	US offers potential advantages of decreasing adverse outcomes, such as seizures and nerve injuries
Liu et al (2009)[26]	Interscalene brachial plexus (230)	Prospective RCT, single-blinded	Ultrasound guided	Nerve stimulation	No differences in block failures, patient satisfaction, or incidence and severity of postoperative neurologic symptoms
Ponde and Diwan (2009)[56]	Infraclavicular brachial plexus (50)	Prospective RCT	Ultrasound guided	Nerve stimulation	US improves success rate
Gurkan et al (2008)[57]	Infraclavicular brachial plexus (80)	Prospective RCT	Ultrasound guided	Nerve stimulation	No statistical difference
Perlas et al (2008)[28]	Popliteal fossa sciatic nerve (74)	Prospective RCT	Ultrasound guided	Nerve stimulation	US resulted in higher rate of success and faster onset block
Kapral et al (2008)[58]	Interscalene brachial plexus (160)	Prospective RCT	Ultrasound guided	Nerve stimulation	US improved success rate
Yu et al (2007)[59]	Axillary brachial plexus (80)	Prospective RCT	Ultrasound guided	Nerve stimulation	US resulted in higher success rate, faster onset, shorter manipulation time, and lower accidental blood vessel puncture
Chan et al (2007)[13]	Axillary brachial plexus (188)	Double-blinded RCT	Ultrasound guided with or without nerve stimulation	Nerve stimulation	Improved incidence of complete sensory block
Casati et al (2007)[39]	Femoral nerve (60)	Up-and-down staircase method for minimum effective volume	Ultrasound guided	Nerve stimulation	Reduced minimum effective anesthetic volume
Dingemans et al (2007)[60]	Infraclavicular brachial plexus (73)	Prospective RCT	Ultrasound guided	Ultrasound guided and nerve stimulation	Faster onset
Casati et al (2007)[33]	Axillary brachial plexus (60)	Prospective RCT	Ultrasound guided	Nerve stimulation	Faster onset
Domingo-Triado et al (2007)[22]	Sciatic nerve (61)	Prospective RCT	Ultrasound guided	Nerve stimulation	Improved quality of sensory block; improved tourniquet tolerance; reduced attempts
Oberndorfer et al (2007)[36]	Pediatric femoral and sciatic (46)	Prospective RCT	Ultrasound guided	Nerve stimulation	Reduced volume of local anesthetic and longer duration of analgesia
Sites et al (2006)[14]	Axillary brachial plexus (56)	Prospective RCT	Ultrasound guided	Perivascular technique	Reduced conversion to general anesthesia; reduced performance time

Continued on following page

TABLE 55-1 **Summary of the Randomized Clinical Trials Comparing Ultrasound Guided– with Nerve Stimulator–Based Peripheral Nerve Blocks** (Continued)

Study (Year)	Site (n)	Study Design	Intervention	Control	Outcomes
Willschke et al (2005)[37]	Pediatric ilioinguinal–iliohypogastric (100)	Prospective RCT	Ultrasound guided	Facial click	Lower local anesthetic volume; lower additional analgesic requirements
Marhofer et al (2004)[23]	Infraclavicular brachial plexus (40)	Prospective RCT	Ultrasound guided	Nerve stimulation	Shorter onset time, lower pain scores during performance, longer sensory block, better sensory and motor block quality
Williams et al (2003)[61]	Supraclavicular brachial plexus (80)	Prospective RCT	Ultrasound and nerve stimulation	Nerve stimulation	Shorter block performance time; better block distribution
Marhofer et al (1998)[38]	3:1 femoral nerve block (60)	Prospective RCT	Ultrasound guided	Nerve stimulation at different volumes	Reduced onset time; improved quality of sensory block
Marhofer et al (1997)[32]	3:1 femoral nerve block (40)	Prospective RCT	Ultrasound guided	Nerve stimulation	Reduced onset time; improved quality of sensory block
Macaire et al (2008)[30]	Wrist blocks (60)	Prospective RCT	Ultrasound guided	Nerve stimulation	Less time to perform the block; similar success rate
Mariano et al (2009)[16]	Popliteal–sciatic perineural catheter insertion (40)	Prospective RCT	Ultrasound guided	Nerve stimulation	Placement of popliteal–sciatic perineural catheters takes less time and produces less procedure-related discomfort when using US guidance compared with ES
Mariano et al (2009)[17]	Infraclavicular brachial plexus perineural catheter insertion (40)	Prospective RCT	Ultrasound guided	Nerve stimulation	Placement of infraclavicular perineural catheters takes less time, is more often successful, and results in fewer inadvertent vascular punctures when using US guidance compared with ES
Mariano et al (2009)[62]	Femoral perineural catheter insertion (40)	Prospective RCT	Ultrasound guided	Nerve stimulation	Placement of femoral perineural catheters took less time with US guidance compared with ES. US guidance produced less procedure-related pain and prevented inadvertent vascular puncture
Fredrickson et al (2009)[18]	Interscalene catheter placement	Prospective RCT	Ultrasound guidance	Nerve stimulation	Interscalene catheters placed with US demonstrated improved effectiveness during the first 24 hr compared with those placed with NS. These catheters were also placed with less needling and a very small reduction in procedure-related pain

ES, electric stimulation; *NS,* neurostimulation; *RCT,* randomized controlled trial; *US,* ultrasound.

template of Accreditation Council of Graduate Medical Education program requirements for residency education in anesthesiology.[63] These guidelines were updated in 2010 and aimed to address three major topics: organization and resources, the educational program, and the evaluation process.[64]

A joint committee from the American Society of Regional Anesthesia and Pain Medicine (ASRA) and the European Society of Regional Anesthesia and Pain Therapy was established to recommend to members and institutions the scope of practice, the teaching curriculum, and the options for implementing the medical practice of USGRA.[65] This document specifically defines the following:

- Ten common tasks used when performing a US-guided nerve block
- The core competencies and skill sets associated with USGRA
- A training practice pathway for postgraduate anesthesiologists
- A residency-based training pathway

In both the residency and postgraduate pathways, training, competency, and proficiency requirements include both didactic and experiential components.

Aside from the guidelines for training in USGRA, the ASRA issued practice advisories for neurologic complications,[66] local anesthetic systemic toxicity,[67] and the practice of regional anesthesia in patients receiving anticoagulants.[68] These practice advisories are not specific to US-guided peripheral nerve blocks, but they were issued to establish practice parameters for the practice of regional anesthesia in general.

AUTHORS' RECOMMENDATIONS

- Based on the review of the evidence, ultrasound (US)-guided nerve blocks are faster to perform, less painful, and more successful. They also have a shorter onset time, result in a better quality block, and last longer. It is presumed that US guidance may reduce complications by avoiding perineural structures such as vessels, pleura, and neuraxis, but no data confirm these presumptions. Data suggest that US guidance may also reduce complications by reducing the dose of local anesthetic, by diminishing painful paresthesias during performance, and by avoiding or limiting intraneural injection.
- For those interested in US-guided regional anesthesia, several training courses are now available and are offered through different institutions, and a certification process may soon be offered.
- We recommend creating some sort of certification process for the trainers in these courses to ensure consistency of the quality of the training offered.
- It is always helpful to interpret the US images and make reference to the landmarks used with conventional techniques.
- The increased rate of success and the quality of the US-guided blocks make regional anesthesia more or less reproducible and will help expand the scope of practice of regional anesthesia.
- For good performance of any regional anesthetic under US guidance, anatomy must be relearned, scanning must be practiced repeatedly, and experts must review images.
- There is a role for a combined US and nerve stimulation technique. Nerve stimulation in this case may not be used to localize the nerve or nerves, but it may be beneficial in helping to prevent intraneural injection. It may also be helpful to combine both techniques in deeper blocks or in patients with challenging anatomy.

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CHAPTER 56

Should Regional Anesthesia Be Used for Orthopedic Trauma Patients?

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INTRODUCTION

Trauma is a major cause of morbidity and mortality worldwide, responsible for 8% of all deaths. In the United States, it is the leading cause of death for individuals younger than 30 years.[1] Anesthesia and acute pain management for trauma victims can be very challenging to anesthesiologists, critical care physicians, and surgeons. Inadequate treatment of acute pain can potentiate the stress response associated with trauma and may lead to the development of chronic pain syndromes in the long term. The prevalence of chronic pain after orthopedic trauma varies among published series. One study found that 37% of orthopedic trauma patients complained of moderate to severe pain 6 months after the injury.[2] In a separate series,[3] this rate was doubled (73%) at 7 years after lower extremity (e.g., calcaneus and distal tibial fractures) orthopedic trauma. Regional anesthesia (RA) has been shown to improve acute pain control and decrease the development of chronic pain.[4,5] However, it is still underused in orthopedic trauma for several reasons, including the emergent or urgent nature of the surgery, lack of resources and infrastructure, the challenges associated with polytrauma (e.g., multiple surgical sites, contaminated wounds, and spine fractures), and the concern of delaying a diagnosis of acute compartment syndrome (ACS).

OPTIONS

RA can be used in the setting of orthopedic trauma for intraoperative anesthesia, postoperative analgesia, or both. RA includes neuroaxial techniques (spinal and epidural), plexus blocks, and peripheral nerve blocks. RA may also be used as part of a multimodal pain regimen. The choice of medication, dose, route, and duration of therapy should be individualized. RA should be used only after careful consideration of the risks and benefits for the individual patient. The selected technique should reflect the individual anesthesiologist's expertise, as well as the capacity for its safe application in each practice setting.

EVIDENCE

Potential of Regional Anesthesia for the Orthopedic Trauma Patient

Traditional endpoints used to measure the effect of RA on patients' outcomes include morbidity and mortality and postoperative analgesia. Spinal and epidural anesthesia has been shown to decrease mortality[6,7] and postoperative pulmonary complications[6] in patients with hip fractures. RA also provides better pain control when compared with systemic narcotics in different practice settings.[8-13] Chelly and colleagues[14] found that lumbar plexus blocks reduced morphine requirements and were associated with earlier recovery of unassisted ambulation in patients undergoing open reduction and internal fixation of acetabular fractures. Advantages of regional techniques include providing site-specific analgesia and avoidance of narcotic-induced side effects. These side effects include but are not limited to sedation, nausea and vomiting, itching, and respiratory depression.[15,16] Avoiding systemic sedation in polytrauma patients makes it easier to monitor the mental status of patients with head injuries.[1,17] The possibility of avoiding management of a difficult airway may offer an advantage in some cases based on the individual circumstances of each case. RA may also decrease intraoperative blood loss,[18] decrease the incidence of deep venous thrombosis,[19] and increase range of motion for the injured extremity, which may lead to a better functional outcome.[20,21] Whether RA decreases the incidence of postoperative cognitive dysfunction is questionable. Some studies support this hypothesis[22] and others do not.[23]

Patient-centered outcomes (e.g., patient satisfaction, quality of recovery, and health-related quality of life) are also improved with the use of RA when compared with general anesthesia.[24] RA can reduce the length of stay in the postanesthesia care unit and the hospital length of stay.[25,26] This is especially important in patients with isolated extremity injuries who can have surgery performed as an outpatient or with a short hospital stay. Trauma patients admitted to the intensive care unit can also benefit from RA in terms of reduced pain scores, increased

comfort, and decreased length of stay in the intensive care unit.[27,28]

The use of RA on the battlefield in recent military conflicts facilitated transport of soldiers from the hospital field with extensive trauma to the extremities.[5,29] This work suggests that the use of RA as an early intervention reduces pain and injury-related complications. In addition to the short-term benefits of acute pain control, early treatment of injuries to the extremities has potential long-term benefits including reduction in the incidence and severity of chronic pain sequelae such as chronic regional pain syndrome and posttraumatic stress disorder.[4,5] Despite these known benefits, RA techniques have been underused in trauma patients, especially during the early phase of injury.[30] One study reports that up to 36% of patients with acute hip fractures in the emergency department received no analgesia and even fewer patients were considered for regional nerve blocks.[31,32] The perioperative use of RA for orthopedic trauma is no exception. Side effects and the potential risk for complications after RA are often cited as reasons to avoid regional techniques.[17]

There are numerous studies that have been unable to show a benefit of RA in orthopedic trauma patients. One study concluded that epidural analgesia was not associated with reducing narcotic requirements or hospital lengths of stay after repair of a posterior wall fracture of the acetabulum.[33] Patients who received popliteal blocks for open reduction and fixation of ankle fractures experienced a significant increase in pain between 12 and 24 hours when compared with their counterparts who received general anesthesia alone.[34] Koval et al[35] followed up 641 hip fracture patients and found that the anesthetic technique (general versus regional) was not associated with improvement in functional recovery at 3, 6, and 12 months after surgery, respectively. Foss and colleagues[36] found that superior analgesia with epidural analgesia after hip fracture surgery did not translate into enhanced rehabilitation.

Risk of Regional Anesthesia

Deep venous thrombosis prophylaxis is often used in trauma patients.[37,38] This practice often complicates the decision to use RA, especially a neuraxial technique. The major concern is the development of spinal or epidural hematoma in this setting.[39] Patients receiving postoperative epidurals for lower extremity surgery must be followed up closely for the development of ACS. Patients undergoing tibial fracture fixation who received a postoperative epidural were four times as likely to develop neurologic complications or missed compartment syndrome compared with those receiving only narcotics. Epidural analgesia increases local blood flow secondary to sympathetic blockade and can lead to increased swelling of an injured limb. The concern about masking or delaying the diagnosis of ACS is often cited as a reason to avoid RA in the setting of orthopedic trauma.[40]

ACS commonly develops in traumatized patients with distracting or neurologically inhibiting injuries. Physicians must have a high degree of suspicion when treating these patients. Time to diagnosis is the most important prognostic factor in these patients. Insufficient understanding of the natural history and limited evaluation of signs and symptoms primarily account for delays in diagnosis. Risk factors for development of ACS include male gender, age younger than 35 years, and tibial shaft fractures.[41]

ACS is a result of two factors occurring in isolation or simultaneously: an increase in the contents of an enclosed space (e.g., bleeding) and/or a decrease in the volume of the space (e.g., tight cast). Compartment syndrome occurs when the interstitial pressure within the compartment exceeds the perfusion pressure at the level of the capillary beds. Elevated intracompartmental pressure (ICP) leads to increased pressure at the venous end of the capillary beds, causing increased hydrostatic pressure and a further increase in ICP, eventually leading to arteriolar compression. Loss of the perfusion pressure gradient results in the onset of ischemia and, ultimately, cellular anoxia and death.[42]

Clinical Diagnosis

Compartment syndrome is, for the most part, a clinical diagnosis. It is a diagnosis made over time, assessing the evolution of signs and symptoms, rather than a diagnosis made in isolation.[43] Serial examinations should always be performed, preferably, by the same experienced examiner. The classic *P*s described in compartment syndrome are pain, paresthesia, paralysis/paresis, pulselessness, and pallor.[44] Although all have a role in the diagnosis of compartment syndrome, the constellation of signs and symptoms and overall clinical picture is more important than the presence or absence of any particular finding. Overall, the absence of symptoms is more useful in excluding ACS than the presence of symptoms is for diagnosing ACS.

Compartment Pressure Monitoring

ICP monitoring is a controversial component in evaluating the patient with suspected ACS. Normal resting ICP is around 8 mm Hg in adults and slightly higher (13 to 16 mm Hg) in children.[45] A number of different techniques have been described for ICP monitoring including "the slit catheter," the side portal needle (Stryker needle), and a regular 18-gauge needle with a setup similar to an arterial line. When techniques were compared, no significant difference was found between compartment pressures measured by slit catheters and side portal needles. Compartment pressures also vary by location, both within normal compartments and in relation to an injury.

AREAS OF CONTROVERSY

The major area of concern is whether delaying or masking the diagnosis of ACS precludes the use of RA. Should it be used, provided certain conditions are met and certain guidelines are followed? Specifically, does RA by itself mask or delay the pain associated with ACS, or is it the dosage of RA or of any modality of analgesia that is implicated? Finally, how much postoperative pain

should trigger clinical suspicion for the diagnosis of ACS, and is this pain different in nature from acute postoperative pain?

The debate about whether RA delays the diagnosis of ACS in the setting of orthopedic trauma is old. It will continue as long as we do not have class I or II evidence that would support or refute either side of the debate. ACS is a rare event that, unfortunately, does not lend itself to randomized clinical trials to define whether it is associated with the use of regional techniques.

Epidural Analgesia

In 2008 Mar and colleagues[46] published a comprehensive review of the reports of ACS associated with postoperative analgesia (i.e., epidural/spinal, peripheral nerve blocks, and intravenous patient-controlled analgesia [IV-PCA]) after orthopedic and nonorthopedic surgery. A total of 28 case reports and case series referred to the influence of analgesic technique on the diagnosis of ACS, of which 23 discussed epidural analgesia. Some of the cases described gluteal ACS related to a prolonged lithotomy position in urologic surgery.[47,48] In 32 of 35 patients, classic signs and symptoms of ACS were present while the epidural infusion was still running. However, the significance was not recognized until the epidural infusion had been stopped. A delay occurred in the diagnosis in three cases.[47,49,50] All three had dense motor blocks. The conclusion of the authors was that "there is no convincing evidence that patient-controlled analgesia opioids or regional analgesia delay the diagnosis of compartment syndrome provided patients are adequately monitored."[46] Johnson and Chalkiadis[51] reviewed pediatric and adolescent cases of ACS associated with epidural analgesia. They identified warning signs that should trigger clinical suspicion for the diagnosis, including increased analgesic requirements, pain remote from the surgical site, paresthesia, pain on passive movement of the extremity involved, swelling, and decreased perfusion of the painful site. The authors suggested a clinical pathway for management of patients at high risk for the development of ACS. Table 56-1 summarizes the case reports associated with epidural analgesia in the setting of orthopedic surgery.

TABLE 56-1 **Summary of Case Reports Associated with Epidural Analgesia in the Setting of Orthopedic Surgery**

Report	Patient Demographics	Procedure	Local Anesthetic Used	Presentation
Hailer and colleagues[70]	43-yr-old female	TKA	Ropivacaine and sufentanil (no dose details)	Paraesthesia, swelling, pain, increased analgesic requirements
Kumar and colleagues[71]	46-yr-old female	TKA	NS	Increased pressure, swelling, pain once epidural removed
	71-yr-old male	THA	NS	Pain 16 hr after epidural removed. Tense, firm, tender, swollen buttock
	55-yr-old male	Hip resurfacing arthroplasty	NS	Pain 4 hr after epidural removed
	72-yr-old male	TKA	NS	Foot drop, paralysis, buttock swelling
Haggis and colleagues[72]	69-yr-old female	TKA revision	NS	No pain. Tight, swollen calf
	53-yr-old male	TKA	NS	Pain, cold, pulselessness, swelling
	48-yr-old female	TKA	NS	Swelling, foot drop
	49-yr-old female	Bilateral TKA	NS	Pain, foot drop
	61-yr-old male	TKA	NS	Pain, paralysis, paraesthesia, tight swollen calf
Bezwada and colleagues[73]	60-yr-old male	Bilateral TKA	Bupivacaine and fentanyl (no dose details)	Weakness, paralysis, swelling, numbness
Somayaji and colleagues[50]	39-yr-old male	THA	Bupivacaine 0.125% and fentanyl	Pain after epidural stopped; paralysis, paraesthesia
Pacheco and colleagues[74]	47-yr-old male	TKA	NS	Back pain once epidural stopped, then buttock pain
	71-yr-old male	TKA	NS	Foot drop, paraesthesia once epidural stopped
Tang and Chiu[49]	62-yr-old female	TKA	Bupivacaine 0.125%	Decreased capillary return (POD 2), no pain, calf swelling
Dunwoody and colleagues[75]	14-yr-old male	Triple osteotomy, left hip	Bupivacaine 0.1% and fentanyl	Pain, worse pain on movement
	7-yr-old male	Ilazarov frame to the left femur	Bupivacaine 0.25% and fentanyl	Decreased pulse, calf spasm

TABLE 56-1 **Summary of Case Reports Associated with Epidural Analgesia in the Setting of Orthopedic Surgery** (Continued)

Report	Patient Demographics	Procedure	Local Anesthetic Used	Presentation
Kontrobarsky and Love[47]	70-yr-old male	Ankle fusion	Bupivacaine 0.125%	Buttock pain
Nicholl and colleagues[76]	65-yr-old male	THA revision	Morphine	Pain, pain with passive stretch, swelling, tenderness
Price and colleagues[77]	16-yr-old male	Distal femur and proximal tibial osteotomy	Fentanyl	Discomfort, numbness, and increased pressure
Seybold and Busconi[78]	18-yr-old male	Scapular fasciocutaneous-free flap graft	NS	Swelling, rigid compartment; pain after epidural was stopped
Morrow and colleagues[79]	18-yr-old male	Bilateral femoral IM nail	Bupivacaine 0.2% and fentanyl	Unilateral paresis and anesthesia
Strecker and colleagues[80]	45-yr-old male	Free fibular flap	Bupivacaine 0.125% at 10 mL/hr	Pain after the epidural was stopped on POD 1. Pain, swelling of the donor site, and dysesthesia on the planter surface of the foot
Ross[81]	6-yr-old female	External fixation midshaft tibia	15 mL bupivacaine; 0.25% of caudal epidural	Pain 7 hr postoperative; nonresponsive IV opioids
Llewellyn and Moriarty[82]	NS	Tibial osteotomy	NS	Audit concluded that occurrence of compartment syndrome does not appear to be masked by the presence of working epidural
Whitesides[63]*	15-yr-old male	Proximal tibial osteotomy	NS	NS; however, the patient developed ACS on one side
	23-yr-old male	Repair of ligamentous injury of the knee and closed reduction of spiral fracture of the tibia and fibula	NS	NS; however, the patient developed ACS

ACS, acute compartment syndrome; *IM,* intramedullary; *IV,* intravenous; *NS,* not specified; *POD,* postoperative day; *THA,* total hip arthroplasty; *TKA,* total knee arthroplasty.
*This review also reports three more cases of ACS in the context of IV and oral opioids.

Peripheral Nerve Blocks

Table 56-2 summarizes the case reports of ACS in orthopedic surgery associated with peripheral nerve blocks. Similar to epidural analgesia, peripheral nerve blocks are a cause of concern in patients at risk of ACS because of the possibility that they may mask pain, which orthopedic surgeons consider the hallmark for diagnosis of ACS. Currently, five cases in the literature cite the use of peripheral nerve block in the context of development of ACS. Three of the cases[52-54] describe ACS with single-shot nerve blocks, and two cases reports feature ACS in the context of a continuous nerve catheter.[55,56] In all five case reports, ACS was suspected on the basis of significant pain, despite the presence of a nerve block. However, it is possible that the increase in pain was concurrent with fading of the strength of the initial single-shot block. Patients still were seen with breakthrough pain, even when a higher concentration of local anesthetic (0.75% of ropivacaine) was used.[53] In one case,[52] the distribution of pain and the final diagnosis did not match the sensory distribution of the peripheral nerve block. However, the authors concluded that the nerve block masked the pain and delayed the diagnosis. Cometa and colleagues[56] went further to explain the mechanism of activation of the ischemic pain pathway and postulated that hydrogen ion activation resulting from ischemic injury in the muscle and the resulting acidosis, which is the case with ACS, produces nonadapting activation of the pain receptors.[57,58] In contrast, the inflammatory markers associated with tissue injury and trauma undergo tachyphylaxis after activation of the nociceptor.[57] This theory would explain why patients with evolving ACS would still be seen with breakthrough pain even if they had received a nerve block. A local anesthetic used in concentrations low enough to provide postoperative analgesia may aid the diagnosis of ACS, provided that there is vigilance in monitoring and a high index of suspicion for not only the development of pain out of proportion to the surgical pain but also any other symptoms suggestive of the development of ACS.

Intravenous Analgesia and Compartment Syndrome

The use of IV analgesia is not a safeguard against a timely diagnosis of ACS. IV-PCA has been implicated as a cause of delay in diagnosis of ACS in two case reports[59,60] and

TABLE 56-2 **Summary of Case Reports of Acute Compartment Syndrome in Orthopedic Surgery Associated with Peripheral Nerve Blocks**

Report	Patient Demographics	Surgical Procedure	Type of Block	Local Anesthetic Used	Presentation
Hyder and colleagues[52]	28-yr-old male	Intramedullary nail of the tibia	Three in one	Bupivacaine 0.5%	Patient seen with pain in leg; diagnosed with anterior tibial compartment syndrome 48 hr later
Noorpuri and colleagues[54]	30-yr-old female	Revision arthroplasty of the forefoot	Ankle block	30 mL of 0.25% bupivacaine	Patient seen with pain unresponsive to oral analgesic 12 hr after surgery
Uzel and colleagues[53]	26-yr-old male	Intramedullary nail of a femur	Femoral block	Ropivacaine 0.75%	Patient complained of pain in the anterior thigh 4 hr after surgery
Cometa and colleagues[56]	15-yr-old male	Distal femoral and proximal tibial osteotomy	Continuous sciatic and femoral nerve blocks	Ropivacaine 0.2%	Severe lower extremity pain after catheter infusions turned off to transition to oral analgesics on postoperative day 2; pain on dorsiflexion of the foot and tenderness of the calf muscle
Walker and colleagues[55]	19-yr-old female	Left calcaneal lengthening osteotomy and percutaneous Achilles tendon lengthening	Popliteal nerve catheter and single-shot saphenous nerve block	Bupivacaine 0.5% for the initial block, then running the catheter at 8 mL/hr of bupivacaine 0.2%	Patient complained of pain and tightness in lower leg that prompted emergency department visit and loosening of the cast

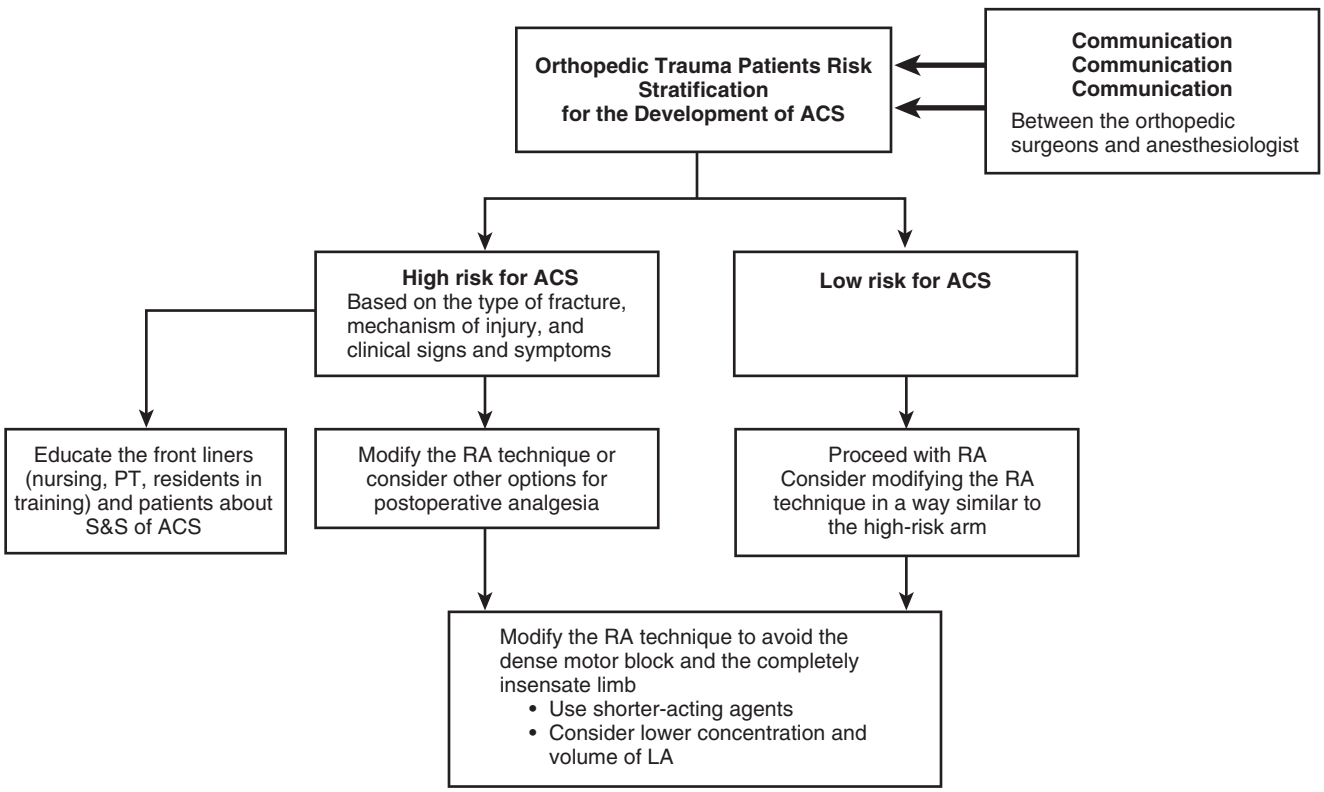

FIGURE 56-1 ■ Clinical Pathway/Protocol for Using Regional Anesthesia in Acute Perioperative Pain Management of Orthopedic Trauma Patients. *ACS,* acute compartment syndrome; *LA,* local anesthetic; *PT,* physical therapists; *RA,* regional anesthesia; *S&S,* signs and symptoms.

in one case series[61] of four patients with tibial fractures. Patients in the case series had PCA doses of 0.5 to 1 mg/hr morphine. Even with this relatively small dose, patients did not have severe pain. Pain may also not be present in about 10% of ACS patients. Therefore its absence does not exclude the diagnosis.[45,62] These case reports cast some doubt on the sensitivity of pain as a marker for the diagnosis of ACS. Some authors preferred using intermittent nurse-administered boluses of narcotics over IV-PCA because this strategy may facilitate more frequent contact between patients and nurses.[59,60] Others have gone even further to wonder whether pain is a friend or a foe.[63] Most practitioners would agree that withholding pain medication would be inhumane.[64] However, to achieve a balance between patient comfort and safety we should have a high index of suspicion for the diagnosis of ACS in orthopedic trauma patients, irrespective of the modality of postoperative analgesia.

GUIDELINES

The American Society of Anesthesiologists Practice Guidelines for Acute Pain Management[65] in the Perioperative Setting can be applied to orthopedic trauma. The guidelines emphasize the role of the anesthesiologist in providing perioperative analgesia within the framework of an acute pain service and their role in developing standardized institutional policies and procedures. The guidelines also emphasize the value of the use of multimodal pain therapy whenever possible.

The Eastern Association for Surgery and Trauma (EAST) developed practice management guidelines for prevention of venous thromboembolism in trauma patients.[66] The EAST guidelines support the use of low-molecular-weight heparin over low-dose heparin for venous thromboembolism prophylaxis in moderate- to high-risk trauma patients. This practice may have an implication for the choice of RA technique in the setting of orthopedic trauma. Plexus and peripheral nerve blocks seem to be a safer approach when compared with neuroaxial techniques because of the concern about development of spinal and epidural hematomas. The American Society of Regional Anesthesia and Pain Medicine practice guidelines address the risk of RA in patients receiving antithrombotic or thrombolytic therapy.[39] The details of these recommendations are beyond the scope of this chapter.

AUTHORS' RECOMMENDATIONS

Clinical Pathway/Protocol for the Management of Orthopedic Trauma Patients

To optimize the benefits of regional anesthesia (RA) in the setting of orthopedic trauma and minimize the potential for masking or delaying the diagnosis of acute compartment syndrome (ACS), anesthesiologists and orthopedic surgeons should reach a consensus on local guidelines for management of orthopedic trauma patients (Figure 56-1). These guidelines should consider the available resources at each individual institution and the level of expertise of the physicians and nursing staff.

- Clinical criteria should be established to stratify orthopedic trauma patients on the basis of their risk for development of ACS. These criteria should consider the compartment involved in the fracture (e.g., leg, arm, thigh, or hand), mechanism of injury, and clinical signs and symptoms. These criteria should be established based on the experience of the orthopedic surgeons and the resources available in each institution. The importance of communication between different disciplines cannot be emphasized enough. Even with these criteria in place, clear communication between the anesthesiologist and the orthopedic surgeon is still recommended to establish an individualized plan for perioperative pain management, regardless of whether it involves RA.
- If RA is to be used in patients at risk, the regional technique has to be modified.
  - If RA will be used as a single-shot anesthetic, agents whose duration of action does not extend much past the operative period should be chosen. A multimodal regimen should be introduced early so that the transition from the block to no-block state is smooth.
  - If RA is used mainly for postoperative analgesia, continuous peripheral nerve blockade may be a better option because anesthesiologists have the capacity to titrate the dose of local anesthetic (volume and concentration) to patient comfort and density of the block. A lower basal rate of a low-concentration local anesthetic can be used with intermittent on-demand patient boluses.

This strategy may result in less local anesthetic consumption and a lower incidence of motor block.[67] This strategy also highlights the importance of patient education about signs and symptoms of ACS and the adverse effect of a dense motor block.

- Evidence-based protocols should be designed and implemented for multimodal analgesia for perioperative management of orthopedic trauma patients.[65,68] Multimodal therapy includes a wide range of procedures and medications, including regional analgesia, judicious use of opioids, acetaminophen, antiinflammatory agents, anticonvulsants, *N*-methyl D-aspartate receptor antagonist (ketamine), gabapentinoids, antidepressants, and anxiolytics, as options to treat or modulate pain at various receptor sites.[69]
- Education of the personnel in direct contact with the patients (e.g., nursing staff, physical therapists, and physicians in training) about signs and symptoms of ACS should be undertaken. Patients should be also educated about signs and symptoms of ACS and the effect of different modalities of analgesia on the diagnosis.

Application to the Local Environment

- Anesthesiologists and orthopedic surgeons in each institution should reach an agreement and establish their own guidelines that will fit their own environment, manpower, and resources. Education and communication are key components to the success of any collaborative effort in this regard.

Continued on following page

AUTHORS' RECOMMENDATIONS (Continued)

- The lack of classes I and II evidence that RA can mask or delay the diagnosis of ACS does not simply mean that RA is entirely safe to use in orthopedic trauma settings without caution.
- Criteria should be established to identify patients at high risk for development of ACS. Physicians involved in the care of patients at risk should have a high index of suspicion for the diagnosis of ACS.
- The "all or none" approach should not be taken when it comes to the practice of RA in the orthopedic trauma setting. RA techniques can be modified to avoid the dense motor blocks and the completely insensate extremity.
- The balance between patient safety and patient comfort and satisfaction should be found. Regardless of the modality of analgesia, any pain out of proportion to the degree of injury or any new-onset symptoms should trigger a careful clinical assessment.
- A robust "acute pain service" is a key resource in the orthopedic trauma setting for making adjustments to doses, concentration, and volume of local anesthetic in continuous perineural catheters and for making recommendations for effective pain management strategies.
- Multimodal analgesia is increasingly recognized as one of the better options for pain management in orthopedic trauma. An excess of one modality (regardless of this modality, systemic narcotics, or regional techniques) seems to be implicated in most of the case reports associated with adverse outcomes in the literature.
- Education of those on the front lines (e.g., nursing staff, physical therapists, and physicians in training) about signs and symptoms of ACS should be undertaken.

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CHAPTER 57

What Is the Best Method of Diagnosing Perioperative Myocardial Infarction?

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INTRODUCTION

Perioperative myocardial infarction (PMI) is a leading cause of postoperative morbidity and mortality in patients undergoing noncardiac surgery.[1] Although it appears that its incidence and associated mortality rate have declined substantially over the past 10 to 15 years, likely due to improvements in preoperative risk stratification, perioperative management, and prophylaxis (e.g., beta-blockers and other sympatholytic strategies), in aggregate it remains a costly and largely preventable complication. Prior reviews have estimated associated costs in the billions of dollars from resources consumed and adverse outcomes.[2] However, these estimates are poorly supported by hard data, and as of yet, no definitive large-scale prospective economic analyses have been reported.

OPTIONS/THERAPIES

A variety of diagnostic approaches are available for detecting myocardial infarction (MI). The strengths and limitations of the most commonly used modalities are presented in Table 57-1. Older enzymes previously used to detect MI, including total creatine kinase (CK) (without MB fractionation), lactate dehydrogenase isoenzymes, and glutamic-oxaloacetic transaminase, are no longer recommended for clinical use because of their poor specificity.

EVIDENCE

Studies dating back to the 1950s have reported that PMIs tended to occur with a peak incidence several days after surgery (postoperative days 2 and 3). Half were of the Q wave variety, and the remainder were non-Q wave; they rarely caused classic chest pain (although other associated cardiac signs, such as pulmonary edema, reduction in cardiac output, new ventricular dysrhythmias were common); and the associated mortality rate was high, averaging 50%. Patients undergoing vascular surgery or those with prior MI were at highest risk with incidences exceeding 5% and in some subgroups (e.g., high-risk vascular surgery) up to 20%. Patients sustaining PMI have been shown to have a substantially elevated long-term cardiovascular mortality rate over the first 1 to 2 years after surgery.[3,4] More recent reports, in general, have reported lower rates of PMI, and a temporal shift in the peak incidence has been seen earlier, closer to the first postoperative day, or, in some studies, on the night of surgery.[5-7] A distinct predominance of non-Q-wave MIs are reported, and the associated short-term mortality rate is appreciably lower, although long-term mortality and morbidity rates remain higher than in the non-MI population.[8]

In the mid to late 1990s, a major shift occurred in the classic paradigms for diagnosing infarction.[9,10] The rise to prominence of the troponins (cardiac structural protein markers with high sensitivity and of particular interest perioperatively) with nearly 100% specificity has radically changed cardiology practices and the epidemiologic implications of this diagnosis. Much of this is based primarily on clinical studies in patients with acute coronary syndromes (ACSs), where the need for rapid decision making regarding thrombolysis and revascularization strategies is critical. Several large studies of ACS patients support the clinical efficacy of troponin over the previous gold standard, the less specific cytoplasmic enzyme CK (and its MB fraction). Older studies used CK-MB elevations (determined by a mass assay that supplanted older activity-based assays) usually exceeding 5% of the total as diagnostic of MI when accompanied by at least one of the two following signs or symptoms: associated chest pain or electrocardiogram (ECG) changes (Q-wave or ST-T changes) as defined by the World Health Organization (WHO).[11] These WHO criteria have been used in epidemiologic studies evaluating temporal patterns in coronary artery disease (CAD), and, as such, altering them has substantial implications.[12] Perioperatively, it has long been appreciated that the low specificity of total CK mass (due to muscle injury) and even the CK-MB fraction (due to gene expression in injured muscle), a lack of classic chest pain (attributed in part to analgesic use, although not completely explained),[13] and problems with ECG diagnosis (including sensitivity/specificity issues due to high resting sympathetic tone, changes in electrolyte and acid–base status, and patients with abnormal resting baseline ECGs) greatly complicated coding of MI using standard criteria.[14] Despite these difficulties, it is important to understand that nearly all the well-accepted

TABLE 57-1 **Strengths and Limitations of Modalities for Detecting Perioperative Myocardial Infarction**

	Strengths	Limitations	Recommendations
ECG	New Q waves, "tombstone" ST-segment elevation, horizontal or downsloping ST-segment depression, hyperacute T waves, deep symmetric T-wave inversion, involvement of multiple contiguous leads	Narrow septal or inferior Q waves, LVH, LBBB, repolarization-type ST-segment abnormalities, upsloping ST-segment depression, baseline ST-segment abnormalities, diffuse T-wave flattening, asymmetric T-wave inversion	At time of suspected event, for several days during clinical resolution, with suspected reinfarction
Biochemical Markers			
CK-MB	Characteristic rise and fall, shorter time course than troponins, CK/CK-MB ratio > 5%, AUC time activity curve related to infarct size	Non–CAD-related cardiac and other noncardiac pathology, sustained elevation, gene expression in injured skeletal muscle, renal failure	Helpful in detecting recurrent infarction with serial sampling
Troponin I	Later peak, more sustained duration, prognostic significance of low-level elevation	Non–CAD-related cardiac pathology, long duration of elevation, lack of a baseline measurement, multiple assays in use, variable detection limits	All patients with suspected PMI
Troponin T	Same as troponin I, only one assay in use, well-standardized detection limits	Release with nonischemic cardiac pathology, long duration of elevation, lack of a baseline measurement, low-level chronic elevation in ESRD	All patients with suspected PMI, troponin I preferable for patients with ESRD
Imaging Modalities			
TTE	New or worsening of baseline SWMA, akinesia, dyskinesia, reduction in ejection fraction, ischemic mitral regurgitation, change from prior TTE	Small Q-wave MI, non-Q-wave MI, prior MI with baseline SWMAs, reversible ischemia, stunning, hibernating myocardium	All patients with suspected PMI; document size of MI, impact on ventricular function
Perfusion imaging	Quantitative analysis, changes in flow	Prior MI, reversible ischemia, stunning, hibernating myocardium, technical/anatomic artifacts	Expensive, not recommended except possibly in patients with poor TTE imaging

AUC, area under the curve; *CAD,* coronary artery disease; *CK-MB,* creatine kinase MB fraction; *ECG,* electrocardiogram; *ESRD,* end-stage renal disease; *LBBB,* left bundle branch block; *LVH,* left ventricular hypertrophy; *MI,* myocardial infarction; *PMI,* perioperative myocardial infarction; *SWMA,* segmental wall motion abnormality; *TTE,* transthoracic echocardiography.

studies of clinical risk stratification are based, at least in part, on the diagnosis of PMI using adaptations of WHO critieria.[15]

In late fall 2007, shortly after the official release of the updated 2007 American Heart Association/American College of Cardiology (AHA/ACC) perioperative guidelines, the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation (ESC/ACCF/AHA/WHF) Task Force for the Redefinition of Myocardial Infarction released its extensive document providing a long-awaited "universal definition of myocardial infarction."[16] This task force essentially updated a widely cited and influential prior report that evaluated the changing diagnosis of MI given the rapidly expanding use of troponins in the late 1990s.[17] The earlier report outlined recommendations for two specific categories: (1) acute, evolving, or recent MI and (2) established MI (Box 57-1), specifically incorporating use of either troponin I (TnI) or troponin T (TnT), criteria that have in some instances dramatically increased sensitivity in the diagnosis of MI in ACS patients while appearing to maintain specificity. The updated ACC/AHA Guidelines for the Management of Patients with Unstable Angina/Non-ST Elevation Myocardial Infarction used these criteria, defining *necrosis* as elevation of troponin above the 99th percentile of normal and *infarction* as the latter along with a clinical finding such as ischemic ST- and T-wave changes, new left bundle branch block, new Q waves, percutaneous coronary intervention (PCI)–related marker elevation, or imaging showing a new loss of myocardium.[18] Although these guidelines state that CK-MB and myoglobin may be useful for diagnosis of early infarct extension or periprocedural MI, it is likely that introduction of more sensitive TnI assays now commercially available will eventually supplant this recommendation.[19] A major change in the new ESC universal guidelines is adoption of a clinical classification system for different types of MI into five major types: type 1, spontaneous MI related to ischemia due to a primary coronary event; type 2, MI secondary to ischemia due to increased demand or decreased supply; type 3, sudden cardiac death; type 4a, MI associated with PCI; type 4b, MI associated with

BOX 57-1 Universal Definition of Myocardial Infarction (MI)

Criteria for Acute MI (One of the Following):

1. Rise and/or fall of cardiac biomarkers (troponin is preferred) with at least one value above the 99th percentile of the URL with at least one of the following:
   a. Ischemic symptoms
   b. Development of pathologic Q waves
   c. ECG changes indicative of ischemia (ST-T changes or new LBBB)
   d. Imaging evidence of loss of viable myocardium (includes echo regional wall motion change)
2. Sudden death or cardiac arrest with symptoms suggestive of ischemia accompanied by new ECG changes, evidence of thrombus at angiography or autopsy (in the situation when death occurred before blood sampling)
3. For PCI: biomarker elevation three times the 99th percentile URL
4. For CABG: biomarker elevation five times the 99th percentile URL plus new Q waves or LBBB or angiographic evidence of graft or native vessel occlusion or imaging loss of viable myocardium
5. Pathologic findings of acute MI

Criteria for Prior MI (One of the Following):

1. Development of new pathologic Q waves
2. Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract
3. Pathologic findings of a healed or healing myocardial infarction

CABG, coronary bypass graft surgery, *ECG*, electrocardiogram; *LBBB*, left bundle branch block; *PCI*, percutaneous coronary intervention; *URL*, upper reference limit.

Adapted from Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Eur Heart J 2007;28(20):2525–38.

coronary stent thrombosis; and type 5, MI associated with coronary artery bypass graft (CABG).[16] The new definitions for diagnosis are presented in Box 57-1.

Despite the initial enthusiasm resulting from the widespread availability of TnI, it was rapidly appreciated by clinicians and laboratory managers alike that there was substantial variability in the levels of detection and variability of measurement (coefficient of variation) between different vendors. This has prompted substantial ongoing efforts toward standardization.[20,21] In 2007, the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction and the National Academy of Clinical Biochemistry recommended that a TnI elevation greater than the 99th percentile of a normal reference range in the first 24 hours after the clinical event define cardiac injury; this included a coefficient of variation (CV) of 10% or less for the individual assay used.[16,22] In addition, a rise or fall of the TnI level confirms acute cardiac injury because multiple chronic conditions may have an elevated TnI. Newer "high-sensitivity" TnI assays have dramatically lowered the limits of detection and thus lowered diagnostic levels.[23-25] The clinical implications of these high-sensitivity assays include earlier detection and intervention[24] but also include the risk of lower specificity with a higher false-positive rate. More recently, in 2010 the Biochemistry Subcommittee of the Joint ESC/ACCF/AHA/WHF Task Force recommended that the 99th percentile of a normal reference range be adopted for assays regardless of whether the CV is less than 10%.[26] This change dramatically lowered the threshold for TnI diagnostic levels, therefore potentially increasing the number of patients receiving a diagnosis of MI.[27] It is not clear that the patients now included with this lower threshold will benefit from improved outcomes based on interventions or management changes because prospective studies are lacking.[28] Because troponin T is only available from one vendor, variability is not an issue.

Contemporary studies evaluating the efficacy of the troponins and CK-MB in detection of PMI are presented in Table 57-2.[5,8,9,29-39] In general, they note a higher specificity of the troponins over CK-MB (although conclusive demonstration of significant differences in sensitivity for MI are limited) and an apparent correlation of troponin leakage with either short- or intermediate-term outcomes (although not conclusively in all studies). The low outcome rates of most of the single-center studies limit statistical power; thus the positive predictive values of most markers studied is very limited.

The largest study was published by Devereaux and colleagues[39] and included 15,133 patients undergoing noncardiac surgery. Eligible patients had noncardiac surgery that required hospital admission and were 45 years of age or older. A TnT assay was performed 6 to 12 hours after surgery and on postoperative days 1, 2, and 3, respectively. The authors reported that a peak TnT level of 0.02, 0.03 to 0.29, and 0.3 ng/m/L or greater correlated with a 30-day mortality incidence of 4%, 9.3%, and 16.9%, respectively. In addition, higher peak TnT levels were associated with a shorter median time to death. This study is relevant in demonstrating the utility of the TnT assay as a risk classification tool, but further study is necessary to determine whether this risk is modifiable.

Evidence is accumulating that other biochemical markers may further enhance sensitivity for MI or improve risk stratification in patients with ACS. In particular, both C-reactive protein (CRP) (a marker of inflammation that is increasingly appreciated as the primary acute physiologic process leading to plaque rupture and thrombosis) and brain natriuretic peptide (BNP) (i.e., BNP or N-terminal probrain natriuretic peptide (NT-proBNP), a sensitive but nonspecific response to left ventricular pressure or volume overload caused by severe ischemia or heart failure, are of intense interest in the ACS arena. Perioperatively, it is likely that CRP is of very limited value given its frequent elevation in surgical conditions. Several publications have purported strong value for BNP in risk stratification for short- and long-term adverse outcomes in vascular and other major noncardiac surgery based on either isolated preoperative or postoperative measurements.[40-43] Several recent meta-analyses have been performed in an attempt to assess the utility of BNP as an independent prognostic marker for adverse cardiac events and

TABLE 57-2 **Contemporary Studies Evaluating Biochemical Markers of Perioperative Myocardial Infarction**

Reference	Cohort	Variables	Gold Standard	Perioperative Findings	Mortality/ Long-Term	Comments
Adams[9] (1994)	108 patients, vascular or spine surgery	ECG, total CK, CK-MB, cTnI	New akinesia or dyskinesia on postoperative TTE	Eight patients MI; sensitivity: cTnI 100% versus CK-MB 75%; specificity: cTnI 99% versus CK-MB 81%; CK-MB/total CK > 2.5: sensitivity 63%	Three deaths, all with elevated cTnI; perioperative FU only	First major study to evaluate perioperative use of cTnI
Lee[29] (1996)	1175 NCS patients age >50	ECG; total CK, CK-MB, cTnT	CK, CK-MB, and ECG changes	17 patients MI; cTnT (>0.1 ng/mL); sensitivity: 87%; specificity: 84%; ROC analysis for MI: no difference CK-MB versus cTnT; ROC analysis for complications: cTnT superior	One sudden death with no elevation of either marker; perioperative FU only	cTnT very low PPV, 90% of patients with elevations without complications
Lopez-Jimenez[30] (1997)	772 NCS patients, age >50	Same as Lee (1996)	Same as Lee (1996); cTnT >0.1 ng/mL postoperatively as risk factor for long-term outcome	12% of cohort had cTnT elevation postoperatively; higher rates of postoperative CHF and new arrhythmias	2.5% had cardiac outcomes by 6 mo; PPV, 9%; RR, 5.4; CK-MB not correlated with outcome	cTnT independent predictor of 6-mo cardiac outcomes
Metzler[31] (1997)	67 patients, known CAD or risk factors, vascular and other NCS	ECG, cTnT, CK-MB, cTnI for patients with elevated cTnT	CK-MB >12 IU/L and Q waves	13 patients elevated cTnT and cTnI; earlier rise in cTnI; CTnT >0.6 ng/mL; PPV, 87%; NPV, 98%; CK-MB elevated in 14 patients (seven patients discordant)	No perioperative deaths; perioperative FU only	Favor cTnT with cutoff value of 0.6 ng/mL
Badner[5] (1998)	323 NCS patients, age >50, known CAD	ECG, total CK, CK-MB, cTnT	Total CK >174 U/L and 2 of CK-MB >5%, new Q waves, cTnI >0.2 mcg/L, (+) pyrophosphate scan	18 patients with MI, 14 on POD 0-1, use of cTnT alone would double MIs	1-yr FU: two of 15 MI patients death or unstable angina	cTnT not used in first 92 patients, lower rate of long-term complications than other studies
Neill[32] (2000)	80 vascular or orthopedic patients	Ambulatory ST monitoring, CK-MB, cTnI, cTnT	CK-MB >5 mcg/L and troponins >1 mcg/L, ECG changes	cTnT and I specificity for major complications 96%/97%, sensitivity 29%/43%	3-mo FU: cTnT best correlated with complications	No correlation of serum markers with ST-segment ischemia
Godet[33] (2000)	329 vascular patients	cTnI	ST depression > 2 days or new Q wave or cTnI > 1.5 ng/mL	13 patients with cardiac complications; peak cTnI POD 1; 27 patients cTnI > 1.5 ng/mL; cTnI > 0.54 ng/mL; sensitivity, 75%; specificity, 89%	1-yr FU; nine patients (3%) with cardiac complications	1-yr FU: no correlation with cTnI

Continued on following page

TABLE 57-2 **Contemporary Studies Evaluating Biochemical Markers of Perioperative Myocardial Infarction** (Continued)

Reference	Cohort	Variables	Gold Standard	Perioperative Findings	Mortality/ Long-Term	Comments
Haggart[34] (2001)	59 vascular patients; 24 emergent	cTnI	WHO criteria	Elective: 10/35 cTnI detected, no CK-MB >5%; emergent: 14/24 cTnI detected, four CK-MB >5%	Perioperative FU only: no deaths elective group; eight deaths emergent group; three cTnI elevated	CK-MB low sensitivity
Jules-Elysee[35] (2001)	85 patients CAD or risk factors, orthopedic surgery	CK-MB, cTnI	cTnI > 3.1 ng/mL and CK-MB index > 3.0	11 patients (+) CK-MB; five of 11 patients (+) cTnI; all others (–)cTnI; all (–) cTnI patients had uneventful course	No deaths; perioperative FU only	cTnI better specificity
Kim[8] (2002)	229 vascular patients	cTnI	WHO criteria	Peak cTnI > 1.5 ng/mL: 12% postoperatively; two of nine ESRD patients (+)cTnI	OR, 5.9 cTnI > 1.5 ng/mL for 6-mo mortality; OR, 27.1 for MI; dose-response relation	Diabetes only preoperative predictor of cTnI elevation
Le Manach[36] (2005)	1316 vascular patients	cTnI	Abnormal cTnI > 0.2-0.5 ng/mL; PMI cTnI > 1.5 ng/mL	Abnormal cTnI (14%), PMI (5%)	Inhospital mortality: early MI, 24%; delayed MI, 21%; abnormal, 7%; normal, 3%	Early MI: increase in cTnI less than 24 hr, delayed MI > 24-hr period of increased cTnI
Domanski[37] (2011)	Meta-analysis including seven studies with 18,908 patients, CABG	cTnI, CK-MB	Enzyme elevation	Abnormal cTnI or CK-MB	Increased CK-MB or troponin ratio after CABG: increased intermediate- and long-term mortality	Enzyme ratio: peak/upper limit of normal
Levy[38] (2011)	Meta-analysis including 14 studies with 3318 patients, NCS	cTnT, cTnI, CK-MB	Enzyme elevation	Abnormal cTnI or cTnT	459 deaths at 1-yr follow-up, increased troponin postoperatively is an independent predictor of mortality	Various troponin thresholds used in studies analyzed
VISION study investigators[39] (2012)	15,133 NCS patients; age >45	cTnT	Peak cTNT ≥ 0.02 ng/mL	11.6% of patients had peak TnT ≥ 0.02 ng/mL	Peak postoperative TnT associated with 30-day mortality	Higher peak cTnT correlated with earlier mortality

CABG, coronary bypass graft surgery, *CAD,* coronary artery disease*; CHF,* congestive heart failure; *CK,* creatine kinase; *CK-MB,* creatine kinase MB fraction; *cTnI*, troponin I; *cTnT*, troponin T; *ECG,* electrocardiogram; *ESRD*, end-stage renal disease; *FU,* follow-up; *IU/L,* International units/liter; *MI,* myocardial infarction; *NCS*, noncardiac surgery; *NPV,* negative predictive value; *OR*, odds ratio; *PMI,* perioperative myocardial infarction; POD, postoperative day; *PPV,* positive predictive value; *ROC*, receiver operator characteristic curve; *RR,* relative risk; *TTE*, transthoracic echocardiography; *WHO*, World Health Organization.

mortality after surgery.[44-47] These meta-analyses found an association between elevated preoperative BNP levels and a variety of adverse outcomes including mortality, cardiovascular events, and major adverse cardiac events. Unfortunately, there is tremendous heterogeneity in the normal BNP range based on the commercially available test used and the surgical population tested.[44-47] In addition, BNP's utility in changing clinical management and improving outcomes based on these changes remains to be studied.

AREAS OF UNCERTAINTY

Given continuing diagnostic advances (especially in biochemical markers), establishing a simple (e.g., binary) definition for PMI capable of rigorous categorization and standardization between centers remains problematic. This complicates uniform reporting of outcomes used for benchmarking of outcomes between hospitals. However, establishing an approximate quantitative index of damage with the use of troponin elevation, ECG changes, NT-proBNP levels, and indices of ventricular function is a reasonable and necessary clinical goal. Comparison of perioperative studies has been difficult because of variable definitions of MI and different time periods for sampling and endpoint detection used. The recent contemporary studies are better designed, although they also suffer from variable or imprecise definitions and lack of a clear gold standard on which to assess predictive values of new markers. The value of perioperative surveillance identifying clinically asymptomatic troponin leakage, which may indicate patients at higher risk of intermediate-term morbidity or mortality, is controversial. It is likely that cost considerations in our increasingly resource-constrained health care systems and confidentiality issues related to insurance companies, with potential adverse patient-level economic impact, will limit such an approach despite its intellectual appeal.

GUIDELINES

The 2007 ACC/AHA Perioperative Guidelines have extensively addressed the issue of PMI and presented recommendations for surveillance strategies in various risk groups (in contrast to the 2002 guidelines in which this was not addressed in detail) (Box 57-2).[14]

BOX 57-2 Recommendations of the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery

Class I

Perioperative troponin measurement is recommended in patients with ECG changes or chest pain typical of acute coronary syndrome. (Level of Evidence: C)

Class IIb

The use of troponin measurement is not well-established in patients who are clinically stable and have undergone vascular and intermediate-risk surgery. (Level of Evidence: C)

Class III

Postoperative troponin measurement is not recommended in asymptomatic stable patients who have undergone low-risk surgery. (Level of Evidence: C)

For patients with high or intermediate clinical risk undergoing high- or intermediate-risk surgical procedures obtaining an ECG at baseline, immediately after surgery, and daily for the first 2 days postoperatively appears to be the most cost-effective strategy.

ACC/AHA, American College of Cardiology/American Heart Association; *ECG*, electrocardiogram.

Adapted from Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al: ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 2007;116:e418–99.

AUTHORS' RECOMMENDATIONS

- The Universal Definition of Myocardial Infarction Guidelines document and other cardiology-based guidelines of the American College of Cardiology/American Heart Association and National Academy of Clinical Biochemistry provide a comprehensive framework for the diagnosis of myocardial infarction. These principles are applicable to the perioperative setting. At this point, troponin I is the most commonly used biomarker and will likely remain so for years to come. Wide variability in 99th percentile limits between manufacturers greatly complicates comparison of absolute values between centers.
- Substantial evidence exists that even low levels of troponin elevation in otherwise clinically asymptomatic patients are associated with higher long-term (6 months to 1 year) cardiac morbidity and mortality rates. Whether this should change our current patterns of perioperative surveillance and the aggressiveness of postoperative cardiac risk stratification is uncertain.
- Supplementing surveillance strategies with either preoperative or postoperative measurement of N-terminal probrain natriuretic peptide in high-risk patients appears to be a promising approach, although its cost-effectiveness has not been validated.

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CHAPTER 58

Does Neurologic Electrophysiologic Monitoring Affect Outcome?

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INTRODUCTION

Neurologic injury from surgery results in substantial increased morbidity, mortality, and cost, and, most important, it is devastating to patients and their families. Thus techniques to lessen, reverse, and even avoid neurologic injury are very valuable. Neurologic intraoperative electrophysiologic monitoring (NIOM) can identify impending or ongoing intraoperative injury, thus allowing for interventions. Changes to a patient's neurologic electrophysiologic baseline values during the procedure alert the operative team that a potential injury may be occurring. The goal of NIOM is to detect dysfunction caused by ischemia, mass effect, stretch, heat, and direct injury in real time before it causes permanent neurologic injury. Monitoring may also be useful in identifying and preserving neurologic structures during a procedure where they are at risk (mapping).

There are several challenges to establishing the efficacy of NIOM. The first is that blind or randomized trials assessing the efficacy of NIOM in humans are lacking. Unfortunately, a substantial trial will likely never examine this issue.[1] The reason behind the lack of high-level evidence is that monitoring is well-established and accepted in clinical practice. Moreover, it is generally extremely low risk to the patient. The general consensus in the surgical community is that monitoring is useful and there would be ethical and medicolegal dilemmas in withholding monitoring in patients who are at potential risk of injury. A second limitation in establishing outcomes for NIOM is that the goal of monitoring is to reverse a significant change if one is seen during a procedure. Thus monitoring may detect an impending injury, which is reversed, but the benefit can never be confirmed because the patient wakes up with a normal examination. The utility of monitoring is based on animal studies and case series with comparisons to historical control subjects. The utility of NIOM may be supported by establishing that monitoring can, in fact, detect injury in cases where injury has occurred (true-positive outcomes), and limiting false-negative outcomes (injury occurred and was not detected) and persistent false-positive outcomes (injury was predicted by NIOM at the end of a procedure but did not occur).[2] Multimodality monitoring is possible, so the ability of different NIOM techniques to predict injury can be compared in the same patient.

THERAPIES

Various portions of the nervous system can be monitored by using several NIOM techniques. The specific neurologic tissues at risk, as well as the type of potential injury, vary with different surgical procedures. Specific techniques include electroencephalographic (EEG) and evoked potentials, including somatosensory evoked potentials (SSEPs), brainstem auditory evoked potentials (BAEPs), visual evoked potentials (VEPs), electromyography (EMG), nerve conduction studies (NCSs), and transcortical electrical motor evoked potentials (TcMEPs).

EEG is a measure of spontaneous electrical brain activity recorded from electrodes placed in standard patterns on a patient's scalp or directly on the cortex with sterile electrode strips or grids. The differences in activity between individual electrodes is amplified and then recorded as continuous wavelets that have different frequencies and amplitudes. These data can be displayed as a raw EEG on a display in a series of channels or broken down into the basic components of frequency and amplitude and displayed as a spectral analysis. A change in a patient's background EEG activity from baseline during a procedure may indicate ischemia of the cerebral cortex either focally or through a generalized loss of activity over the entire cortex. A 50% decrease in EEG amplitude is generally considered a significant change. EEG is routinely used intraoperatively during carotid endarterectomy (CEA), cerebral aneurysm, and arteriovenous malformation surgery or in other procedures that place the cortex at risk.[1,3-5]

Evoked potentials are measures of nervous system electrical activity resulting from a specific stimulus that is applied to the patient. Electrodes record responses to repetitive stimuli as averaged wavelets at different locations in the nervous system as this evoked activity propagates along its course.

SSEPs are produced by repetitive electrical stimulation of a peripheral nerve while averaged potentials are recorded as they travel through the afferent sensory system. SSEP waveforms are recorded from peripheral nerve, spinal cord, brainstem, and primary somatosensory cortex. The recording of waveforms at sequential locations along the complete afferent sensory system allows for localization of dysfunction during procedures.

This dysfunction could be caused by ischemia, mass effect, or local injury. SSEPs recorded from stimulation of the median nerve are used intraoperatively during CEA and intracranial surgery for anterior circulation vascular lesions.[6,7] SSEPs recorded from stimulation of the posterior tibial nerve in the leg are used during intracranial surgeries involving vascular lesions in the posterior cerebral circulation.[8] Monitoring both upper and lower extremity SSEPs during procedures that place the spinal cord at risk may be useful in procedures to treat scoliosis, spinal tumors, or descending aortic repairs. The accepted criterion for significant SSEP change, suggesting a potential injury, is a decrease of spinal or cortical amplitudes by 50% or an increase in latency by 10% from baseline.

BAEPs are wavelets generated by the auditory nerve and brainstem in response to repetitive clicks, delivered to the ear. Typically, five wavelets are recorded from electrodes placed near the ear: the first recorded wavelet represents the response from the peripheral cochlear nerve, and the next four wavelets are generated from ascending structures in the brainstem. Changes in latency and amplitude of these five waves are used to assess the integrity of the auditory pathway during procedures that put them at risk.[9] BAEPs are commonly used in posterior fossa neurosurgical procedures such as acoustic neuroma resections, which place the eighth nerve at risk from either ischemia or stretch injury. BAEPs may also be useful in identifying and preventing injury in procedures such as tumor resections or arteriovenous malformation repairs that place the brainstem itself at risk because of ischemia or mass effect.

VEPs are wavelets generated by the occipital cortex in response to visual stimuli (typically flashing lights delivered with light-emitting diode [LED] goggles in the operative setting). VEPs are recorded from electrodes overlying the occipital cortex and provide information about the integrity of the visual pathway during procedures. VEPs have been have been monitored during neurosurgical procedures involving mass and vascular lesions near the optic nerve and chiasm.

EMG and NCSs can be performed on both peripheral and cranial nerves to assess their integrity and to localize these nerves by recording compound motor action potentials (CMAPs) from the muscles they supply. Monitoring involves placement of pins or electrodes in muscles and identification of the nerve supplying the muscle by stimulating it during the procedure (mapping). NCSs involves determination of whether a specific length of nerve will conduct electrical activity between a stimulating and recording electrode. If a nerve does not conduct the signal, this may indicate that it has been significantly injured along its course. Peripheral nerves are at risk of crush, stretch, ligation, ischemic, and hyperthermic injury during many surgical procedures due to malpositioning, electrocautery, or direct injury. Monitoring is also performed by observation of spontaneous activity from the muscle, which may indicate that a nerve supplying it is suffering unexpected injury. Cranial motor nerves are often monitored in this fashion. Monitoring has been performed on oculomotor, trochlear, abducens, trigeminal, facial, glossopharyngeal, vagus, spinoaccessory, and hypoglossal motor nerves.[10-13] Cranial nerve VII (facial nerve) is often monitored during posterior fossa procedures where it is at high risk of injury and also during parotid gland procedures or other ear, nose, and throat (ENT) procedures involving the face, ear, or sinuses. The external branch of the superior laryngeal nerve (EBSLN) and recurrent laryngeal nerve (RLN) can be injured during thyroidectomies and other ENT procedures in the anterior neck and have been monitored by detection of movement in the vocal cords. All peripheral nerves in the extremities and trunk can similarly be monitored. Monitoring of peripheral nerves can aid in localizing and protecting nervous tissue during nerve repairs or during spinal surgery for structural repairs or tumor resections.[14]

TcMEPs are measured after an electrical current is delivered to the motor cortex from electrodes on the scalp and a recording is made of either motor evoked potential (MEP) waveforms (D and I waves) from epidural electrodes near the spine itself or myogenic evoked potentials from muscles (CMAPs) in the upper and lower extremities. MEPs may also be recorded by direct electrical stimulation of the motor cortex after craniotomy (as a means of functional mapping of the motor cortex) or via transcortical magnetic stimulation. TcMEPs provide a real-time assessment of the descending motor pathway from the cortex to muscle during procedures that place the corticospinal tracks at risk. TcMEPs are increasingly being used in advanced neurosurgical, aortic, and orthopedic centers for monitoring motor pathways of the brain and spinal cord during procedures. MEPs appear to have a superior temporal resolution for detection of ischemia compared with SSEPs (less than 5 minutes versus 30 minutes). This is likely because TcMEPs measure spinal gray matter, which is very sensitive to ischemia, in addition to spinal motor myelinated tracts. One downside is that no clear criteria exist in the literature to define a critical change warning that injury is occurring. Studies have used different losses in CMAP amplitude (25% versus 50% versus 80%) or threshold changes (i.e., the amount of stimulation current it takes to obtain the CMAP) to signify a critical change.[15,16] The ability to perform TcMEPs is also limited by its sensitivity to anesthetics, paralytic agents, and temperature. The use of paralytic agents is discouraged and, if used at all, should be extremely limited and kept relatively constant (at less than 40% neuromuscular blockade). This also means that patients are at higher risk of injury due to spontaneous movements or stimulation during their procedures. Another limitation is the major concern that TcMEPs are often difficult to obtain from the leg. Whether this is because of technical limitations of the modality or pre-existing injury in patients is unclear.[15-19] Complications are of greater concern than in other modalities because of the stimulus intensity required to induce the response; complications may include rare instances of seizures and tongue lacerations.[17,20,21] Finally, the establishment of efficacy for TcMEPs has been limited by the lack of approved equipment and experience in performing the technique.

EVIDENCE

Evidence Supporting the Use of Electroencephalography in Carotid Endarterectomy

One of the most common uses of NIOM is EEG during CEA and other intracranial vascular procedures in which the brain is at risk of ischemic injury from hypoperfusion. Although commonly used to monitor CEAs, few data exist to support its use, including a lack of randomized trials. Intraoperative strokes are rare, occurring in approximately 2% to 3% of CEAs, and a large proportion of these strokes are due to embolism.[4,5] Despite this, it is clear that a small proportion of these strokes are due to hypoperfusion, and it is known from both animal studies and human blood flow studies that loss of EEG activity reflects a reduction of blood flow in the brain.[22,23] In a large series of 1152 CEAs, a persistent significant change on intraoperative EEG (12 cases) had 100% predictive value for an intraoperative neurologic complication.[5] A critical point during CEA is clamping of the carotid artery so that the endarterectomy can be performed. If ischemia is detected, elevating the blood pressure or placement of a carotid shunt may be used to alleviate the ischemia. Significant EEG changes can occur in up to 25% of cases during carotid clamping; however, strokes do not occur in a majority of these cases even without shunting.[5,23-25] In two separate series with a total of 469 patients undergoing CEA with EEG monitoring but without shunting, 44 patients had significant EEG changes and six of these had intraoperative strokes.[23-25] Although not all patients experiencing EEG changes during CEA in this cohort had strokes, it is possible that the strokes that occurred in this study could have been averted with the use of selective shunting based on EEG. The use of selective shunting based on EEG is further supported by a series of 369 patients in which 73 patients received shunting based on significant EEG changes; no intraoperative strokes occurred. In addition, in another study of 172 patients the use of EEG and selective shunting reduced neurologic complications from 2.3% to 1.1% in 93 patients.[26,27]

Evidence Supporting the Use of Somatosensory Evoked Potentials to Detect Brain and Spinal Injury

The use of SSEPs to identify early spinal cord injury has become widespread. The risk of spinal injury varies with different surgeries but has been reported to occur in 1% to 2% of scoliosis repairs. Significant changes in SSEPs have been predictive of injury in several small case series in complex cervical and thoracic spine procedures, but false-positives and false-negatives do occur.[28-33] The risk of injury in cases involving intramedullary spinal lesions, such as tumors, has been reported to be up to 65.4%.[34,35] In a prospective and retrospective cohort study of 19 patients with adequate baseline SSEP signals undergoing intramedullary tumor resections, SSEPs successfully predicted a postoperative motor deficit in five patients, and there were no false-negative results.[36] In a large survey of 242 experienced surgical groups performing major spinal surgery, neurologic complications occurred twice as often in unmonitored cases as in the monitored cases (51,263 total cases).[37] In the monitored cases, 184 neurologic complications occurred, of which 150 (81%) were predicted by SSEPs, although 34 were not identified, resulting in a false-negative rate of only 0.063%.[37] The authors concluded that SSEP monitoring detected greater than 90% of neurologic injuries with a sensitivity of 92% and a specificity of 98.9%. In a second large series by the same investigators,[38] 33,000 SSEP-monitored spinal cases were retrospectively reviewed. In this survey, 0.75% false-positive, 0.48% true-positive, and 0.07% false-negative rates were reported and yielded a sensitivity of 86.5% and a specificity of 99.2%. Specific data were collected for 77 patients who were injured in this group (30 injuries were severe): 17 false-negative and 60 true-positive outcomes occurred. Of the severe injuries, five were not detected by SSEP monitoring. A retrospective review of 508 patients undergoing cervical spine corpectomies was performed with upper and lower extremity SSEPs.[39] In this series, of 27 significant intraoperative SSEP changes, only one of these was persistent, and this patient awoke with quadriparesis. Of the remaining 26 cases with transient SSEP changes, three patients developed peripheral nerve injuries. Eight additional peripheral nerve injuries went undetected by SSEPs, although no spinal cord injuries went undetected in this series. A similar study of monitoring of upper extremity SSEPs in 182 cervical spine procedures demonstrated the identification eight patients with significant persistent loss of SSEPs.[40] Two of the eight patients developed quadriparesis, and two additional patients developed significant transient motor and sensory symptoms on arousal from anesthesia. No spinal injuries went undetected in this study.

In descending aortic repairs, permanent loss of SSEP signals, indicating spinal ischemia, has accurately predicted paraplegia. Furthermore, good outcomes have been reported when a spinal SSEP change is reversed with maneuvers that improve spinal perfusion in small case series.[41-45] There is a direct correlation with the time of loss of SSEPs (40 to 60 minutes) and the incidence of paraplegia.[46] However, other data in a nonblinded prospective study of 198 patients undergoing thoracic aortic aneurysm (TAA) and thoracoabdominal aortic aneurysm (TAAA) repairs (99 patients underwent surgery with distal artery bypass and SSEP monitoring versus 99 patients without bypass and monitoring) demonstrated no significant differences in neurologic outcomes between the two groups (8% neurologic complication rate in the SSEP group versus 7% in the unmonitored group).[47] No statistical difference was found after logistic regression analysis between the two groups. In a study of 33 patients undergoing TAAA repair with SSEP monitoring, 16 patients had significant changes in their SSEPs. Five patients developed paraplegia in this group, but no paraplegia occurred in cases without SSEP

changes.[48] A majority of the SSEP changes in this cohort were transient, likely because of interventions to reverse these findings; however, five of seven patients who had significant changes to their SSEPs lasting longer than 30 minutes developed paraplegia.

Upper extremity SSEPs have been used for monitoring during CEA. A benefit of using SSEPs over EEG in CEA is that they allow for monitoring of subcortical structures, although EEG does provide neurophysiologic information for a much larger area of cortex. In a meta-analysis of seven large studies assessing the use of SSEPs during CEA in 3028 patients, significant central SSEP changes indicated ischemia in 170 patients (5.6%).[49] Although some of these 170 cases used carotid shunting to reverse significant SSEP changes, 34 patients had an ischemic complication. Eight false-negative results were reported in this analysis, but not every study included in the analysis reported false-negative results. The authors concluded that SSEPs and EEG had similar sensitivities and specificities in detecting ischemia during CEA. Another meta-analysis of 15 studies of 3036 patients identified 10 false-negative cases. Of note, there was some overlap between this analysis and the previous review of seven large studies. This study also looked at the predictive value of significant SSEP changes and concluded that it was poor in predicting outcome and in determining the need for carotid shunting. This was based on comparing similar outcomes in patients undergoing selective shunting with SSEP monitoring and 317 patients who had monitoring but who did not undergo shunting regardless of the changes seen on SSEP.[50]

The utility of SSEP monitoring during intracranial aneurysm repair has also been studied. In repairs of intracranial aneurysms, temporary occlusion of a proximal vessel such as the carotid may be necessary to increase the safety of aneurysm clip placement. During these periods, monitoring with SSEPs may enable longer periods of temporary ischemia, identification of inadequate collateral flow, or identification of malpositioning of aneurysm clips. In a series of 67 aneurysm clippings, 24 significant SSEP changes were noted during temporary clipping, yet only one patient awakened with a deficit.[51] In a similar study involving 58 intracranial aneurysm repairs, 13 significant SSEP changes were demonstrated, of which only one was persistent and resulted in a neurologic deficit.[8] All the transient changes in this study resolved with intervention, including temporary clip removal, permanent clip adjustment, increase in systemic pressure, or retractor adjustment.[8]

Evidence Supporting the Use of Brainstem Auditory Evoked Potentials in Posterior Fossa Neurosurgical Procedures

BAEPs may be used to monitor surgical procedures involving the brainstem and posterior fossa that place the eighth cranial nerve and the auditory pathway at risk. In a series of 144 acoustic neuroma resections, the normal presence of wave V at the end of the resection, regardless of whether a transient change occurred during the procedure, was consistent with preservation of useful hearing.[52] In a retrospective study, 70 patients undergoing microvascular decompression of the trigeminal nerve with BAEP monitoring were compared with 150 unmonitored patients. In the monitored group, none of the patients experienced hearing loss, whereas 10 patients developed hearing loss in the unmonitored group.[53] In a retrospective study of 156 patients undergoing posterior fossa procedures, the permanent loss of wave V was significantly associated with hearing loss.[54] Finally, in a study of 90 acoustic neuroma resections with BAEP monitoring compared with 90 matched historical controls without monitoring, hearing loss was significantly less in those patients with tumors smaller than 1.1 cm who were monitored.[55]

Evidence Supporting the Use of Electromyography and Nerve Conduction Studies

Cranial nerve monitoring is used in operations of the posterior fossa and brainstem. In a series of 104 acoustic neuroma resections in which only 29 underwent facial nerve monitoring with EMG, significantly better outcomes were seen in monitored patients at 1 year.[56] In a study that compared 56 patients with facial nerve monitoring with EMG during parotidectomy with 61 patients who did not have monitoring, early facial weakness was significantly lower in the monitored group—43.6% versus 62.3%—although the incidence of permanent facial weakness was not significantly different.[57] A randomized study examined monitoring of the EBSLN and RLN during 201 thyroidectomies in female patients.[58] It compared visual inspection to identify the nerves versus use of surface electrodes placed on an endotrachial tube inserted between the vocal cords followed by identification of the nerves by direct simulation using a monopolar handheld stimulator by the operating surgeon. The results of this study demonstrated that the intraoperative monitoring (IOM) technique was significantly able to identify the EBSNL more often (83.8%) than visual inspection (34.3%). The RLN was identified 100% of the time in both groups. Most importantly, the presence of postoperative paresis of the EBSLN was significantly less in the IOM group (5% versus 1%), and significantly improved voice parameters were also noted in the IOM group postoperatively. No large studies evaluating the utility of monitoring other cranial and peripheral nerves have been published.

Evidence Supporting the Use of Visual Evoked Potential Monitoring

The evidence supporting VEP monitoring has been sparse in part because of difficulty in obtaining signals in the operating room.[59,60] Recent improvements in stimulating devices and anesthetic techniques have shown promise in obtaining VEPs in the operative setting.[61] In a recent study of VEP monitoring in 100 patients (200

eyes) undergoing operations that placed them at risk of visual dysfunction, the authors were able to obtain reproducible signals in 187 eyes.[61] Of the remaining 13 eyes, 12 had severe preoperative visual loss and one eye was unable to be recorded because of technical factors. The authors used a new device consisting of 16 red LEDs embedded on silicon disks. The monitoring detected no changes in 169 patients; one patient had visual loss in both eyes in this group, and the loss went undetected by monitoring. In the remaining 17 eyes in which significant intraoperative VEP changes occurred (50% decrease in amplitude), 14 of these patients had significant visual loss. A study in which a group of 22 patients undergoing VEP monitoring during macroadenoma resection was compared with 14 patients undergoing the procedure without monitoring demonstrated no significant difference in visual outcome.[62] Other small clinical case series have also reported no clear benefits of VEP monitoring.[63]

Evidence Supporting the Use of Transcortical Electrical Motor Evoked Potentials in Spinal and Descending Aortic Surgery

The optimal approach to monitor the spinal cord during high-risk procedures is controversial, and it is unclear whether SSEPs or TcMEPs are superior. Patients who may benefit from spinal cord monitoring include those undergoing orthopedic procedures involving structural or vascular lesions and patients undergoing repairs of the descending aorta, which put the spinal cord at risk of ischemia.[64,65] SSEP monitoring has been the traditional standard, and it has been used in routine clinical practice for spinal procedures since the 1980s.[1] However, SSEPs theoretically monitor only the sensory white matter tracts of the spinal cord, specifically, the posterior columns. The question that arises is whether SSEPs are adequately sensitive for injury to the corticospinal tracts in the cord, which are of primary importance during these procedures. Multiple studies have reported improved outcomes with SSEP monitoring during aortic and spine surgery.[38,42,43,66] As noted previously, significant challenges are associated with TcMEP use. Thus the question is whether TcMEP monitoring provides greater sensitivity to injury of spinal cord structures that are most meaningful to outcome, thereby justifying its use over SSEPs in procedures placing the spinal cord at risk.[17,20,67] The fact that TcMEPs may be too sensitive and may identify a significant number of false-positive results may lead to unnecessary interventions during procedures, which, in and of themselves, may lead to injury.[68]

In a study of 142 patients undergoing complex spinal deformity repairs with TcMEP monitoring, 16 patients had significant changes indicating spinal cord motor tract dysfunction during their procedures.[16] In these 16 cases, 11 of the TcMEP changes were reversed during the procedure and no deficit occurred, whereas the five patients with persistent changes awoke with motor deficits. In a cohort of 100 intramedullary spinal tumor resections, TcMEPs were detectable in all nonparaplegic patients. TcMEPs were 100% sensitive and 91% specific, and no patient with stable MEP signals throughout the case awoke with a deficit.[69] Similarly, a study of 50 patients monitored with TcMEPs and SSEPs during intramedullary tumor resection were compared with a group of 50 matched patients without monitoring from a historical cohort of 301 patients.[70] Neurologic outcomes were evaluated at discharge and at 3 months and demonstrated a strong trend at the time of discharge and significant improvement in outcomes at 3 months in the monitored group. Case series have shown a low rate of paraplegia in TAAA procedures when TcMEPs are employed for monitoring. In a study of 75 TAAA repairs, all patients with normal TcMEPs awoke without paraparesis, whereas eight of nine patients with significant changes consistent with spinal cord injury awoke with deficits.[71] Twenty patients in this study had significant MEP changes that resolved intraoperatively, and none of these patients awoke with deficits. Other investigators have demonstrated that significant changes in intraoperative TcMEPs during aortic surgery can be reversed with techniques that increase spinal perfusion, including reimplantation of intercostals and increasing systemic pressure.[72]

Several series have been performed in which TcMEPs and SSEPs were monitored during the same procedure (Table 58-1). This is a rare instance in which head-to-head comparisons have been performed between two monitoring techniques, although analysis of these data is flawed. In all cases, anesthesia was tailored to optimize TcMEPs. Paralytic agents were not used, which increases the difficulty of optimally monitoring SSEPs because of motor artifacts generated from performing stimulation.

A number of series involve orthopedic and neurosurgical spinal procedures with both SSEPs and TcMEPs. In a cohort of complex spinal surgeries, 104 patients were monitored with both TcMEPs and SSEPs simultaneously.[19] Ninety patients had no significant changes, and none of these patients awoke with new deficits. In seven of the remaining 14 cases, changes were seen in both modalities: five patients had transient changes and awoke without deficits, whereas the remaining two patients had persistent SSEP or TcMEP changes that predicted one motor deficit and a sensory deficit. In the seven remaining cases, only TcMEP changes occurred: four patients had transient changes and aroused without deficits. One patient had a permanent TcMEP change and awoke with a deficit, and another had a transient TcMEP change and awoke with right leg weakness. One patient had a significant persistent TcMEP change without neurologic deficit. In a cohort of 427 patients undergoing anterior or posterior cervical spine repairs with both SSEPs and TcMEPs, the monitoring identified 12 patients who developed significant loss of signals indicating a spinal injury.[18] All 12 developed significant TcMEP changes, and four also had significant SSEP changes. Seven of the patients with TcMEP-only changes and three of the patients with both TcMEP and SSEP changes had reversal with intraoperative adjustments. Of the remaining two patients with postoperative motor deficits, one had persistent TcMEP decrements and the other had both persistent TcMEP and SSEP changes, which resulted in one patient in the cohort having an intraoperative injury that was not identified by SSEPs. In another series of

TABLE 58-1 **Motor Outcomes of Spinal and Aortic Procedures Using Both TcMEP and SSEP and a Comparison of Modalities**

Study, Year, Type of Surgery*†	No. of Patients	No. of Subjects with Significant Intraoperative SSEP/TcMEP Changes			No. of Subjects with Persistent Significant Changes Who Awoke with Motor Deficit‡				Sensitivity (%)§		Specificity‖	
		Both SSEP/TcMEP	TcMEP Alone	SSEP Alone	Total	Both SSEP/TCMEP	TCMEP	SSEP	TcMEP	SSEP	TcMEP	SSEP
Pelosi, 2002[19]*	104	7	7	0	3	1	2**(1)***(1)*	1**(2)**	67	33	99	100
Hilibrand, 2004[18]*	427	4	8	0	2	1	2	1**(1)**	100	50	100	100
van Dongen, 2001[74]†	118	5	37	0	5	1**(4)**	4**(1)***(14)*	1**(4)**	80	20	88	100
Weinzierl, 2007[15]*	69	6	12	2	10	2**(1)***(1)*	8**(2)***(1)*	2**(8)***(2)*	80	20	98	97
Meylaerts, 1999[76]†	38	5	13	11	0	0	0	0**(15)**	N/A	N/A	60	100
Costa, 2007[75]*	38	3	0	1	1	1	1	1**(1)**	100	100	100	97
Etz, 2006[79]†	100	1	2	3	1	1	1	1	100	100	100	100
Total	894	31	78	16	22	7**(1)***(5)*	18**(4)***(16)*	7**(16)***(18)*	82	30	98	98

SSEP, somatosensory evoked potential; *TcMEP,* transcortical electrical motor evoked potential.
*Cervical/thoracic/spine.
†Thoracoabdominal aortic aneurysm repair.
‡Additional false-negative results are boldface; false-positive results are in italics.
§Sensitivity of having a significant change and having a motor deficit.
‖Specificity of having a significant change and having a motor deficit.

1445 cervical spine procedures, significant changes in evoked potentials indicating a spinal cord compromise occurred in 145 cases.[73] In this series, only one patient awoke with a quadriparesis and one patient awoke with left hand weakness; both were predicted by both SSEPs and TcMEPs. There were no spinal injuries that occurred without significant changes in evoked potentials. It should be noted that because eight patients had persistent TcMEP changes without SSEPs changes in the series resulting in aborted procedures in which the patients aroused with no neurologic deficit, the false-positive rate for TcMEPs was at least 5.5%. Unfortunately, further details comparing SSEPs and TcMEPs in this series were not given, which makes comparisons difficult.

Series have also been reported in which SSEPs and TcMEPs are performed during aortic repairs. In a study of 118 patients undergoing TAAA repairs using both modalities, 42 patients had significant TcMEP changes whereas only 5 patients had significant SSEP changes.[74] Aggressive measures were taken to reverse the IOM changes, but despite these interventions, 18 patients had persistent TcMEP changes and four patients had persistent SSEP changes at the time of skin closure. Five patients awoke with paraplegia; four of these were predicted by TcMEPs and one was predicted by SSEPs.

Several smaller case series appear to confirm the findings of these larger case studies, except for an increase in false-positive results in both modalities.[15,70,75-80] TcMEPs appear to have increased sensitivity at predicting motor injury compared with SSEPs, although it also appears the TcMEPs may be less specific, thus potentially resulting in false alarms during procedures.[15,18,19,68,73-76]

CONTROVERSIES AND AREAS OF UNCERTAINTY

Although there is a legitimate concern regarding the unproven benefit of NIOM because of the lack of randomized trials, monitoring appears to have an established utility in several situations. Specifically, the improved outcomes reported in large case series support the continued use of EEG in CEA, SSEP in spinal surgery, BAEP in posterior fossa procedures, and EMG in procedures placing the facial and tenth nerves (EBSLN and RLN nerves) at risk. In several areas, either the evidence has not supported the use of monitoring or further clinical research needs to be performed to demonstrate a clear benefit before a recommendation is made that these techniques become the standard of care in clinical practice. These techniques include VEP monitoring, SSEP and BAEP monitoring in procedures placing the brainstem at risk, EEG in neurosurgical vascular procedures, SSEP in CEA, and EMG in cases placing peripheral and cranial nerves at risk other than the seventh and tenth nerves.

Early evidence supports the use of TcMEPs in complex cervical and thoracic spinal procedures and descending aortic procedures. It appears that TcMEPs may be more sensitive than SSEPs in detecting and predicting motor

deficits in patients undergoing procedures that place their spinal cords at risk of motor deficits. This benefit must now be weighed against the potential risks of using TcMEP monitoring before it becomes the standard over SSEP for these procedures. The risks include potential skin injury, anesthetic restrictions, cost, oversensitivity, and the need for increased professional oversight. Further clinical research in the use of TcMEPs is necessary to establish this promising technique. The exception at this time may be a clear benefit of the use of TcMEPs in the treatment of intramedullary spinal cord tumors when the technique is performed with SSEPs.

The difficulty of assessing the benefit of IOM techniques in isolation raises the question of whether using multiple electrophysiologic techniques or nonelectrical techniques during high-risk procedures adds any benefit. Adding multiple techniques during one procedure may aid in identifying injury but also may add confusion when the modalities do not correlate, as well as adding cost. Another benefit of dual monitoring is that if one modality fails for technical reasons the other modality is still available.

GUIDELINES

In 1990, the Therapeutics and Technology Subcommittee of the American Academy of Neurology (AAN) determined that the following techniques were useful and noninvestigational: EEG and SSEPs as adjuncts in CEA and brain surgeries where cerebral blood flow was to the spine and BAEP and cranial nerve monitoring in surgeries performed in the region of the brainstem or ear.[15,73,75,79,80] The Therapeutics and Technology Subcommittee of the AAN and the American Clinical Neurophysiologic Society made a Level A evidence–based update guideline on intraoperative spinal monitoring with SSEPs and TcMEPs stating that the "operating team should be alerted to increased risk of severe adverse neurologic outcomes in patients with important IOM changes." This recommendation was determined after a panel of experts identified and reviewed four class I and eight class II studies (classification per AAN guidelines[2]) that met their criteria for analysis after an extensive literature search to identify studies in which either SSEPs or TcMEPs were predictive of adverse surgical outcomes.[2,16,18,19,39,40,48,72] These studies were large consecutive cohort studies and were selected by the authors from 604 reports based on inclusion criteria, which included sufficient patient number, detailed patient outcomes, and scientific merit. All of these studies were reviewed in prior sections of this chapter. No comparison was made regarding whether SSEPs or TcMEPs were performed. Of the four class I studies, 16% to 40% of the patients with significant IOM changes developed paraplegia, paraparesis, and quadriparesis, but none of the patients without significant IOM changes developed injury.[15,48,75,80] Of the class II studies, again, no patients developed injury without significant IOM changes, but a wide range of patients developed injury with IOM changes; seven of the eight studies had IOM significantly predicting injury.[16,18,19,39,40,72,73,79]

AUTHORS' RECOMMENDATIONS

These recommendations serve as a guide only and are based on the authors' interpretation of the available data and should not replace clinical judgment. There should be judicial use of neurophysiologic monitoring. It should be reserved for surgical cases in which the nervous system is at significant risk. When neurologic injury is expected, neurophysiologic monitoring becomes mandatory.

- Although it is relatively rare, neurologic injury due to hypoperfusion may occur during carotid endarterectomy. Electroencephalography (EEG) can identify this complication and appears to improve outcomes by indicating when carotid shunting is necessary. The available data support its use over other modalities at this time, although a randomized trial comparing modalities such as transcranial Doppler ultrasound, somatosensory-evoked potentials (SSEPs), stump pressure, and nonselective shunting is needed. EEG use in other procedures in which the cerebral cortex is at risk may be beneficial, but data to support it are lacking.
- SSEPs are useful in identifying ischemia in the brain during complex neurosurgical vascular procedures, injury to the spinal cord in complex cervical and thoracic spinal procedures, and ischemia in descending aortic repairs. It is unclear whether SSEPs or transcortical electrical motor evoked potentials (TcMEPs) are superior for detecting potential injury in the spinal cord given the current data available. This is deserving of further study. It is the current recommendation based on this review that SSEPs be used during all complex cervical and thoracic spine and descending aortic procedures that place the spinal cord at any risk.
- At this time, TcMEPs should be considered as a useful adjunct in monitoring the spinal cord during procedures placing it at risk of injury, but more clinical data need to be collected before TcMEPs should be considered the standard. SSEPs should also be monitored in all cases in which TcMEPs are attempted. A randomized controlled trial comparing TcMEP and SSEP spinal monitoring may be possible from an ethical standpoint and should be considered.
- Brainstem auditory evoked potentials (BAEPs) are useful in identifying injury and improving outcomes during neurosurgical procedures involving the posterior fossa that place the eighth cranial nerve at risk and should be used. This is especially true in acoustic neuroma resections in which the tumor is less than 2 cm in diameter. It is unclear whether BAEP and SSEP monitoring during procedures that put the brainstem at risk is useful, but given the potential benefit of monitoring during these procedures, it should be continued while more outcome data are collected.
- Seventh cranial nerve monitoring in surgeries performed in the region of the brainstem or ear with the use of spontaneous electromyography and mapping with direct

AUTHORS' RECOMMENDATIONS (Continued)

simulation of seventh cranial nerves improves outcomes and should be used. Whether there is a benefit from monitoring of other cranial nerves or peripheral nerves during procedures that put them at risk is unclear, but a potential benefit does exist, so monitoring here should be continued while further outcome data are collected.

- Monitoring of the tenth nerve (external branch of the superior laryngeal nerve and recurrent laryngeal nerve) has now been shown to improve outcomes in a randomized trial of thyroidectomies in women.[58] Vocal cord monitoring in thyroid surgical procedures should strongly be considered, although further study in other populations should be undertaken before it can be considered the standard of care in all patients.
- Because of recent improvements in visual evoked potential (VEP) monitoring techniques, it appears that if performed properly, VEPs can be recorded in patients who have normal preoperative vision during procedures that place visual pathways at risk.[61] It appears that significant changes in VEP monitoring during procedures can predict patients who will arouse with visual dysfunction. It remains unclear at this time, despite the ability to identify visual pathway injury with VEP monitoring, whether VEPs can improve outcomes. These techniques are deserving of further study and may be potentially useful if performed properly in procedures in which central visual pathways may be at risk.

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CHAPTER 59

Is Regional Superior to General Anesthesia for Infrainguinal Revascularization?

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INTRODUCTION

Infrainguinal revascularization includes endarterectomy, bypass of the femoral artery or its branches, or both. Patients with peripheral vascular disease often have conditions associated with generalized vascular disease, such as diabetes, nicotine use, hypertension, or dyslipidemias. Some may have pre-existing endovascular stents at risk of perioperative thrombosis. Risk factors for or the presence of coronary artery disease has been associated with an increased risk of perioperative cardiac morbidity in numerous studies. Patients having infrainguinal revascularization surgery are at high risk of perioperative complications including graft failure, myocardial infarction, respiratory failure, and death.[1] In a large cohort study, patients undergoing infrainguinal bypass had a 30-day mortality rate of 5.8% and a 1-year mortality rate of 16.3%.[2] About half of all perioperative deaths in this population are caused by cardiac complications.[3]

Neuraxial anesthesia has two primary postulated benefits for patients undergoing this surgery. First, patients may benefit with respect to outcomes related to concurrent diseases, for example, reduction in myocardial infarction rates or respiratory complications. Second, they may benefit from reduced complications related directly to their surgery, for example, a reduction in the rate of vascular graft failure that leads to infection, a second procedure, or even an amputation. Harm may also come to patients because of neuraxial anesthesia. The most obvious concern is about neurologic injury secondary to epidural or subdural hematoma, but another concern is about direct nerve root or spinal cord trauma. Evidence for and against these benefits and harms follows.

THERAPEUTIC OPTIONS

Typical anesthetic options for patients having lower extremity vascular grafting include general anesthesia (GA), epidural anesthesia, spinal anesthesia, and combinations thereof. It is important to consider that clinical practices in any hospital or study may differ in basic choices that in turn may influence outcomes to a similar or perhaps greater degree than the variable studied. When studies designed to address anesthetic choice and infrainguinal revascularization outcomes are interpreted, the use of postoperative epidural infusion, invasive monitoring–guided hemodynamic optimization, and antithrombotic therapy are examples of "standardized" therapeutic choices that, in fact, vary between studies. Anesthesiologists must evaluate these choices in their own practices and clinical settings, as well as in the body of published evidence, to determine how best to serve their patients.

EVIDENCE

Benefits

Mortality and Morbidity in Mixed Surgical Populations

Rodgers and colleagues[4] performed a large meta-analysis of 141 randomized trials comparing neuraxial anesthesia with GA for all types of patients. Neuraxial anesthesia was associated with a significant (approximately 30%) reduction in the postoperative mortality rate. When odds of dying were examined by type of surgery, neuraxial blockade appeared salutary for orthopedic surgery more than for vascular, general, or urologic procedures. When odds of dying were examined by type of anesthesia, neuraxial blockade alone was superior to GA alone. Nonfatal operative morbidities including deep venous thrombosis, pulmonary embolism, perioperative transfusion, pneumonia, and respiratory depression were reduced for patients randomly assigned to neuraxial blockade. Myocardial infarction was possibly reduced (odds ratio [OR] 0.67; 95% confidence interval [CI], 0.45 to 1.00) in patients receiving neuraxial blockade.

The Multicentre Australian Study of Epidural Anesthesia (the MASTER Anesthesia Trial) included 888 patients with high-risk comorbidities undergoing major abdominal surgery or esophagectomy, randomly assigned to either GA with epidural anesthesia/analgesia or GA with postoperative intravenous opioids.[5,6] Pain scores were lower at rest on the first postoperative day (POD) and with coughing on POD 1 to 3 in the epidural group. The respiratory failure rate was also reduced, but no significant differences in mortality rate or cardiovascular morbidity were demonstrated. The rate of death or at least one major complication was 57.1% in the epidural group and 60.7% in the GA group; to demonstrate a

statistically significant 3.6% benefit of regional anesthesia/analgesia would require a study of roughly 6000 patients. Ultimately, it remains controversial whether a small but significant benefit of regional anesthesia exists for high-risk mixed surgical populations.

Bode and colleagues[7] tested the hypothesis that regional anesthesia reduces operative cardiovascular morbidity and mortality rate associated with infrainguinal revascularization. A total of 423 patients were randomly assigned to receive general (138), epidural (149), or spinal (136) anesthesia for femoral-to-distal-artery bypass surgery. Epidural catheters were removed at the time of discharge from the postanesthesia care unit, but some patients received epidural morphine before catheter removal. All patients were monitored for at least 48 hours postoperatively with arterial lines and pulmonary artery catheters (but without standardized treatment protocol). Patients received subcutaneous heparin on POD 1 until ambulation, then 81 mg aspirin daily thereafter. There was no significant reduction of myocardial infarction, angina, congestive heart failure, or all-cause mortality rates between GA (16.7%), epidural (15.4%), or spinal anesthesia (21.3%). Because of the study design, the potential benefit of postoperative epidural infusion was not addressed. In sum, current evidence for significant reduction of mortality rate and *cardiac* risk by use of regional anesthesia during infrainguinal revascularization is limited. If favorable, the benefit of regional anesthesia is small.

Graft Failure in Lower Extremity Revascularization

In two randomized studies, one of which (Christopherson and colleagues[8]) compared epidural with GA for patients having lower extremity grafts and the other of which (Tuman and colleagues[9]) compared epidural-supplemented with unsupplemented GA for patients having either aortic or lower extremity vascular surgery, vascular graft failure was reduced in patients with epidurals. Both these studies reported high rates of vascular graft failure, and both of them continued epidural analgesia into the postoperative period. In the study by Christopherson and colleagues,[8] preoperative aspirin was withheld and heparin was continued into the postoperative period only when there was suspicion of graft failure. Few patients in that study were monitored with pulmonary artery catheters.[8] In the study by Tuman and colleagues,[9] intraoperative heparin was reversed with protamine at the end of surgery. High rates of graft failure in these two studies might have been reduced had different antithrombotic strategies been used. However, high rates of adverse outcomes made it possible for these two studies to show a significant reduction of graft failure in patients who received epidural anesthesia.

A focused retrospective chart review by Kashyap and colleagues[10] also showed a possible benefit to regional anesthesia. This review examined graft survival after infrapopliteal revascularization with polytetrafluoroethylene graft material for critical ischemia. These criteria narrowed the results to 77 patients from 1500 lower extremity revascularization surgeries over the period of 1978-1998 and functionally selected for a study population with a high rate of graft failure, thus strengthening the ability to detect a small effect. GA accounted for 75% of these cases and regional anesthesia, mostly spinal anesthetics, accounted for 25% of the cases. There were 11 incidents of acute graft thrombosis, all in the GA group. The regional group had prolonged primary graft patency at 36 months (35%) when compared with the GA group (15%). The specific breakdown of which patients had neuraxial analgesia continuing into the postoperative period was not reported. Postoperative warfarin use was not statistically associated with an improvement in graft patency, but only some of the patients received warfarin in this retrospective, nonrandomized study.

A large chart review study using data from the Veterans Affairs National Surgical Quality Improvement Program (NSQIP) was done by Singh et al.[11] Patients undergoing infrainguinal vascular bypass surgery during the period from 1995 to 2003 were identified by Current Procedural Terminology (CPT) codes and their charts retrospectively reviewed for type of anesthetic and its effect on 30-day graft failure, cardiac events, pneumonia, length of stay, and surgery-related return to the operating room. A total of 14,788 patients were identified: 9757 (66%) received general endotracheal anesthesia (GETA), 2848 (19%) were administered a spinal anesthetic (SA), and 2183 (12%) had an epidural anesthetic (EA). The study showed the odds of graft failure were 43% higher with GETA versus SA and EA, which represented a 40% increase in the need to return to the operating room versus SA and a 17% increase versus EA The study also showed a significantly greater number of cardiac events and double the rate of postoperative pneumonia within 30 days of the procedure. However, the inherent limitations of a nonrandomized, retrospective study apply. Differences in the specifics of operative complexity (e.g., redo surgery, spliced or arm vein, longer operative times, and urgency of surgery) were not reliably captured in the database and may have been associated with bias in the selection of the type of anesthesia. Of note, the authors projected that a well-controlled randomized study would require more than 20,000 patients to demonstrate a statistically significant outcome effect of anesthetic choice on the rate of graft failure using the rate of failure found in this chart review.

In contrast to the already mentioned studies, a retrospective chart review by Schunn and colleagues[12] examined 294 primary femoral–popliteal–tibial bypass surgeries occurring between 1989 and 1994 and found no significant difference of early graft thrombosis rates between GA alone (9.4%) and epidural alone (14%). It is unclear whether epidural analgesia was always continued into the postoperative period or continued selectively in certain cases, and, as a chart review, there was no randomization between the two groups. In two prospective randomized trials, one study of 101 patients comparing spinal to GA (Cook and colleagues[13]) and one of 264 patients (Pierce and colleagues[14]) in which patients were randomly assigned to SA, EA, or GA but without neuraxial analgesia in the postoperative period,

there was no graft patency benefit associated with regional anesthesia. Rates of graft failure were very low overall; in fact, rates were so low in the study by Pierce and colleagues[14] that the study was underpowered to find a difference in rates of graft failure. In the study by Pierce and colleagues[14] no difference was found in the rate of postoperative amputation. All patients received aspirin and either subcutaneous heparin or oral warfarin. Additionally, all patients were monitored with arterial lines and pulmonary artery catheters for 24 to 48 hours after surgery.[14] It has been shown that patients undergoing lower extremity vascular surgery under GA had improved vascular graft survival if they were monitored and treated appropriately with the use of pulmonary artery catheters.[15]

As with most complex questions, interpretation of available research is equally complex and presents a number of contradictions. As such, it is important to carefully weigh the quality of each study. In this context, it is evident that the best designed studies—those using adequate blinding and randomization—show little outcome differences among the choices of anesthetics but are limited by small sample size. It will continue to be difficult to be guided by the available literature in choice of anesthetic techniques. These decisions will need to continue being made on a patient-by-patient and practice-by-practice basis.

Risks

The rapid evolution of antiplatelet and anticoagulant therapies may have a greater effect on outcome than anesthetic choice. Furthermore, these therapies affect anesthetic choice because of an elevated risk of neuraxial bleeding that may be associated with SA or EA techniques. Antithrombosis therapy is important in the maintenance of vascular graft patency. In some institutions aspirin is routinely given before surgery. Intravenous heparin is almost always given intraoperatively before clamping of the arteries to be grafted. Thus a spinal or an epidural needle might be placed into a patient whose platelet function is impaired from aspirin, and subsequent to placing of an epidural catheter, an anticoagulant is almost always given. Furthermore, intravenous heparin may be continued into the postoperative period, or low-molecular-weight heparin (LMWH) may be given subcutaneously. Because of concomitant diseases, vascular surgery patients may be taking warfarin or antiplatelet therapy.

The American Society of Regional Anesthesia and Pain Medicine (ASRA) has recently reviewed the evidence of risk of epidural hematoma for patients receiving neuraxial blockade while undergoing anticoagulation.[16] Pertinent recommendations related to heparin and antiplatelet agents are summarized as follows. For more details or for evidence-based management of neuraxial anesthesia for patients taking other anticoagulants, the reader is referred to the ASRA consensus document, available at www.asra.com (accessed June 11, 2012).

1. Unfractionated heparin: patients undergoing vascular surgery who will receive heparin intraoperatively should not receive neuraxial anesthesia if they have other coagulopathies. If there is difficult or bloody needle placement, they may be at increased risk of neuraxial hematoma; there should be a discussion with the surgeon as to whether the case should proceed or be canceled. In general, heparin should not be given until at least 1 hour after needle placement. In the postoperative period, there should be careful monitoring of neurologic status, and concentrations of local anesthetics should be limited to those that allow assessment of motor strength. Epidural catheters should be removed at least 2 to 4 hours after a heparin dose. Patients receiving heparin for 4 days or longer are at risk of heparin-induced thrombocytopenia; therefore a platelet count should be obtained before neuraxial block is performed.
2. LMWH: patients receiving preoperative LMWH should be assumed to have impaired coagulation. The safest timing and type of anesthesia is likely a single-injection SA given at least 10 to 12 hours after the last thromboprophylaxis-dosed LMWH; patients receiving higher (treatment) doses of LMWH should not receive neuraxial anesthesia for at least 24 hours. If LMWH is to be started postoperatively, dosing and epidural catheter removal must be timed. Additional care and consideration of the risk and benefits of regional techniques should be considered when the patient is being treated with other drugs that may act synergistically with LMWH.
3. Antiplatelet medications: nonsteroidal antiinflammatory drug therapy alone is not a contraindication to a regional technique. Before neuraxial regional anesthesia, an interval of 14 days is suggested for ticlopidine and 7 days for clopidogrel. The family of platelet glycoprotein (GP) IIb/IIIa inhibitors deserves special mention. Platelet aggregation is impaired for 24 to 48 hours after administration of abciximab and for 4 to 8 hours after eptifibatide and tirofiban.

AREAS OF UNCERTAINTY

To the best of our knowledge, no studies have been published to date to determine whether SA affects graft survival, as EA does in some studies.

GUIDELINES

We recommend two guidelines published by national societies to address issues discussed here. Both can be found on websites, where they are updated from time to time as new information becomes available. With respect to perioperative cardiac morbidity and mortality rates, the reader is referred to the website of the American College of Cardiology (www.acc.org) (accessed June 11, 2012). With respect to management of neuraxial blockade for patients receiving anticoagulation, the reader is referred to the website of the ASRA (www.asra.com).

AUTHORS' RECOMMENDATIONS

Patients with peripheral vascular disease have a significant rate of perioperative mortality and cardiac morbidity. Therefore any reduction of risk would provide a relatively large decrease in the absolute number of operative complications. The literature reveals contradictory studies, which only hint that neuraxial techniques may show a small benefit to mortality and cardiac event rates in a mixed population of surgical patients. Specific to the current practice of regional anesthesia, in addition to the usual consideration of anatomy, risk of infection, and patient preference, increasing use of perioperative antithrombotic therapy adds complexity both to analysis of potential risks and benefits and to actual patient management.

Graft survival may be similar with general anesthesia as with neuraxial blockade, especially if patients receive optimized hemodynamic therapy, perioperative antithrombosis therapy, or both. If epidural anesthesia is given, epidural therapy should be continued into the postoperative period because the only randomized studies that demonstrated reduction of graft failure were performed with continued postoperative epidural therapy.

In our hospital we have a very low rate of graft failure. Our patients receive aspirin before surgery. Arterial, central venous, and pulmonary artery catheters are used only for medical indications, and most patients do not receive these monitors. When deemed safe and feasible, regional anesthesia techniques are offered as options to patients undergoing infrainguinal revascularization but with the acknowledgment that the most likely benefit is superior postoperative analgesia.

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CHAPTER 60

Is There a Best Technique to Decrease Blood Loss and Transfusion after Coronary Artery Bypass Grafting?

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INTRODUCTION

The importance of excessive blood loss after coronary artery bypass grafting (CABG) is related to its significant association with deleterious perioperative outcomes, including all the risks of blood transfusion.[1-3] Blood transfusion after CABG significantly increases mortality risk, ischemic morbidity (e.g., stroke, myocardial infarction, and renal failure), infections (e.g., wounds, pneumonia, and sepsis), hospital stay, and overall health costs.[3-6]

The techniques for reducing bleeding and transfusion should collectively be focused on all CABG patients, particularly the high-risk subgroups. In the initial clinical practice guideline on blood transfusion and blood conservation in cardiac surgery by the Society of Thoracic Surgeons (STS) and Society of Cardiovascular Anesthesiologists (SCA), six important risk factors for increased bleeding and transfusion risk were identified: advanced age, low preoperative red blood cell volume, preoperative antiplatelet or antithrombotic drugs, reoperative or complex procedures, emergency surgery, and noncardiac patient comorbidity.[6,7] These risk factors are again emphasized in the recent update to the guidelines[4] as they continue to identify high-risk CABG subgroups that merit aggressive intervention to limit perioperative risk due to bleeding and transfusion.

Furthermore, it is essential to have guideline-driven transfusion of blood components to optimize the risk–benefit ratio of this intervention. The practice guidelines for blood transfusion and adjuvant therapies by the American Society of Anesthesiologists (ASA) recommend red blood cell administration when the hemoglobin concentration is less than 6.0 g/dL, particularly during acute anemia. Transfusion is generally not indicated when the hemoglobin concentration is greater than 10.0 g/dL. The need for transfusion in the intermediate range of 6.0 to 10.0 g/dL requires evaluation for ongoing organ ischemia, potential or active bleeding, intravascular volume status, and coexisting risk factors such as poor cardiopulmonary reserve and high oxygen consumption.[8] It is important to note that these ASA guidelines are not specific to cardiac surgery. The concept of transfusion algorithms is further supported by recommendations from the STS/SCA guidelines as well as the 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines for CABG surgery.[4,9]

OPTIONS TO DECREASE BLOOD LOSS AND TRANSFUSION AFTER CORONARY ARTERY BYPASS GRAFTING

The perioperative options for limiting blood loss and transfusion after CABG are presented in Table 60-1. The evidence for each option will be reviewed to assess its quality and to determine a recommendation, according to the schema of the ACCF/AHA Task Force on Practice Guidelines.[10] The recommendation classes and evidence levels are summarized for rapid review in Table 60-2 (Class I recommendations), Table 60-3A (Class IIa recommendations), Table 60-3B (Class IIb recommendations), and Table 60-4 (Class III recommendations). The discussion of the evidence will focus on selected representative references. Further recommendations and a complete reference list are available from the recent comprehensive 2011 STS/SCA Blood Conservation Clinical Practice Guidelines dedicated to this topic (available at www.scahq.org or www.sts.org, accessed June 12, 2012).[4]

EVIDENCE

Pharmacologic Hemostasis by Preoperative Recovery of Coagulation

Potent preoperative anticoagulants and antiplatelet drugs frequently increase bleeding and transfusion significantly after CABG. Therefore, when clinically feasible, they should be discontinued preoperatively to allow recovery of the coagulation system (Class IIb recommendation; Level C evidence). The timing of discontinuation depends on the half-life of the particular agent and the

TABLE 60-1 **Perioperative Options to Minimize Blood Loss and Transfusion after Coronary Artery Bypass Grafting**

Interventions	Examples
Preoperative interventions	Discontinue anticoagulation and certain antiplatelet therapy
	Preoperative autologous blood donation
	Recombinant erythropoietin
Intraoperative pharmacologic interventions	Antifibrinolytic agents (lysine analogs)
	Desmopressin acetate
	Recombinant factor VIIa
Intraoperative surgical interventions	Off-pump coronary artery bypass
Intraoperative blood management and perfusion interventions	Platelet plasmapheresis
	Red cell salvage
	Intraoperative autotransfusion
	Minicircuits/heparin-coated circuits
	Retrograde autologous priming
	Heparin and protamine management
	Acute normovolemic hemodilution
	Modified ultrafiltration
	Transfusion protocol/algorithm
Postoperative interventions	Positive end-expiratory pressure

TABLE 60-2 **Class I Multimodal Recommendations to Minimize Bleeding and Transfusion after Coronary Artery Bypass Grafting**

Recommendation	Class and Evidence
Drugs that inhibit the platelet P2Y12 receptor should be discontinued before elective CABG, if possible. The interval between discontinuation and surgery depends on the drug pharmacodynamics.	I (Level B)
Lysine analogs such as epsilon-aminocaproic acid and tranexamic acid reduce blood loss and transfusion.	I (Level A)
Minicircuits reduce hemodilution and are indicated for blood conservation, especially in high-risk patients.	I (Level A)
Modified ultrafiltration is indicated for operations using CPB.	I (Level A)
Routine use of red cell salvage with centrifugation limits blood transfusion in CABG with CPB.	I (Level A)
A multimodality evidence-based approach will limit blood transfusion and promote blood conservation after CABG. Multiple stakeholders, institutional support, transfusion algorithms, and point-of-care testing are important components.	I (Level A)

CABG, coronary artery bypass grafting; *CPB,* cardiopulmonary bypass.

Adapted from the following guideline: The Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 2011;91:944–82.

TABLE 60-3A **Class IIa Multimodal Recommendations to Minimize Bleeding and Transfusion after Coronary Artery Bypass Grafting**

Recommendation	Class and Evidence
Preoperative erythropoietin, plus iron, can increase red cell mass in patients with preoperative anemia, in patients who refuse transfusion, and in patients at high risk of postoperative anemia.	IIa (Level B)
Use of leukoreduced donor blood, if available, may have more pronounced benefits in patients undergoing CABG.	IIa (Level B)
Intraoperative platelet plasmapheresis is reasonable in high-risk patients if an adequate platelet yield can be reliably obtained.	IIa (Level A)
Pump salvage and reinfusion of residual pump blood at the end of CPB is reasonable for minimizing blood transfusion.	IIa (Level C)
Off-pump CABG is a reasonable means of blood conservation, provided that emergent conversion to on-pump CABG is unlikely.	IIa (Level A)
Patients with qualitative platelet defects or severe thrombocytopenia (<50,000/mm^2) are at high risk of bleeding and should have maximal blood conservation interventions.	IIa (Level B)
It is reasonable to discontinue low-intensity antiplatelet drugs (e.g., aspirin) in elective patients without acute coronary syndromes to reduce bleeding and transfusion.	IIa (Level A)

TABLE 60-3A **Class IIa Multimodal Recommendations to Minimize Bleeding and Transfusion after Coronary Artery Bypass Grafting** (Continued)

Recommendation	Class and Evidence
When the hemoglobin level is less than 6 g/dL, red cell transfusion can be lifesaving. Transfusion is reasonable in postoperative patients with a hemoglobin level less than 7 g/dL.	IIa (Level C)
It is reasonable to transfuse non–red-cell hemostatic blood products based on clinical evidence of bleeding, preferably guided by timely and accurate point-of-care testing.	IIa (Level C)
For hemoglobin levels greater than 6 g/dL on CPB, it is reasonable to transfuse based on the patient's clinical situation, and this should be considered the most important part of the decision-making process.	IIa (Level C)
Creation of multidisciplinary blood management teams is a reasonable means of decreasing transfusion and perioperative bleeding.	IIa (Level B)
A comprehensive multimodality blood conservation program in the intensive care unit is a reasonable means of limiting blood transfusion.	IIa (Level B)
Total quality management, including continuous assessment of existing and emerging blood conservation techniques, is reasonable for implementation of a complete blood conservation program.	IIa (Level B)

CABG, coronary artery bypass grafting; *CPB,* cardiopulmonary bypass.

Adapted from the following guideline: The Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 2011;91:944–82.

TABLE 60-3B **Class IIb Multimodal Recommendations to Minimize Bleeding and Transfusion after Coronary Artery Bypass Grafting**

Recommendation	Class and Evidence
Point-of-care testing for platelet adenosine diphosphate responsiveness might be reasonable for identifying clopidogrel nonresponders who are candidates for earlier CABG.	IIb (Level C)
Recombinant erythropoietin can be considered to restore red cell volume in patients undergoing autologous preoperative blood donation before CABG.	IIb (Level A)
Most high-intensity anticoagulants increase bleeding after CABG. It is not unreasonable to stop these agents preoperatively, taking into account the half-life and potential lack of reversibility. Unfractionated heparin is an exception because it may be discontinued very shortly before surgery or not at all.	IIb (Level C)
In CPB, it is not unreasonable to maintain the hemoglobin level at 7 g/dL or greater in patients at risk of critical end-organ injury.	IIb (Level C)
In patients with critical noncardiac end-organ ischemia, it is not unreasonable to maintain the hemoglobin concentration at 10 g/dL or greater.	IIb (Level C)
Desmopressin acetate therapy is not unreasonable for attenuating excessive bleeding in patients with platelet dysfunction secondary to uremia, CPB, and type I von Willebrand disease.	IIb (Level B)
Recombinant factor VIIa therapy is not unreasonable for the management of intractable nonsurgical bleeding that is unresponsive to routine hemostatic therapy.	IIb (Level B)
A trial of therapeutic positive end-expiratory pressure to ameliorate excessive postoperative bleeding is not unreasonable.	IIb (Level B)
Open venous reservoir membrane oxygenator systems during CPB may be considered for reduction in blood utilization and improved safety.	IIb (Level C)
It is not unreasonable to maintain higher heparin concentrations for CPB durations greater than 2 hr to reduce hemostatic system activation, blood loss, and transfusion.	IIb (Level B)
Protamine titration or empiric low-dose regimens can be used (e.g., 50% of total heparin dose) to lower the total protamine dose at the end of CPB to reduce bleeding and transfusion.	IIb (Level B)
Biocompatible CPB circuits are not unreasonable for promoting blood conservation.	IIb (Level A)
Low-dose heparin therapy for CPB (ACT, approximately 300 sec) is less well established for blood conservation. The safety concerns have not been well studied.	IIb (Level B)
Routine use of a microplegia technique can be considered for minimizing the volume of crystalloid cardioplegia, especially in fluid overload conditions.	IIb (Level B)
Acute normovolemic hemodilution is not unreasonable for blood conservation in cardiac surgery.	IIb (Level B)
Retrograde autologous priming of the CPB circuit can be considered for blood conservation.	IIb (Level B)
Intraoperative autotransfusion directly from cardiotomy suction or recycled from a cell-saving device is not unreasonable for augmenting blood conservation.	IIb (Level C)
Postoperative mediastinal shed blood reinfusion processed by centrifugation may be considered for blood conservation when used in conjunction with other interventions.	IIb (Level B)

ACT, activated clotting time; *CABG,* coronary artery bypass grafting; *CPB,* cardiopulmonary bypass.

Adapted from the following guideline: The Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 2011;91:944–82.

TABLE 60-4 **Class III Multimodal Recommendations to Minimize Bleeding and Transfusion after Coronary Artery Bypass Grafting**

Recommendation	Class and Evidence
Routine addition of P2Y12 inhibitors to aspirin therapy early after CABG may increase risk of bleeding and re-exploration. It is indicated if the patient meets ACC/AHA criteria for dual antiplatelet therapy.	III (Level B)
Transfusion is unlikely to improve oxygen transport when the hemoglobin level is greater than 10 g/dL and is not recommended.	III (Level C)
Routine prophylactic desmopressin acetate is not recommended for reducing bleeding and transfusion.	III (Level A)
Prophylactic positive end-expiratory pressure does not reduce postoperative bleeding.	III (Level B)
Leukocyte filtration during cardiopulmonary bypass is not indicated for perioperative blood conservation.	III (Level B)
Direct infusion of shed mediastinal blood from postoperative chest tube drainage is not indicated for perioperative blood conservation.	III (Level B)

ACC/AHA, American College of Cardiology/American Heart Association; *CABG,* coronary artery bypass grafting.
Adapted from the following guideline: The Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 2011;91:944–82.

possibility of reversibility. The exception to this principle is unfractionated heparin, which may be discontinued shortly before CABG or not at all.

High-intensity platelet blockade with thienopyridines such as clopidogrel may be associated with life-threatening bleeding after CABG.[11] It is reasonable to discontinue this potent platelet blockade before elective surgery to limit blood loss and transfusion (Class I recommendation; Level B evidence). The period of discontinuation is dependent on the properties of the drug, but a period of at least 5 days is recommended for clopidogrel and ticagrelor.[9,12] However, based on the variability in response and resistance to common antiplatelet agents, the period of discontinuation may be as short as 3 days.[4] The use of point-of-care testing for platelet adenosine diphosphate (ADP) responsiveness may be reasonable for identifying nonresponders and those eligible for earlier CABG; however, strong evidence is lacking for this recommendation (Class IIb recommendation; Level C evidence). The recommendation for prasugrel is for the drug to be stopped at least 7 days before planned surgery.[12] In the presence of coronary stents, whether bare-metal or drug-eluting stents, early withdrawal of antiplatelet therapy can precipitate stent thrombosis.[13] The options to maintain stent patency must be considered, including preoperative hospitalization to substitute thienopyridine therapy with short-acting intravenous platelet blockade.[13-15] Cangrelor is a promising new short-acting, intravenous P2Y12 inhibitor that has already shown maintenance of platelet inhibition when used as a bridging agent without a significant increase in operative bleeding when compared with placebo.[16]

It is reasonable to stop low-intensity antiplatelet therapy (e.g., aspirin) preoperatively in elective patients without acute coronary syndromes to reduce blood loss and transfusion after CABG (Class IIa recommendation; Level A evidence).[17] In the setting of emergent CABG, aspirin should be continued because the small bleeding risk is outweighed by its overall benefits (Class IIa recommendation; Level A evidence).[18]

Limiting Bleeding and Transfusion with Autologous Donation and Erythropoietin

Preoperative autologous blood donation is reasonable in selected patients, especially when combined with appropriate erythropoietin and iron therapy (Class IIa recommendation; Level A evidence).[7] Although common in noncardiac surgical cases, cardiac surgery does not routinely use this technique because of concerns about an increased incidence of myocardial infarction before surgery in CABG patients.[7] However, autologous donation can be used safely before elective CABG, and this practice is associated with a significant reduction in allogeneic blood transfusion.[19-21] The use of recombinant human erythropoietin to restore red cell volume in those patients undergoing autologous donation should be considered, but it should be balanced with the potential for thrombotic cardiovascular events in this population (Class IIb recommendation; Level A evidence).[4] Preoperative erythropoietin, plus iron, given several days before surgery is also indicated for boosting red blood cell mass in anemic patients, in patients who refuse allogeneic blood transfusion (e.g., Jehovah's Witness patients), or in patients who are at high risk of postoperative anemia (Class IIa recommendation; Level B evidence).[4,22] Given the evidence that preoperative anemia independently predicts death, stroke, and renal failure after CABG, randomized trials with preoperative erythropoietin to augment red blood cell mass have already shown effectiveness in decreasing the incidence of postoperative transfusion and increasing postoperative hemoglobin values.[23-25]

Pharmacologic Hemostasis with Antifibrinolytic Agents

Activation of the fibrinolytic cascade in cardiac surgery patients contributes to bleeding. Therefore antifibrinolytic agents were introduced as a pharmacologic technique aimed at improving hemostasis. Antifibrinolytics are the most extensively studied blood conservation

agents, and they have been shown to decrease postoperative bleeding and the need for allogeneic blood transfusion in CABG patients, as well as other cardiac and noncardiac surgical cases. The antifibrinolytic agent aprotinin was withdrawn from the market in late 2007 because of concerns about patient safety when used in cardiac surgery. The Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study was suspended for the apparent increase in mortality rate caused by aprotinin as compared with tranexamic acid and aminocaproic acid.[26] Even before this development, safety concerns related to anaphylaxis and renal dysfunction had already significantly limited the clinical application of aprotinin.[27,28] Two further massive outcome analyses of aprotinin in CABG (cumulative n = 88,474) have also documented a significant increase in mortality rate in CABG patients exposed to perioperative aprotinin as compared with aminocaproic acid.[29,30] Given this information and despite the fact that aprotinin decreases postoperative bleeding and transfusion, the use of aprotinin for CABG receives a Class III recommendation (Level A evidence) because risks outweigh benefits.[4] Since its removal from the market, further analyses and newer data suggest that aprotinin may continue to have a role in cardiac surgery, particularly in patients who are at high-risk of bleeding.[31]

The remaining available antifibrinolytics are the lysine analogs, tranexamic acid and aminocaproic acid. High-quality meta-analyses consistently support the safety and efficacy of the lysine analogs for blood conservation in CABG surgery.[32-34] These agents significantly reduce bleeding and blood component transfusion across multiple randomized trials. There are reports of increased occurrence of seizures with tranexamic acid use, but this has not been confirmed by large randomized trials.[35] Based on the available data, the application of these agents, particularly in high-risk CABG subgroups, has received a Class I recommendation (Level A evidence).[4]

Pharmacologic Hemostasis with Desmopressin and Recombinant Factor VIIa

Desmopressin acetate is a synthetic analog that releases factor VIII precursors and von Willebrand factor from vascular endothelium.[7] Desmopressin therapy is not unreasonable to attenuate excessive bleeding in patients with platelet dysfunction secondary to uremia, cardiopulmonary bypass, and type I von Willebrand disease (Class IIb recommendation; Level B evidence).[4] Furthermore, preoperative platelet dysfunction detectable by point-of-care testing can often be reversed by desmopressin therapy.[36,37] Thus desmopressin is indicated perioperatively in selected cases with evidence of platelet dysfunction. However, routine prophylactic desmopressin does not reduce bleeding and transfusion after CABG (Class III recommendation; Level A evidence).[38]

Recombinant factor VIIa (rFVIIa) therapy has demonstrated efficacy in the management of nonsurgical bleeding after CABG. This efficacy is based on a consistent trend from multiple case series that have been systematically reviewed.[39] Although rFVIIa has been shown to decrease reoperation and blood transfusion in a randomized trial, concerns regarding adverse events such as thrombotic complications limit routine use.[40] Until larger randomized controlled trials become available to further evaluate the safety and efficacy of this intervention, rFVIIa should be considered only in those CABG patients with massive and refractory nonsurgical bleeding that has not responded to routine hemostatic treatment options (Class IIb recommendation; Level B evidence).[4]

Limiting Bleeding and Transfusion with Avoidance of Cardiopulmonary Bypass

Because cardiopulmonary bypass (CPB) is associated with hemostatic disturbances, it is not surprising that CABG without CPB was associated with decreased bleeding and transfusion when compared with CABG plus CPB in a meta-analysis of randomized trials.[41] Off-pump CABG is reasonable for blood conservation, provided that emergent conversion to on-pump bypass is unlikely based on surgeon experience or patient characteristics (Class IIa recommendation; Level A evidence).[4] Emergent conversion to CABG with CPB is associated with significantly greater bleeding and reoperation.[42]

Limiting Bleeding and Transfusion with Modified Cardiopulmonary Bypass

The conduct of CPB may significantly affect bleeding and transfusion after CABG. The design of the CPB circuit is the first major consideration. The hemostatic possibilities in CPB hardware design include oxygenator design (bubble or membrane), pump type (centrifugal or roller), and circuit type (biocompatible and/or minimized low-prime). The second major consideration is anticoagulation management for CPB with heparin and protamine. The evidence and recommendations for each of these considerations are as follows.

A membrane oxygenator during CPB is not unreasonable for reducing blood utilization (Class IIb recommendation; Level C evidence).[7] Membrane oxygenators have largely replaced bubble oxygenators in contemporary clinical practice because they are associated with reductions in cerebral emboli and blood transfusion.[43,44] CPB pump design, however, has less of a role in perioperative blood conservation after CABG. All pump designs, whether centrifugal or roller, provide acceptable hemostatic performance. Despite theoretical advantages of the centrifugal design over the roller design such as less hemolysis and reduced complement activation, consistent clinical reductions in bleeding and transfusion after CABG have not been observed in randomized trials.[7,45,46] However, it is not unreasonable to prefer centrifugal pumps for their enhanced safety elements (Class IIb recommendation; Level B evidence).[4]

Biocompatible CPB circuits are not unreasonable for promoting blood conservation (Class IIb recommendation; Level A evidence).[4] Because they attempt to mimic the endothelial surface by coating the bypass circuit with various compounds (such as heparin), these circuits have

shown benefit in decreasing the inflammatory response and hemostatic activation associated with CPB.[47,48] A large meta-analysis of more than 4000 patients concluded that biocompatible circuits are associated with a lower incidence of blood transfusion; however, they are best used in conjunction with other blood conservation techniques for the greatest benefit to be observed.[47] Minicircuits have been shown to reduce hemodilution and should also be used for blood conservation, especially in patients with preoperative anemia (Class I recommendation; Level A evidence).[4] These minimized circuits contain a reduced priming volume that limits hemodilution on initiation of CPB. Benefits are especially noted in pediatric patients or Jehovah's Witness patients, but they can also be used with efficacy in CABG patients.[49] Clinical trials have documented significant reductions in bleeding and transfusion after CABG with the low-prime CPB circuit as compared with conventional CPB.[50] Furthermore, there is high-quality evidence that these beneficial outcomes are similar in magnitude to the hemostatic benefit from CABG without CPB.[51]

Anticoagulation for CABG with CPB is used to limit cellular and coagulation factor activation and to prevent circuit thrombosis. Unfractionated heparin is the anticoagulant of choice because it is effective, reversible with protamine, generally well-tolerated, and inexpensive. The activated clotting time (ACT) is a standard point-of-care test to monitor heparin effect during CPB. An ACT time of greater than 400 seconds is the traditional standard for safe CPB, originally based on a 1978 primate study with bubble oxygenators.[52] For reduction of the total protamine dosing needed for heparin reversal, the idea of low-dose heparin therapy, in conjunction with heparin-coated CPB circuits, has been evaluated.[53] Aiming for an ACT of 300 seconds, the goals of this concept were to limit bleeding and transfusion after CABG by decreasing heparin exposure and the need for protamine reversal.[7] This intervention was considered as not unreasonable for promoting blood conservation, but safety concerns such as thrombosis have not been well studied (Class IIb recommendation; Level B evidence).[7] In contrast to lower heparin dosing, the use of high-dose heparin therapy during prolonged CPB (longer than 2 to 3 hours) has also been suggested for blood conservation. High-dose heparin therapy can decrease thrombin generation, fibrinolytic activity, and platelet activation.[54,55] In a randomized study with point-of-care testing (heparin concentration and ACT) to maintain appropriate heparin concentrations for an ACT greater than 480 seconds, a reduction in blood product utilization was observed, likely secondary to preservation of the coagulation system.[56] Considering this evidence, it is not unreasonable to use high-dose heparin therapy monitored with point-of-care testing to reduce hemostatic activation, platelet consumption, and need for transfusion in prolonged CPB cases (Class IIb recommendation; Level B evidence).[7]

Heparin reversal with protamine can affect bleeding and transfusion after CABG with CPB because excess protamine is itself an anticoagulant. Protamine titration or empiric low-dose regimens not only lower the total protamine dose but also have been shown in clinical trials to reduce bleeding and transfusion but not consistently.[57,58] One randomized trial found 80% fewer transfusions when patient response tests were incorporated into the management.[57] However, another randomized trial noted no difference in postbypass hemostasis when titration methods were used.[58] Results from other similar trials are also inconclusive regarding the benefits of this method. Although protamine titration or empiric low-dose protamine therapy is not unreasonable (Class IIb recommendation; Level B evidence), more consistent evidence of benefit is required before a higher class recommendation can be assigned.[7]

Limiting Bleeding and Transfusion with Modified Blood Management

Conservation of the patient's red cell volume with a multimodal approach is the first principle of modified blood management for limitation of bleeding and transfusion after CABG. Routine red-cell saving with centrifugation limits blood transfusion in CABG with CPB (Class I recommendation; Level A evidence).[4] Because of safety concerns, this is not indicated in patients with infection (the concern is septicemia). A change from prior guidelines is that cell salvage from the operative field in patients with known malignancy should now be considered in high-risk patients (Class IIb recommendation; Level B evidence).[4] This change comes from evidence that suggests worsened outcomes and increased recurrence rates in patients with malignancy when allogeneic blood is transfused.[59,60] Intraoperative autotransfusion directly from cardiotomy suction or recycled from a cell-saving device is also not unreasonable to augment blood conservation (Class IIb recommendation; Level C evidence). Extensive cell-saving, however, leads to loss of coagulation factors and platelets, which may result in a bleeding diathesis.[61] This deleterious effect of extensive cell-saving can be offset after CPB by some form of pump salvage and reinfusion of residual pump blood, which is considered a reasonable means of blood conservation (Class IIa recommendation; Level C evidence). Centrifugation, rather than direct infusion, of this residual pump blood is preferred (Class IIa recommendation; Level A evidence) because increased fibrin degradation occurs with direct infusion.[4,62] This can lead to increased bleeding and transfusion requirements.

Acute normovolemic hemodilution is not unreasonable for blood conservation in cardiac surgery (Class IIb recommendation; Level B evidence).[4] This often involves the removal of one to two units of autologous blood immediately before initiation of CPB. For the circulating blood volume to be maintained, the volume of removed blood is replaced 1:1 with crystalloid or colloid. An advantage of this technique, along with decreasing allogeneic blood use, is that platelet function and clotting factors are preserved in the autologous blood because it does not undergo the deleterious effects of CPB. This is especially beneficial for hemostasis when the blood is returned to the patient after CPB. Another advantage is that the blood can be used as a first source of volume should transfusion be needed while the patient is

undergoing bypass. Although it is considered safe in several patient groups, patient groups with contraindications to this technique include unstable patients and those with preoperative anemia.[7,63]

Retrograde autologous priming is an intervention for blood conservation that, similar to acute normovolemic hemodilution, is instituted just before initiation of CPB. The crystalloid prime volume of the arterial limb of the CPB circuit is cleared retrograde by back bleeding from the aortic cannula. Similarly, the venous limb is cleared in an antegrade manner. While recent trials[64,65] have shown that this technique decreases hemodilution and the need for transfusions, others have demonstrated no significant benefit.[66] Despite this limitation, retrograde autologous priming is not unreasonable for blood conservation after CABG (Class IIb recommendation; Level B evidence).[4]

The use of platelet plasmapheresis is a reasonable strategy for conserving blood as part of a multimodality approach in high-risk patients (Class IIa recommendation; Level A evidence).[4] Selective removal during continuous centrifugation results in platelet-rich-plasma, which can be returned to the patient after CPB for hemostasis because these platelets have been spared from CPB dysfunction. Although current evidence ranges from either no benefit to significant benefit in reducing bleeding and transfusion, platelet plasmapheresis should only be performed if an adequate platelet yield can be reliably obtained.[4,67,68]

The presence of leukocytes in packed red cells can lead to inflammatory effects and the potential for infection. Therefore, if allogeneic blood is needed, it is reasonable to use leukoreduced donor blood if available (Class IIa recommendation; Level B evidence).[4] Leukocyte filtration during CPB may theoretically improve bleeding and transfusion after CABG. However, clinical trials of this intervention have failed to show consistent hemostatic benefit after CABG.[69] Furthermore, there is evidence that leukocyte depletion during CPB may activate white cells.[70] For these reasons, the use of leukocyte filters during CPB are not indicated for blood conservation in CABG (Class III recommendation; Level B evidence).[4]

Modified ultrafiltration (MUF) is a form of ultrafiltration that removes water and inflammatory mediators from blood after completion of CPB. This results in less hemodilution. A large meta-analysis of 1004 patients revealed that MUF decreases postoperative bleeding and transfusion requirements in patients undergoing cardiac surgery.[71] Consequently, MUF is now indicated for blood conservation in patients undergoing CABG with CPB (Class I recommendation; Level A evidence).[4]

Although postoperative transfusion of shed mediastinal blood may limit blood transfusion, multiple clinical trials have failed to demonstrate consistent benefit. Furthermore, there is potential for harm, including sternal and systemic infection.[72,73] Given the lack of consistent clinical benefit and evidence of harm, direct infusion of shed mediastinal blood from postoperative chest tube drainage is not indicated for perioperative blood conservation after CABG (Class III recommendation; Level B evidence).[7]

Another principle of modified blood management for limitation of bleeding and transfusion after CABG is a perioperative transfusion protocol to standardize institutional transfusion practice as far as possible.[4] Based on expert opinion and consensus, the following recommendations all relate to this principle, and they can guide the decision of whether to transfuse.

It is reasonable to transfuse hemostatic blood products based on clinical evidence of bleeding, preferably guided by point-of-care testing (Class IIa recommendation; Level C evidence). In CPB, it is not unreasonable to maintain the hemoglobin level at 7 g/dL or greater in patients with a risk of critical end-organ injury (Class IIb recommendation; Level C evidence). Transfusion is not recommended for a hemoglobin concentration greater than 10 g/dL (Class III recommendation; Level C evidence), except in patients with critical noncardiac end-organ ischemia, in which case it is not unreasonable to maintain the hemoglobin concentration at greater than 10 g/dL (Class IIb recommendation; Level C evidence).[4]

Mechanical Hemostasis with Positive End-Expiratory Pressure

Positive end-expiratory pressure (PEEP) exerts mechanical pressure on the heart and so may limit bleeding after CABG. Two clinical studies with no control group have documented control of excessive bleeding with escalating levels of PEEP up to a maximum of 20 cm H_2O.[74,75] A trial of therapeutic PEEP to ameliorate excessive bleeding is not unreasonable (Class IIb recommendation; Level B evidence).[4] In those cases in which the use of PEEP is effective, a reduction in postoperative bleeding often becomes apparent within an hour of initiation. When significant mediastinal bleeding is not already apparent, the use of prophylactic PEEP does not reduce postoperative bleeding (Class III recommendation; Level B evidence).[4,76] It is also important to keep in mind the risks of cardiovascular compromise after CABG with escalating levels of PEEP.

AREAS OF UNCERTAINTY

Discontinuation of preoperative antiplatelet therapy continues to receive significant attention because of associated risks and benefits. A clearer role for preoperative platelet function testing needs to be defined, as well as the use of short-acting intravenous antiplatelet therapy as a bridging option. Currently, there are also no standard recommendations on the timing and dosing of preoperative erythropoietin for those who may benefit from this option. rFVIIa continues to be studied to determine a better a safety–risk profile. Further investigation is needed on optimal heparin and protamine management during CPB. These are just a few areas of uncertainty that present opportunities to further explore the topic of bleeding and transfusion after CABG. With appropriate randomized controlled clinical trials, each clinical recommendation can be supported with higher levels of evidence.

GUIDELINES AND AUTHORS' RECOMMENDATIONS

The recent update to the Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists guidelines on perioperative blood conservation in cardiac surgery is comprehensive and current with respect to evidence-based reduction of bleeding and transfusion after coronary artery bypass grafting (CABG).[4] As per this guideline, we endorse a multimodality approach to minimizing bleeding and transfusion after CABG (Class I recommendation; Level A evidence), as well as the creation of multidisciplinary blood management teams that include all perioperative stakeholders in the operating room and the intensive care unit (Class IIa recommendation; Level B evidence). All of the aforementioned evidence-based interventions should be integrated appropriately and be focused on the patient at high risk of bleeding and transfusion after CABG, as outlined in the introduction. Incorporation of a perioperative transfusion protocol supplemented with appropriate point-of-care testing is recommended. Lastly, total quality management, which includes continuous assessment of existing and emerging blood conservation techniques, is strongly recommended for implementation of a complete blood conservation program (Class IIa recommendation; Level B evidence).[4]

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CHAPTER 61

Should Thoracic Epidural/Spinal Analgesia be Used for Coronary Artery Bypass Grafting?

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INTRODUCTION

In recent years, neuraxial analgesia for cardiac surgery has become an area of intense interest and debate in the adult cardiothoracic anesthesiology literature. Although spinal and epidural analgesia have been in use for at least two decades,[1] these techniques have not yet gained widespread clinical acceptance. The theoretical benefits and risks of neuraxial analgesia and anesthesia will be reviewed in the adult cardiac surgical patient population. We will survey the current literature regarding outcomes and the use of spinal and epidural techniques in this setting and conclude with our recommendations on the basis of this literature.

POTENTIAL BENEFITS OF NEURAXIAL TECHNIQUES

The theoretical advantages of spinal/epidural over parenteral opioid use in adult cardiac surgical patients can be compartmentalized into three broad areas: pain control, cardiac sympathectomy, and pulmonary function. In each of these areas, there are several potential benefits related to the use of neuraxial techniques.

Pain Control

The most direct beneficial effects of adequate postoperative analgesia include prevention of unnecessary patient discomfort and improved patient satisfaction. In addition, adequate postoperative analgesia may decrease morbidity and postoperative hospital length of stay and, consequently, may decrease cost. Conversely, inadequate postoperative analgesia may increase morbidity by causing hemodynamic, metabolic, immunologic, and hemostatic alterations. Thus aggressive control of postoperative pain may improve some or all of these variables as well as outcomes in high-risk patients after both noncardiac[2,3] and cardiac surgery.[4,5] However, achieving optimal pain relief after cardiac surgery may be challenging both because of significant incisional pain (e.g., sternotomy, thoracotomy, and chest tubes) and patient characteristics (e.g., advanced age and pulmonary pathology).

Postoperative analgesia may be attained with a wide variety of techniques (e.g., local anesthetic infiltration, nerve blocks, opioids, nonsteroidal antiinflammatory drugs, or alpha-adrenergic drugs). Traditionally, parenteral opioid administration has been used as first-line therapy for postcardiac surgery pain control. Intravenous opioid use is associated with definite detrimental side effects, most notably respiratory depression and sedation, which may be magnified in the adult cardiac surgical population. Intrathecal and epidural techniques clearly produce reliable analgesia in patients undergoing cardiac surgery[6] and during the last 10 to 15 years have, in fact, been used more often clinically.[7] The use of neuraxial techniques may also help avoid some of the aforementioned side effects encountered with parenteral narcotic administration, particularly if epidural analgesia with local anesthetic is used.

An important potential advantage of the dense analgesia afforded by neuraxial techniques is attenuation of the stress response. Pain, as well as its concomitant sympathetic activation, induces the stress response in surgical patients. Elevated levels of circulating catecholamines can cause unfavorable myocardial oxygen supply and demand profiles by both increasing demand secondary to elevated heart rate and contractility and limiting supply secondary to decreased coronary perfusion time.[8] Increased levels of corticotropin-releasing hormone and other stress hormones and inflammatory mediators may be seen in surgical patients with inadequate analgesia. In addition, these mediators likely play a role in the prothrombotic and immunosuppressed states observed in postsurgical patients.[9] In cardiac surgical patients this stress/inflammatory response may be further compounded and amplified by the humoral response to cardiopulmonary bypass. None of these alterations is desirable in the postcardiac surgery patient, and they have been linked to postoperative organ dysfunction and cardiac events. Theoretically, these deleterious effects of perioperative pain may be attenuated by aggressive use of neuraxial analgesia.

Cardiac Sympathectomy

Intimately related to spinal/epidural analgesia's attenuation of the pain-induced stress response is the cardiac sympathectomy induced when neuraxial local anesthetics are used. The myocardium and coronary vasculature are densely innervated by thoracic sympathetic nerve fibers

that arise from T1 to T5 and profoundly influence total coronary blood flow and distribution. Cardiac sympathetic nerve activation initiates coronary artery vasoconstriction and paradoxic coronary vasoconstriction in response to intrinsic vasodilators. In patients with coronary artery disease, cardiac sympathetic nerve activation disrupts the normal matching of coronary blood flow and myocardial oxygen demand. Furthermore, myocardial ischemia initiates a cardiocardiac reflex mediated by sympathetic nerve fibers, which augments the ischemic process. Cardiac sympathetic nerve activation likely plays a central role in initiating postoperative myocardial ischemia by decreasing myocardial oxygen supply while increasing myocardial oxygen demand.[10] Neuraxial block using local anesthetics produces sympatholysis and prevents many of these undesirable sympathetic effects. In fact, epidural local anesthetics have been shown to attenuate the stress response[11] and improve coronary arteriolar flow[12] secondary to this sympatholytic effect.

Pulmonary Function

As less invasive techniques for cardiac surgery have evolved, such as off-pump coronary artery bypass grafting (CABG), heartport, and robotic procedures, there has been a push toward streamlining postoperative care with a focus on anesthetic techniques that permit early postoperative extubation. Early extubation after cardiac surgery decreases the length of intensive care unit (ICU) stay, decreases the length of the hospital stay, and, consequently, decreases the cost of care.[13] Multiple studies have demonstrated that fast-tracking is at least as safe as traditional perioperative management, including a meta-analysis of 10 trials published in 2003.[14] It is important to note, however, that fast-tracking after cardiac surgery has not been shown to improve outcomes. A 2003 meta-analysis showed no difference between fast-track (extubation earlier than 8 hours after surgery) and traditional approaches in mortality rates, myocardial ischemia, or respiratory dysfunction.[15] This study did confirm that fast-tracking decreases length of ICU and hospital stays. Neuraxial anesthesia offers the potential advantage of dense analgesia with less of the sedative and respiratory depressive side effects that can delay extubation. In fact, perhaps the greatest impetus behind the recent interest in neuraxial techniques has been this focus on so-called fast-track anesthesia for cardiac surgery.

Neuraxial analgesia may also help preserve perioperative pulmonary function through opioid sparing, early extubation, and early mobilization. Thoracic epidural anesthesia in patients undergoing major abdominal and noncardiac thoracic surgery has been shown to result in improved postoperative lung function and has been shown to reduce the risk of pulmonary complications.[16]

POTENTIAL RISKS OF NEURAXIAL TECHNIQUES

As in the previous discussion about potential benefits of neuraxial techniques, the potential risks associated with spinal/epidural analgesia in the setting of cardiac surgery can be divided into three categories: hemodynamic effects, pulmonary effects, and neurologic complications.

Hemodynamic Effects

The hemodynamic consequences of neuraxial analgesia vary considerably with the selected technique and agent. When local anesthetics are used, both in the epidural and intrathecal spaces, sympathetic blockade results in decreased heart rate, peripheral vasodilation, venous pooling, and arterial hypotension. These effects are most pronounced with epidural local anesthetic administration (the risk of a total spinal technique precludes the use of intrathecal local anesthetics for patients with advanced cardiac disease) and are mostly absent when narcotics are used alone. Arterial hypotension in CABG patients can cause decreased coronary perfusion and myocardial ischemia. In patients with valvular heart disease or poor ventricular function, both hypotension and bradycardia may cause dramatic drops in cardiac output and, consequently, global hypoperfusion.

Respiratory Effects

High thoracic neuraxial techniques may have negative effects on the respiratory system. When local anesthetics are used in doses sufficient to produce neuraxial anesthesia, intercostal muscle strength may be compromised, which may be clinically significant in patients with preexisting pulmonary disease.

Neuraxial opioids, on the other hand, may induce respiratory depression. Patients who receive single-shot epidural and intrathecal opioid injections may run the risk of respiratory depression as high as 3% and 7%, respectively.[17] It must be noted, however, that parenteral opioids may carry an even greater risk of causing respiratory depression.

Neurologic Effects

Perhaps the greatest barrier to widespread clinical use of neuraxial analgesia in cardiac surgical patients is the perceived risk of epidural hematoma development. Although results taken directly from cardiac surgery literature are somewhat lacking, there are data regarding the risk of vertebral canal hematoma after neuraxial block placement. A recent prospective study in the United Kingdom estimated the risk of development of epidural hematoma after perioperative (noncardiac) central neuraxial blockade at between 1:5700 and 1:12,200.[18] This study did not distinguish between lumbar and thoracic block placement, and it is believed by many clinicians that the risk of epidural hematoma is greater with thoracic blocks (although no definitive data are currently available).

In addition, there are several other factors that may raise the risk of epidural hematoma formation in cardiac surgical patients. The majority of patients undergoing cardiac surgery receive full systemic heparinization. Epidural instrumentation in this setting poses a theoretically increased risk of vertebral canal bleeding complications, even when guidelines regarding placement and removal

of catheters are adhered to strictly. Furthermore, renal dysfunction, a not infrequently encountered complication of cardiac surgery, as well as the effects of cardiopulmonary bypass, may lead to platelet dysfunction and increased risk of bleeding complications.

OPTIONS FOR NEURAXIAL ANALGESIA

Both spinal and epidural techniques have been used for neuraxial analgesia in cardiac surgical patients. Each has its own advantages and limitations. The alternative is intravenous analgesics.

Spinal Analgesia

Spinal analgesia for cardiac surgery has several advantages. The use of a small-bore needle may help minimize the risk of a "bloody tap" and epidural hematoma formation.[19] When compared with high thoracic epidural injections, spinal injections are technically easier to perform. In addition, because intrathecal techniques are one-shot injections, postoperative anticoagulation need not be discontinued for catheter removal after surgery.

There are also disadvantages to the intrathecal approach. Select centers have been using a "total spinal" technique for adult cardiac surgical patients,[20] but the administration of sufficient local anesthetic doses to achieve this can result in dramatic drops in both heart rate and blood pressure and has precluded wider clinical use. Given this limitation, spinal administration of opioids has become the more widespread intrathecal approach. Although intrathecal opioids given before surgery provide analgesia that persists into the postoperative period, they have several disadvantages when compared with local anesthetics. Unlike local anesthetics, neuraxial opioids do not produce sympathetic blockade. Thus many of the theoretical advantages already listed do not apply when intrathecal opioids are selected for neuraxial analgesia. Furthermore, as already described, intrathecal opioids can cause significant respiratory depression in up to 7% of patients.[17] Another disadvantage of spinal analgesia when compared with epidural techniques is the inability to continue to provide supplemental analgesia after the effects of the initial injection dissipate.

Epidural Analgesia

Although in theory a single-shot epidural injection for analgesia is feasible for cardiac surgical patients, placement of an indwelling epidural catheter and intermittent dosing or continuous infusion of the drug is the most common approach in both the literature and clinical practice. Epidural catheter placement offers the advantage of incremental dosing and, consequently, tighter hemodynamic control. Safe administration of local anesthetics through an epidural catheter allows modulation of sympathetic tone and the stress response in addition to providing excellent analgesia.[7] Epidural catheters can be left in place after surgery, which allows continued administration of local anesthetics and opioids to help control postoperative pain. The risk of respiratory depression after epidural narcotic administration is significantly less than the risk observed after intrathecal opioid injection.[17]

On the other hand, high thoracic epidural catheters can be challenging to place. The risk of a bloody tap and epidural hematoma formation may be significantly higher after thoracic epidural placement than after lumbar spinal injection.[21] In addition, removal of the indwelling catheter after surgery may increase the risk of hematoma formation. Finally, removal of epidural catheters requires cessation of anticoagulants and antiplatelet medications and may put patients taking these medications at risk of thrombotic or embolic events.[22]

EVIDENCE

When evaluating the current evidence regarding spinal and epidural analgesia for cardiac surgery, we believe that it is critical to assess the safety of neuraxial analgesia, its efficacy as an analgesic, and how it compares with conventional parenteral opioid administration for adult cardiac surgical patients.

Spinal Analgesia

The overwhelming majority of studies in the literature have used intrathecal morphine (administered before induction of general anesthesia) to provide a prolonged tail of postoperative analgesia. Some investigators have used intrathecal fentanyl[23] and sufentanil[24] in conjunction with morphine to provide enhanced intraoperative analgesia. As already mentioned, other investigators have used intrathecal local anesthetics in attempts to provide dense intraoperative analgesia and induce cardiac sympathectomy.[25] Still others have studied the use of intrathecal clonidine in addition to neuraxial opioids.[22] Regardless of the agent and regimen used, these studies demonstrate the efficacy of intrathecal injections in providing postoperative analgesia.

Two early randomized, blinded, placebo-controlled clinical studies underscore the ability of intrathecal morphine to induce significant postoperative analgesia after cardiac surgery.[21,26] Vanstrum and colleagues[21] prospectively randomly assigned 30 patients to receive either intrathecal morphine (0.5 mg) or intrathecal placebo before induction of anesthesia. Patients who received intrathecal morphine required significantly less intravenous morphine than control subjects receiving placebo during the initial 30 hours after intrathecal injection. Associated with this enhanced analgesia was a substantially decreased need for antihypertensive medications during the immediate postoperative period. Chaney and colleagues[26] prospectively randomly assigned 60 patients to receive either intrathecal morphine (4.0 mg) or intrathecal placebo before induction of anesthesia. The tracheal extubation time was similar in all patients. Patients who received intrathecal morphine required significantly less intravenous morphine than control subjects receiving placebo during the initial postoperative period.

Numerous other nonrandomized clinical investigations (e.g., retrospective and observational) attest to the

ability of intrathecal morphine to produce substantial postoperative analgesia in patients after cardiac surgery,[7] the quality of which depends not only on the intrathecal dose administered but also on the type and amount of intravenous drugs used for the intraoperative baseline anesthetic. The optimal dose of intrathecal morphine or other agents for achieving maximum postoperative analgesia with minimum undesirable drug effects is uncertain.

In examining the safety of spinal analgesia for cardiac surgery, a mathematical model for predicting this outcome concluded that the risk is approximately 1 : 10,000.[27] Therefore none of the available studies is sufficiently powered to assess the risk of epidural hematoma. It is important to note that no cases of epidural hematoma have been reported in cardiac surgical patients who have received spinal analgesia. In addition, no epidural hematoma adverse events have been reported in any of the studies investigating intrathecal analgesia for cardiac surgery.

None of the available investigations alone allows us to reach conclusions regarding the clinically relevant advantages (if any) of spinal analgesia over parenteral opioid administration. There have been, however, two meta-analyses of prospective, randomized controlled trials. In 2004, a meta-analysis by Liu and colleagues[28] of 17 trials encompassing 668 patients showed no significant impact of intrathecal analgesia on major clinical endpoints such as mortality, myocardial infarction, time to extubation, and arrhythmias. More recently, Zangrillo and colleagues[29] performing a meta-analysis of 24 trials totaling 1106 patients confirmed these findings and also demonstrated no decrease in hospital length of stay in the spinal analgesia group.

In summary, clinical investigations involving intrathecal techniques indicate that administration of intrathecal morphine before induction of general anesthesia produces reliable postoperative analgesia after cardiac surgery. To date, no known cases of epidural hematoma have developed after spinal analgesia for cardiac surgery, which suggests that this technique is safe. However, two separate meta-analyses have failed to demonstrate any significant clinical benefit to the use of spinal analgesia for cardiac surgery.

Thoracic Epidural Analgesia

Thoracic epidural analgesia with local anesthetics alone or with epidural narcotics has been shown to provide effective postoperative pain control in patients undergoing CABG surgery. The use of thoracic epidural analgesia for pain control has been consistently shown to be narcotic sparing in the postoperative period. Numerous clinical studies attest to this fact.[7]

An early mathematical analysis by Ho and colleagues[27] in patients subjected to systemic heparinization required for cardiopulmonary bypass (without a single episode of hematoma formation reported in the literature as of the year 2000) estimated that the maximum risk may be as frequent as 1 : 2400. As use of neuraxial techniques in cardiac surgical patients has become more prevalent, reports of epidural hematoma in cardiac surgical patients have begun to surface. In 2004, the first report of hematoma formation associated with epidural instrumentation the day before scheduled cardiac surgery was published.[30] The first report of hematoma formation during the immediate postoperative period after cardiac surgery (catheter inserted immediately before surgery after induction of general anesthesia) occurred the same year.[31] A letter to the editor in 2006 details permanent paraplegia in two patients undergoing cardiac surgery with thoracic epidural supplementation and hints at two additional patients who experienced hematoma formation associated with catheter insertion the day before scheduled cardiac surgery.[32] However, the most recent estimation of epidural hematoma risk in the cardiac surgical population is 1 : 12,000, which is consistent with the upper range of risk seen in the general surgical population.[33] In addition, others have argued that the addition of large series reporting neuraxial analgesia for cardiac surgery to the literature without any cases of epidural hematoma within these series suggests that the risk in this population may not be appreciably greater than the risk observed in general surgery patients.[10] It is important to note that, in much of the thoracic epidural literature, the catheters were placed the day before surgery. There are insufficient data to evaluate whether same-day placement of epidural catheters raises the risk of epidural hematoma occurrence.

Whereas hematoma formation is clearly a major concern, thromboembolic complications when normalization of coagulation variables is achieved for epidural removal may also be a consideration. Chaney and Labovsky[34] report a case in which a patient receiving postoperative anticoagulation for atrial fibrillation and a mechanical aortic valve experienced an embolic stroke after normalization of coagulation variables to remove a thoracic epidural catheter placed electively before cardiac surgery. In light of this report, the risk of thromboembolic events in patients requiring anticoagulants or antiplatelet medication postoperatively also needs to be taken into consideration before a decision is made to place epidural catheters in these subjects.

Some studies suggest that the use of thoracic epidural *anesthesia* may increase the incidence of hypotension requiring vasopressor administration.[35] The ultimate clinical significance, if any, of this hypotension when appropriately managed is unknown.

In the last decade several meta-analyses have suggested that the use of thoracic epidural analgesia for cardiac surgery may be superior to general anesthesia alone. In 2004, Liu pooled data from 15 studies including 1178 patients comparing general anesthesia with thoracic epidural analgesia to general anesthesia alone in patients undergoing CABG surgery.[28] No differences were seen between groups in mortality or myocardial infarction rates, but the meta-analysis did find statistically significant decreases in pulmonary complications, dysrhythmias, pain scores, and time to extubation in the patients who received thoracic epidural analgesia. In 2010, Bignami and colleagues[36] analyzed 33 trials (2336 patients) comparing general anesthesia with thoracic epidural analgesia to general anesthesia alone in patients undergoing cardiac surgery. In their analysis, they found that

thoracic epidural analgesia reduced the time to extubation, the risk of renal failure, and the composite endpoint myocardial infarction/death (although when assessed independently there were no differences in myocardial infarction and mortality). In 2011, Svircevic and colleagues[37] published a meta-analysis of 28 articles including a total of 2731 patients: 1416 patients received general anesthesia alone and 1315 patients received general anesthesia with thoracic epidural analgesia. They concluded that thoracic epidural analgesia in patients undergoing cardiac surgery reduces the risk of postoperative supraventricular arrhythmias and respiratory complications. In addition, their data suggested that thoracic epidural analgesia may reduce the risk of mortality, myocardial infarction, and stroke, although the study was insufficiently powered to achieve statistical significance for these endpoints.

In assessing these meta-analyses, several important factors must be considered. First, the control arms of the analyzed studies included patients who received high-dose narcotic regimens. These subjects may have had an exaggerated effect on extubation times and, by extension, the risk of pulmonary complications and may account for the differences in these endpoints detected by the meta-analysis. In addition, all three of the meta-analysis included data from a large study (420 patients) published by Scott in 2001.[38] In this study, 420 patients undergoing cardiac surgery were prospectively randomly assigned (nonblinded) to receive either thoracic epidural bupivacaine/clonidine and general anesthesia or general anesthesia alone (control group). Epidural infusions were continued for 96 hours after surgery (titrated according to need). In control patients, postoperative analgesia was obtained with intravenous opioids. After surgery, striking clinical differences were observed between the two groups. Postoperative supraventricular arrhythmia, respiratory tract infection, renal failure, and acute confusion were all decreased in thoracic epidural patients when compared with control patients. However, several limitations in this study may account for the observed differences. First and foremost, the clinical protocol dictated that beta-adrenergic blockers could not be used during or after surgery for the 5 days of the study period. Because approximately 90% of this study's patients were taking beta-adrenergic blockers before surgery, this unique perioperative management (discontinuation of beta-adrenergic blockers) clouds interpretation of postoperative supraventricular arrhythmia data. Patients in the epidural group received epidural clonidine, a cardioprotective drug that may also account for the decreased risk of tachyarrhythmias observed in the experimental subjects. Also, despite prospective randomization, substantially fewer patients receiving thoracic epidural catheters were active smokers before surgery when compared with control subjects, which clouds interpretation of postoperative extubation times and respiratory tract infection data. Given the large size of this study relative to the meta-analyses performed, it is possible that some of the favorable outcomes demonstrated by the meta-analyses may be disproportionately due to the included Scott data.

A recent large (654-subject) and well-designed randomized controlled trial by Svircevic and colleagues[6] comparing general anesthesia with epidural analgesia to fast-track (remifentanil-based) general anesthesia showed similar extubation times and composite pain scores and risk of pulmonary complications, cardiac arrhythmias, and myocardial infarction in both groups. The only observed benefit of thoracic epidural analgesia was lower early postoperative pain scores. These data suggest that a regimented fast-track general anesthetic may offer many of the benefits of thoracic epidural analgesia without the additional risk associated with epidural placement.

AREAS OF UNCERTAINTY

One of the greatest obstacles to widespread clinical application of these techniques is the perceived increased risk of epidural hematoma formation in cardiac surgical patients. Despite this perception, a critical review of the literature would seem to suggest that this risk may not be appreciable higher in the cardiac surgical population than in the general surgical population. Nonetheless, given the fact that, in a significant proportion of reported cases, patients had epidural catheters placed the day before surgery to minimize epidural hematoma risk, it is difficult to extrapolate this conclusion to today's clinical environment where, in many institutions, "routine" cardiac surgical patients are not admitted until the morning of surgery, thus precluding this practice.

Although there is some evidence that epidural analgesia may offer some advantages, these advantages may not be evident when epidural analgesia is compared with current fast-track general anesthetic techniques. Therefore, given that the true benefit of epidural analgesia is still largely unknown and that an increased risk of epidural hematoma formation is possible, particularly for same-day placement, epidural analgesia should be used cautiously (i.e., catheter placed the day before surgery) and selectively (consider other approaches in patients who will require postoperative anticoagulants or antiplatelet therapy).

GUIDELINES

There are no specific guidelines regarding the use of neuraxial techniques with respect to cardiac surgery. Nonetheless, guidelines for neuraxial blockade in patients seen for vascular surgery may have some relevance for cardiac surgical patients. The American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines for vascular surgery patients are as follows:

- Do not use neuraxial techniques in patients with coagulopathies.
- Heparin administration should be delayed for 1 hour after neuraxial access.
- Indwelling catheters should be removed 2 to 4 hours after the last dose and after re-evaluation of coagulation status. Heparin should not be reinitiated until at least 1 hour has passed.

- Patients receiving postoperative analgesia with local anesthetics should be monitored for hematoma formation.
- If a bloody tap is encountered, communicate with the surgeon. No data currently support mandatory cancellation of the surgical case.

AUTHORS' RECOMMENDATIONS

The use of spinal and epidural techniques in cardiac surgical patients remains controversial. The decision to use neuraxial analgesia requires a patient specific risk–benefit analysis. On the basis of the current literature, we make the following broad recommendations:

- There is insufficient substantiated benefit to recommend the use of intrathecal opioid analgesia for cardiac surgical patients. The risk of epidural hematoma formation after spinal injection, although likely low even in the cardiac surgical population, adds an additional risk of major morbidity if spinal analgesia is used. Therefore it is our recommendation that intrathecal opioid analgesia should not be used for cardiac surgical patients.
- Although the use of epidural analgesia in cardiac surgical patients may have advantages, these benefits must be balanced against the risks of epidural catheter placement and removal. In addition, many of these benefits may be achievable with more conventional techniques (e.g., fast-track anesthesia and perioperative beta-blockade). At this time, it is our recommendation that epidural analgesia should not be used for cardiac surgical patients.

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CHAPTER 62

Is There a Best Technique in the Patient with Increased Intracranial Pressure?

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INTRODUCTION

The contents of the cranium can be divided into three major constituents. The brain or tissue compartment accounts for approximately 85% of the total intracranial volume, cerebrospinal fluid (CSF) contributes approximately 10%, and the blood in the vasculature contributes approximately 5%. The majority of the cerebral blood volume (CBV) resides in the low-pressure venous system, whereas only 15% of the CBV is found in the arteries and 15% in the venous sinuses.

Intracranial pressure (ICP) is closely regulated, even in the presence of a space-occupying lesion, as long as compensatory mechanisms are operational and the pathologic process evolves slowly. Any increase in intracranial volume must be compensated for by volume reduction of one of the other compartments to maintain normal ICP. The CSF system has the greatest buffering capacity through displacement of CSF from the cranium to the spinal subarachnoid space. CBV reduction occurs first by compression of the low-pressure venous system, followed by capillary collapse, and then arterial compression leading to cerebral ischemia. The impact of ICP on outcome lies in its role in determining cerebral perfusion pressure (CPP) (CPP = mean arterial pressure [MAP] – ICP). There is evidence, at least in head trauma, that a CPP less than 50 mm Hg is associated with a poor outcome.[1] However, an improved outcome does not necessarily result from a higher CPP. For the calculation of CPP, the arterial pressure transducer should be at the level of the ear.

Increased ICP may be caused by changes in the volume of any one or a combination of the intracranial compartments, including hematomas caused by vascular rupture, increases in brain and interstitial volumes caused by tumors, and vasogenic and cytotoxic edema secondary to hypoxia and infection. Increased ICP can also result from obstruction of CSF pathways and alteration of CSF production or reabsorption.

OPTIONS

Management strategies include decisions about the choice of (1) anesthetic drugs, (2) ventilation, (3) hyperosmolar therapy, (4) head and body position, and (5) decompressive craniectomy (Box 62-1). The effects are influenced by whether the ICP increase developed rapidly or slowly; in the latter case, usually some compensation can take place.

EVIDENCE/CONTROVERSIES/AREAS OF UNCERTAINTY/GUIDELINES

What Are the Targets for Intracranial Pressure and Cerebral Perfusion Pressure?

The ICP should be kept below 20 mm Hg because higher values are associated with poorer neurologic outcomes.[1] A CPP greater than 70 mm Hg should be avoided if it requires massive fluid infusion and high-dose catecholamines because hypervolemia and catecholamine therapy increase the incidence of acute respiratory distress syndrome.[2] A spontaneous increase of CPP above 70 mm Hg can be accepted as long as cerebrovascular autoregulation is intact or the neurologic state seems to benefit clinically. When autoregulation is intact, an increase in CPP is associated with autoregulatory vasoconstriction, thereby reducing CBV and ICP. The critical lower threshold for CPP lies between 50 and 60 mm Hg. Therefore a CPP below 50 mm Hg should be avoided.[3]

What Are the Effects of Anesthetics on Intracranial Pressure?

The choice of anesthetic agents and adjunctive drugs is based on consideration of their effects on cerebral blood flow (CBF), CBV, cerebral metabolic rate of oxygen ($CMRO_2$), ICP, cerebrovascular autoregulation, and carbon dioxide (CO_2) reactivity. Most randomized trials have focused on these surrogate endpoints rather than on clinical or neurologic patient outcomes.

Volatile anesthetics depress cerebral metabolism in a dose-dependent fashion while directly inducing cerebral vasodilation, which results in increases in CBV and ICP. Sevoflurane causes less cerebral vasodilation compared with isoflurane or desflurane.[4] Cerebrovascular

BOX 62-1 Management of Rapidly Increasing Intracranial Pressure (ICP)

Standards
- No prophylactic hyperventilation

Guidelines
- Monitoring of ICP
- Barbiturate infusion for intractable increased ICP
- Use of mannitol or hypertonic saline

Options
- Cerebral perfusion pressure 50-70 mm Hg
- Brief hyperventilation for acute ICP increase
- Propofol infusion for sedation
- Positioning patient head up

autoregulation and CO_2 response remain intact with sevoflurane up to 1 minimum alveolar concentration (MAC); therefore it is suitable for neurosurgical patients as long as ICP is not markedly or rapidly increasing.

Nitrous oxide is a potent cerebral vasodilator causing a resultant increase in ICP. Although no outcome studies have demonstrated a deleterious effect, nitrous oxide should not be used in patients with rapidly elevated ICP.

Total intravenous anesthesia has received attention in neuroanesthesia as a means of avoiding the vasodilating effects of nitrous oxide and volatile anesthetics. Intravenous agents such as propofol and etomidate produce cerebral vasoconstriction and a reduction in CBF, CBV, and ICP secondary to a decrease in $CMRO_2$ while preserving autoregulation.[5] Propofol should be used intraoperatively in patients with markedly or rapidly increasing ICP, at least until the mass or the ICP has been reduced. In the intensive care unit propofol can be used for up to 3 to 4 days in a maximal dosage of 4 mg/kg/h. Propofol administered for longer or at higher concentrations might induce the *propofol infusion syndrome*, which includes hyperkalemia, lipemia, metabolic acidosis, myocardial failure, rhabdomyolysis, and renal failure potentially resulting in death.[6] All patients with prolonged propofol sedation should be monitored for symptoms of the propofol infusion syndrome. Dexmedetomidine, an alpha-2-adrenergic agonist that is used for sedation of patients in the intensive care unit seems to provide adequate sedation and has no negative influence on ICP.[7,8]

Barbiturates similarly exert their ICP-lowering effects through vasoconstriction and cause a reduction of CBF and CBV secondary to suppression of cerebral metabolism. Barbiturates can produce ICP control and improved CPP in patients with severe head trauma when other treatments have failed, but there is no evidence that prophylactic barbiturate therapy improves outcomes.[9] Furthermore, high doses of barbiturates decrease immune function and can cause hypokalemia. The slow plasma clearance of barbiturates is another disadvantage because it causes a substantial delay in awakening. Barbiturate coma should be titrated to achieve an electroencephalogram (EEG) burst suppression ratio of 5% to 10% or ICP control.

Propofol and barbiturates reduce MAP, and intravenous fluids and vasopressors to elevate CPP are associated with a better chance of survival of patients in a barbiturate or propofol coma.[10] Etomidate causes less cardiovascular depression and may be the drug of choice in cardiovascular disease or hypovolemia, but its use should be confined to induction because it suppresses the adrenocortical response to stress.

There has been controversy about the effect of opioids on ICP. In one study transient increases in ICP without changes in middle cerebral artery blood flow velocity occurred concomitant with decreases in MAP, whereas in patients with stable blood pressure, ICP was unchanged.[11] This suggests that increases in ICP seen with sufentanil and other opioids may be due to autoregulatory vasodilation secondary to systemic hypotension. This is consistent with a more recent study of remifentanil in patients with head trauma.[12]

Nondepolarizing neuromuscular relaxants have no effect on CBF, $CMRO_2$, and ICP, whereas succinylcholine may transiently increase ICP. Pretreatment with a nondepolarizing neuromuscular relaxant avoids the effect of succinylcholine on the ICP.[13] When appropriate for rapid sequence intubation, rocuronium should be used.

What Is the Effect of Hyperventilation on Intracranial Pressure?

Arterial CO_2 tension is a potent modulator of cerebrovascular tone and CBF. Arterial hypercapnia dilates cerebral blood vessels, decreases cerebrovascular resistance, and increases CBF, CBV, and ICP, whereas hypocapnia has the opposite effect. Hyperventilation is often used in patients with increased ICP to reduce CBV. However, hyperventilation reduces ICP through vasoconstriction of cerebral arteries, and this could critically affect the oxygen and glucose delivery to vulnerable brain areas.

Hyperventilation lowers global hemispheric CBF but does not alter $CMRO_2$. This mismatch between low CBF and normal or elevated $CMRO_2$ caused by hyperventilation after severe traumatic brain injury may lead to cerebral ischemia, which might further compromise neuronal outcome.[14]

Although hyperventilation may produce a rapid reduction in ICP and high ICP is one of the most common precursors of death or neurologic disability, there is no evidence to suggest that hyperventilation improves clinically relevant outcomes. Patients with severe traumatic brain injury were randomly assigned to a hyperventilated group ($PaCO_2$, 25 ± 2 mm Hg) or a normoventilated group ($PaCO_2$, 35 ± 2 mm Hg) for 5 days.[15] Patients in the hyperventilation group had a significantly worse outcome at 3 months than did those in the normocapnic group.

In elective supratentorial craniotomy, aggressive hyperventilation ($PaCO_2$, 25 ± 2 mm Hg) has been found in a multicenter randomized trial to reduce

ICP and improve operating conditions as assessed by surgeons unaware of treatment group allocation.[16] This effect was independent of the use of total intravenous propofol anesthesia or less than 0.8 MAC isoflurane. The hyperventilation was not maintained for the duration of the surgery, and the study did not attempt to determine whether the hyperventilation altered neurologic outcomes. Therefore short periods of hyperventilation to manage rapidly increasing ICP can be accepted.

What Is the Effect of Mechanical Ventilation on Intracranial Pressure?

The effect of positive end-expiratory pressure (PEEP) on ICP has been reported by many investigators without a clear consensus. Mechanical ventilation and PEEP can increase intrathoracic pressure, may increase ICP by impeding venous drainage, or could reduce CPP by reducing blood pressure. Studies suggest that if CPP is maintained, PEEP (up to 15 cm H_2O) seems to have no significant adverse effect.[17] If an adverse effect of PEEP on ICP occurs, it can often be overcome by placing the patient in the head-up position.

Volume recruitment maneuvers with high-peak intrathoracic pressure reduce MAP, increase ICP, and decrease CPP. This technique affects cerebral hemodynamics and can only be recommended when severe lung injury is leading to hypoxia, which, in turn, can increase neuronal injury. Recruitment maneuvers should be performed carefully and under continuous control of ICP and CPP.

What Is the Effect of Hyperosmolar Therapy on Intracranial Pressure?

The administration of mannitol (0.25 to 1.0 g/kg) has been a cornerstone of ICP management. Because of side effects (e.g., tubular necrosis of the kidney) a dose of 4 g/kg/day should not be exceeded and the serum osmolarity has to be kept below 320 mOsm/L. The prophylactic administration of mannitol can cause side effects, so it should only be used in patients with increased ICP.[18]

Mannitol has an immediate plasma-expanding effect that reduces blood viscosity, thereby increasing CBF, which, in turn, induces autoregulatory vasoconstriction. This rheologic effect might explain the early decrease in ICP. Osmotic agents withdraw more water from the brain tissue than from other organs because the blood–brain barrier (BBB) impedes penetration of the osmotic agent into the brain, thus maintaining an osmotic diffusion gradient. Osmotic diuretics may also reduce ICP by retarding CSF formation. However, when the BBB is disrupted, hyperosmolar fluids may enter and raise brain osmolality, pulling water back into the brain (rebound). Interstitial accumulation of mannitol is most marked with continuous infusions; therefore it is recommended that mannitol be administrated as repeated boluses rather than as a continuous infusion.[19] The evidence supporting mannitol is sufficiently strong to warrant guideline status. A bolus of mannitol is also recommended in patients with transtentorial herniation or progressive neurologic deterioration not attributable to extracranial causes.[1]

Hypertonic saline is an alternative to mannitol for hyperosmotic therapy. It also reduces the cerebral water content, and its effect on ICP seems to be equal or even superior to mannitol, especially when short-term ICP outcome is assessed.[19] Hypertonic saline also does not cause systemic hypotension secondary to osmotic diuresis. The tested concentrations of hypertonic saline for clinical use range from 2% to 23.5%, but no consensus exists regarding the optimal concentration. At the moment it is unclear whether hypertonic saline also promotes a rebound phenomenon.

What Is the Effect of the Patient's Position on Intracranial Pressure?

Flexion or torsion of the neck can obstruct cerebral venous outflow and increase brain bulk and ICP. A simple change in head position can immediately decrease ICP. Between 30 and 40 degrees head-up or reverse Trendelenburg position is also effective in reducing ICP as long as MAP is maintained.[20]

What Is the Effect of Decompressive Craniectomy on Intracranial Pressure?

Decompressive craniectomy and opening of the dura mater may be a useful option when maximal medical treatment has failed to control ICP. In children, decompressive craniectomy is recommended as a therapy to control ICP.[21] The prognosis after decompression depends on the clinical signs and symptoms at the time of admission, the patient's age, and the existence of major extracranial injuries.[22,23] One criticism of decompressive craniectomy is that more patients survive in a vegetative state. So that this outcome can be avoided, decompressive craniectomy should be restricted to patients younger than 50 years without multiple traumatic injuries or patients younger than 30 years in the presence of major extracranial injuries; it should *never* be used in patients with a primary brainstem lesion.

A significant decrease in ICP and length of stay in the intensive care unit was shown after decompressive craniectomy in 155 adults with severe diffuse brain trauma in the DECRA study,[24] but patients' neurologic outcomes deteriorated. However, in this study no patients with mass lesions were included, the operative technique might have been inadequate, and the ICP in patients was only at the upper normal limit. This might explain the unfavorable outcome of the DECRA study. It is hoped that the Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intra-Cranial Pressure (RESCUEicp) study will clarify this existing confusion about the indication for a decompressive craniectomy in patients with head trauma. After a massive ischemic stroke and elevated ICP, surgical decompression reduced the risk of death as a short-term outcome in patients who were 60 years or younger.[25]

AUTHORS' RECOMMENDATIONS

- In the patient with rapidly elevated intracranial pressure (ICP), propofol provides the greatest margin of safety and ability to reduce ICP. Care must be taken not to compromise cerebral perfusion pressure through hypotension. High-dose barbiturate therapy may be considered in hemodynamically stable patients with severe head injuries and intracranial hypertension refractory to other ICP-lowering therapies.
- Mannitol or hypertonic saline is effective for the control of raised ICP after a severe head injury. Limited data suggest that intermittent boluses are more effective than continuous infusion. Serum osmolarity should be kept below 320 mOsm/L, and hypovolemia should be avoided.
- The use of prophylactic long-term hyperventilation ($PaCO_2$ less than 30 mm Hg) during the first 24 hours after severe traumatic brain injury should be avoided because it can compromise cerebral blood flow. Hyperventilation may be used for short periods in acute neurologic deterioration or elective supratentorial craniotomy.
- A decompressive craniectomy should be considered in children and patients 60 years or younger with stroke. The benefit of decompressive craniectomy after head trauma is still under discussion.

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CHAPTER 63

What Works for Brain Protection?

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INTRODUCTION

Despite recent advances in anesthesia techniques and monitoring measures, intraoperative and postoperative neurologic events remain the most devastating complications and continue to concern anesthesia providers. Even without any significant intraoperative events, there is a considerable risk for cerebral ischemia in specific surgical populations, such as patients undergoing cardiac surgeries and vascular surgeries.

The neurologic sequelae range from frank stroke to cognitive dysfunction. The incidence of perioperative stroke is reported to be from 1.6% to 5.2% in coronary artery bypass grafting (CABG) and from 0.25% to 7% in carotid endarterectomy (CEA),[1] whereas the incidence of cognitive dysfunction ranges from 24% to 57% at 6 months after cardiac surgery.[2]

There is a substantial amount of interest in research to identify neuroprotective strategies; however, most of the clinical trials have resulted in disappointment, and there are no formal guidelines based on the strongest clinical evidence. This is thought to be because of the complexity of the mechanisms in cerebral ischemia.

Most anesthesia providers strongly agree that maintaining adequate cerebral oxygenation and perfusion pressure is the most effective and important strategy in neuroprotection. Historical clinical evidence also advocates avoiding deleterious factors in the event of ongoing cerebral ischemia or in higher risk populations.

OPTIONS

Neuroprotective strategies are classified into two concepts: passive, which refers to the avoidance of deleterious factors, and active, which refers to the application of beneficial interventions. Hans and Bonhomme[3] proposed categorizing the neuroprotection measures into the following areas: physiology, anesthetics, nonanesthetic pharmacologic agents, and preconditioning. Along with these strategies, the role of monitoring in specific surgical populations will also be discussed.

- *Physiology:* avoidance of hyperthermia, hyperglycemia, cerebral hypoxia, and hypoperfusion
- *Anesthetics:* the use of certain anesthetics that are potentially neuroprotective because of reduction of energy requirements
- *Pharmacology:* the use of potentially neuroprotective agents that can block the pathways of neuronal cell death. This may include *N*-methyl-d-aspartate (NMDA) receptor antagonists, excitatory amino acid (EAA) receptor antagonists, and erythropoietin (EPO)
- *Preconditioning:* the use of physiologic or pharmacologic alterations that could mimic preconditioning for high-risk populations
- *Monitoring:* the use of epiaortic echocardiographic scanning to manage severe atherosclerotic disease and near-infrared reflectance spectroscopy (NIRS) for assessment of bifrontal regional cortical oxygen saturation (rSO_2) in cardiac surgery

EVIDENCE

A number of studies have evaluated neuroprotective strategies and outcomes in the areas of physiology, anesthetics, pharmacology, and monitoring (Table 63-1).

Physiology

To ensure adequate cerebral oxygenation and cerebral perfusion, measures that reduce the cerebral metabolic rate (CMR) are known to be beneficial. Hypothermia has been proposed to offer neuroprotective effects for several decades, but in a recent larger clinical trial in patients with acute traumatic injury, hypothermia failed to improve neurologic outcomes.[4,5] The effect of mild hypothermia (32°C to 35°C) on CMR is negligible, and only deep hypothermia (18°C to 22°C), which is used in specific types of cardiac surgeries, is neuroprotective. However, two prospective randomized trials[6,7] in comatose survivors of out-of-hospital cardiac arrest demonstrated better neurologic outcomes in the patients treated with mild hypothermia. It was also reported that intraischemic or delayed hyperthermia worsens outcome.[8] Grigore and colleagues[9] reported that a slower rewarming rate with lower peak cerebral temperatures results in significantly better cognitive performance after cardiac surgery with hypothermic cardiopulmonary bypass (CPB).

Tight glucose control is associated with reduced mortality and morbidity rates in critically ill patients and postcardiac surgery patients.[10] Persistent hyperglycemia after a stroke has been shown to increase the size of ischemic brain injury and worsen clinical outcomes. A retrospective study demonstrated decreased mortality rates when blood glucose levels were normalized after acute ischemic stroke.[11] One should keep in mind that tight glucose control (80 to 110 mg/dL) is associated with

TABLE 63-1 **Overview of Major Clinical Studies Evaluating Neuroprotective Strategies and Outcome**

Study (Year)	No. of Subjects	Patient Population	Study Design	Intervention	Control	Outcomes
Physiology						
Bernard (2002)[7]	273	Comatose survivors of out-of-hospital cardiac arrest	Prospective randomized	Mild hypothermia	Normothermia	Favorable neurologic outcome
Kammersgaard (2002)[8]	390	Acute stroke	Observational	Hypothermia (≤37° C)	Hyperthermia (>37° C)	Low admission temperature is an independent predictor of good short-term outcome
Grigore (2002)[9]	165	CABG with CPB	Prospective not randomized	Slower rate of rewarming	Conventional rewarming	Better cognitive performance at 6 wk
Gentile (2006)[11]	960	Acute ischemic stroke	Retrospective	Normalization of BG (<130 mg/dL) during first 48 hr	Hyperglycemia (BG ≥ 130 mg/dL)	Associated with a 4.6-fold decrease in mortality risk
Vicek (2003)[16]	372	Acute ischemic stroke	Retrospective	Lowering DBP more than 25% from admission value	Maintained DBP	Associated with a 3.8-fold increased adjusted odds for poor neurologic outcome on day 5
Ahmed (2003)[17]	201	Acute ischemic stroke	Retrospective	Lowering DBP with nimodipine	Maintained DBP	Worsened the neurologic outcome in nontotal anterior circulation infarct
Gold (1995)[19]	251	CABG with CPB	Prospective randomized	High MABP (80-100 mm Hg) during CPB	MABP 50-60 mm Hg during CPB	Fewer myocardial and neurologic complications
Anesthetics						
Michenfelder (1987)[24]	2223	Carotid endarterectomy	Retrospective chart review	Isoflurane	Enflurane, halothane	Lower critical CBF (10 mL/100 g/min) versus 15 in enflurane and 20 in halothane; lower incidence of EEG ischemic change (18% versus 26% in enflurane and 25% in halothane)
Messick (1987)[23]	6	Carotid endarterectomy	Prospective single-arm	Isoflurane	Halothane	Lower critical CBF (less than 10 mL/100 g/min) versus 18-20 in halothane
Kanbak (2004)[37]	20	CABG with CPB	Prospective randomized	Isoflurane	Propofol	Alleviated increase of S-100 beta protein
Hoffman (1998)[22]	12	Middle cerebral artery occlusion	Prospective randomized	Desflurane	Etomidate	Increased brain tissue PO_2 and attenuated acidotic change
Mitchell (1999)[32]	65	Left heart valve operation	Prospective randomized	Intravenous lidocaine	Placebo	Fewer incidences of decreased neuropsychological performance
Wang (2002)[33]	118	CABG with CPB	Prospective randomized	Intravenous lidocaine	Normal saline	Decreased the occurrence of early postoperative cognitive dysfunction

TABLE 63-1 **Overview of Major Clinical Studies Evaluating Neuroprotective Strategies and Outcome** (Continued)

Study (Year)	No. of Subjects	Patient Population	Study Design	Intervention	Control	Outcomes
Pharmacology						
Arrowsmith (1998)[40]	171	CABG with CPB	Prospective randomized	Remacemide	Placebo	Overall postoperative change (reflecting learning ability in addition to reduced deficits) was favorable in treated group
Mathew (2004)[41]	914	CABG with CPB	Prospective randomized	Pexelizumab	Placebo	Decreased visuospatial function impairment but not overall cognitive dysfunction
Ehrenreich (2002)[42]	40	Acute ischemic stroke	Prospective randomized	Recombinant human erythropoietin	Saline	Improvement in clinical outcome at 1 mo
Bhudia (2006)[44]	350	Cardiac surgery with CPB	Prospective randomized	Magnesium sulfate	No intervention	Improved short-term neurologic function
Pandharipande (2007)[47]	106	Mechanically ventilated in ICU	Prospective randomized	Dexmedetomidine	Lorazepam	More days alive without delirium or coma; more time at the targeted level of sedation
Monitoring						
Royse (2000)[49]	46	CABG with CPB	Prospective not randomized	Epiaortic echocardiography and exclusive Y graft	Digital palpation and aorta-coronary operations	Less incidence of late neuropsychological dysfunction
Murkin (2007)[50]	200	CABG with CPB	Prospective randomized	Cerebral regional oxygen saturation monitoring and treatment protocol	No intervention	Avoids profound cerebral desaturation and is associated with fewer incidences of major organ dysfunction

BG, blood glucose; *CABG*, coronary artery bypass grafting; *CBF,* cerebral blood flow; *CPB*, cardiopulmonary bypass; *DBP*, diastolic blood pressure; *EEG*, electroencephalogram; *ICU,* intensive care unit; *MABP*, mean arterial blood pressure.

a higher incidence of hypoglycemia.[12] In a retrospective study of 172 patients with subarachnoid hemorrhage (SAH), lower nadir glucose levels were associated with progressively worse outcomes. The investigators also reported that patients with symptomatic vasospasm had lower nadir glucose levels than those without vasospasm.[13] Nonetheless, on the basis of these clinical data, hyperglycemia should be avoided perioperatively.

The use of corticosteroids is not advocated in ischemic or traumatic brain injury because no strong evidence supports the benefit from treatment with corticosteroids.[14] In addition, hyperglycemia induced by administration of corticosteroids is potentially harmful.[15]

Maintaining baseline blood pressure is an essential measure that ensures vital organ perfusion, including that to the brain. Cerebral perfusion pressure is calculated by subtracting intracranial pressure from mean arterial blood pressure (MABP). Two clinical studies demonstrated that lowering diastolic blood pressure (DBP) in the early phase of ischemic stroke worsened the neurologic outcome.[16,17]

Another retrospective study in patients who sustained sudden cardiac arrest demonstrated that good neurologic recovery was independently and directly related to MABP during the first 2 hours after return of spontaneous circulation.[18] Gold and colleagues[19] found fewer myocardial and neurologic complications after CABG surgery when targeted MABP during CPB was between 80 and 100 mm Hg rather than 50 and 60 mm Hg. In this study, the incidence of cognitive dysfunction at

6 months after surgery was low, and no relation was found between arterial pressure and cognitive outcome. However, maintaining a "higher" MABP target is considered to be acceptable, safe, and useful for patients at high risk of neurologic complications.[20]

Anesthetics

Accumulating experimental evidence confirms the neuroprotective effect of inhalational anesthetics in both focal and global ischemia. The mechanism involves inhibition of excitatory neurotransmission and potentiation of inhibitory receptors, resulting in suppression of energy requirements. Preconditioning from inhalational agents is proposed as an additional mechanism of neuroprotection. The tolerance against ischemia is increased in the future event by activation of adenosine triphosphate (ATP)–dependent potassium channels and adenosine A1 receptors.[1,21] In contrast to the multitude of experimental studies, clinical evidence on the neuroprotective effect of inhalational anesthetics has been scant. Hoffman and colleagues[22] reported that desflurane, in comparison with etomidate, increased brain tissue oxygen pressure and reduced acidosis in patients subjected to temporary middle cerebral artery occlusion. Another prospective study in patients undergoing CEA determined that critical regional cerebral blood flow, which is the flow rate when electroencephalographic signs of ischemia are evident, during isoflurane anesthesia was much lower than during halothane or enflurane anesthesia.[23] In a retrospective study, the incidence of ischemic change was lower with isoflurane anesthesia when compared with halothane or enflurane anesthesia, and no difference was found in neurologic outcomes, despite the fact that the isoflurane group had a higher risk of an adverse outcome.[24] Sufficiently powered, prospective, randomized controlled studies evaluating neurologic outcomes using more appropriate endpoints such as long-term neurocognitive function are still needed. However, the use of volatile anesthetics can be considered as a part of an anesthetic plan when the risk of neuronal injury is anticipated.

Xenon is the most potent inert gas to be used as an anesthetic agent and has been shown to have potential neuroprotective properties because it can inhibit the NMDA receptor. A large number of recent studies report that xenon affords neuroprotection in a variety of animal models, including focal cerebral ischemia, neonatal asphyxia, neurocognitive deficit after CPB, and traumatic brain injury.[25] Xenon has also been shown to be neuroprotective in preconditioning paradigms. Despite promising data from animal studies, very few clinical trials have addressed xenon neuroprotection. The use of xenon is limited because of the significantly high cost of production and complexity of administration that requires closed circuits. Small clinical trials examining the efficacy of xenon in decreasing postoperative cognitive dysfunction after noncardiac surgery failed to show an advantage compared with propofol or desflurane.[26-28]

Lidocaine was shown to have a neuroprotective effect in an in vivo study due to the reduction of energy consumption by delay of ischemia-induced membrane depolarization and also by alleviation of apoptosis.[29-31] In a small clinical trial, lidocaine infusion at an antiarrhythmic dose demonstrated improved long-term neuropsychologic performance in 65 patients with left heart valve procedures.[32] More recently, Wang and colleagues[33] reported that intraoperative administration of lidocaine decreased the occurrence of early postoperative cognitive dysfunction in patients who had undergone CABG surgery. Neither of these studies had enough power to conclude that lidocaine infusion should be used routinely as a neuroprotective agent. Larger clinical trials determining the optimal dosing regimen and long-term results are still needed.

The neuroprotective ability of barbiturates has long been postulated, and their mechanism of action is thought to originate from reduction of the CMR and blockade of glutamate receptors. However, mixed results have been published, and their clinical perioperative efficacy remains controversial.[34,35] One of the problems with using barbiturates is their prolonged duration of action, thus causing delayed emergence. Because the volatile anesthetics have been shown to have similar effects as barbiturates but with shorter emergence time, the popularity of barbiturates has declined.

Propofol and ketamine have also been postulated to be neuroprotective agents; however, both drugs failed to improve long-term neurocognitive performance.[36-38] A recent randomized two-arm prospective study compared propofol with isoflurane using plasma S100beta as a brain injury marker; neurologic outcomes at 6 months postoperatively in the patients with traumatic brain injury demonstrated that propofol attenuated the increase of S100beta and improved neurologic outcomes; however, the latter did not reach statistical significance because of small sample size.[39]

Pharmacology

A few clinical trials with encouraging results deserve mention. Remacemide, an NMDA receptor antagonist, has been shown to improve some measures of postoperative psychometric performance in cardiac surgery patients.[40]

Mathew and colleagues[41] reported that pexelizumab, a humanized monoclonal antibody against the C5 complement component, led to less visuospatial impairment up to 1 month after CABG surgery but failed to decrease the overall incidence of cognitive dysfunction.

EPO has been used for the treatment of anemia and is known to be safe. It blocks apoptosis, blocks inflammation, and induces vasculogenesis and neurotrophic factors. In a clinical trial, high-dose intravenous EPO was shown to improve clinical outcomes at 1 month in patients with acute ischemic stroke.[42]

Magnesium, because of its direct vasodilatory effects and antagonism of the NMDA receptor, has been investigated as a potential treatment for patients with SAH. It also reduces the ischemia-related rise in intracellular Ca^{2+}, thereby preventing cell death. Ma and colleagues[43] reported a meta-analysis of six prospective studies evaluating the beneficial effect of serum magnesium

concentration–targeted therapy on outcomes after SAH. In this analysis, magnesium sulfate was found to reduce the relative risk of poor outcomes as well as the risk of delayed cerebral ischemia. However, the use of magnesium was associated with a higher incidence of hypotension, arrhythmia, renal failure, respiratory arrest, myocardial infarction, and phlebitis. A single randomized placebo-controlled trial enrolling 350 patients undergoing CABG demonstrated that magnesium administration improved short-term postoperative neurologic function but not long-term outcomes.[44]

Dexmedetomidine is a potent and highly selective alpha-2 adrenoceptor agonist with sedative, amnestic, and analgesic properties. It has been used in many clinical settings, including as an anesthetic adjunct and as a sedative for awake intubation or for critically ill patients. There is increasing evidence of its organ-protecting effects against ischemic and hypoxic injury, including cardioprotection, neuroprotection, and renoprotection.[45] It has been shown to attenuate hypoxic–ischemic brain injury in developing brains and to improve functional neurologic outcomes after brain injury.[46] No randomized controlled trials have directly evaluated the neuroprotective effects of dexmedetomidine. The Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) study demonstrated that the use of dexmedetomidine infusion reduced the incidence of delirium or coma and postoperative mortality.[47]

Numerous pharmacologic agents have been investigated for their potential ability to limit neuronal injury. Despite promising data from laboratory work, all had disappointing clinical results. This was mainly due to the complexity of the mechanisms of neuronal injury and the difficulty in controlling physiologic factors. The combination of multiple strategies, including the use of compounds targeting different pathways and the control of physiologic variables, may afford the most meaningful results in perioperative neuroprotection.

Preconditioning

Preconditioning is a novel concept of neuroprotection in which a prior exposure to minor insults will induce an increased tolerance to more serious injury.[1] The mechanism of preconditioning is activation of ATP-dependent potassium channels and adenosine A_1 receptors.[1] Other than a history of transient ischemic attack before acute stroke promoting ischemic tolerance in the human brain, many factors and various drugs can mimic preconditioning, such as hyperoxia, hypothermia, electroconvulsive shock, volatile anesthetics, the potassium channel opener diazoxide, and erythromycin.[3]

Monitoring

In some specific surgical procedures, the use of specific monitoring measures may have an impact on neurologic outcome. The change of surgical approach led by intraoperative epiaortic echocardiography has been shown to lower the incidence of late neurologic dysfunction in a large observational study[48] and also in a smaller case-control study.[49] This strategy is rated as class IIb (acceptable, safe, and useful) for patients undergoing CABG surgery at high risk of neurologic injury in an evidence-based rating by Hogue and colleagues.[20]

The use of NIRS for assessment of rSO_2 has demonstrated a correlation between coronary artery bypass patients having low rSO_2 values and cognitive dysfunction, prolonged hospital length of stay, and cerebrovascular accident. A recent randomized controlled study by Murkin and colleagues[50] demonstrated that the treatment of declining rSO_2 prevented prolonged desaturations and was associated with a shorter intensive care unit length of stay and a significantly reduced incidence of perioperative major organ morbidity and mortality. This result may have been a reflection of the good clinical practice of optimizing organ perfusion instead of the direct effect of rSO_2 monitoring. However, the monitoring would allow early detection and rapid improvement of end-organ compromise.

AREAS OF UNCERTAINTY

An important cause of the mixed results in clinical trials to evaluate perioperative neurologic outcomes is the complexity of the mechanism of neuronal injury. Many layers of pathways and various transmitters and their receptors are involved. The mechanism of global ischemia differs from focal ischemia. For instance, the avoidance of hypoxia and hypoperfusion is essential to perioperative brain protection, and rapid restoration of the oxygen supply is critical after the ischemic insult; however, hyperoxia and excessive hypertension should be avoided because a worsening outcome with hyperoxia after global ischemia is a concern.[15]

The problem in interpreting the results from most of the clinical studies is that the endpoints of these trials are not uniform. Because the mechanism of early neuronal injury is more likely necrosis and the mechanism of delayed injury is apoptosis, the clinical manifestation would be different. Care must be taken in terms of appropriate timing of treatment and neurobehavioral testing when the results of these studies are evaluated.

GUIDELINES

No formal practice guidelines exist regarding perioperative neuroprotection. The clinical evidence of most of the neuroprotective strategies is weak because of the lack of large, prospective, randomized controlled trials. The Internal Liaison Committee on Resuscitation published an advisory statement in 2003 regarding therapeutic hypothermia after cardiac arrest based on two prospective randomized trials that demonstrated promising results with improved neurologic outcomes in the hypothermia group. In addition to ventricular fibrillation of out-of-hospital cardiac arrest, it states that cooling to 32° C to 34° C for 12 to 24 hours after the insult may also be beneficial for other rhythms or an in-hospital cardiac arrest.[51]

AUTHORS' RECOMMENDATIONS

Presently, no definitive neuroprotective strategies are supported by strong clinical evidence. The available data do not support a definite benefit, even for some of the strategies that have been historically used to provide neuroprotection. One example is the use of thiopental and steroids in cardiac surgery with deep hypothermic circulatory arrest. Furthermore, some strategies have been shown to be harmful. Based on very limited aforementioned clinical evidence, the following recommendations can be made when ischemic insults are anticipated in patients at high risk or for the management of patients after the occurrence of a significant insult. These recommendations mainly consist of avoidance of deleterious interventions rather than beneficial measures.

- Hyperthermia, hyperglycemia, hypoxemia, and hypoperfusion should be avoided at all times. Mild induced hypothermia (32°C to 34°C) may be beneficial after recovery from out-of-hospital cardiac arrest or in-hospital cardiac arrest. Insulin therapy should be used to maintain normoglycemia. Hyperoxemia should be avoided in cases of global ischemia. After restoration of spontaneous circulation, oxygen saturation should be maintained within the range of 94% to 96%.
- Volatile anesthetics can be used during the intraoperative period to obtain the benefit of reduced energy requirements and potential preconditioning.
- The use of magnesium may be beneficial for patients with subarachnoid hemorrhage or those undergoing cardiac surgeries with cardiopulmonary bypass (CPB).
- The use of dexmedetomidine may be considered for sedation in the intensive care unit.
- The use of corticosteroids should be avoided in global ischemia.
- In the management of CPB in patients at high risk of neurologic injury (e.g., advanced age, prior stroke, or atherosclerosis of the ascending aorta), higher mean arterial blood pressure should be maintained.
- In coronary artery bypass graft surgery, the use of epiaortic echocardiography scanning and a change of surgical approach may be warranted to prevent macroembolism from manipulation of atherosclerosis in the aorta.

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CHAPTER 64

Anesthesia for Cesarean Delivery: Regional or General?

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INTRODUCTION

The cesarean delivery rate has been steadily increasing and in 2009 climbed to 33%.[1] The most common indications for cesarean delivery include prior cesarean delivery, dystocia, breech position, multiple gestation, and fetal distress. The cesarean delivery rate is likely to increase further as women are requesting an elective cesarean delivery even for their first delivery, also known as "cesarean on demand." Although controversial, the American College of Obstetricians and Gynecologists (ACOG) has opined that it is ethical for an obstetrician to perform an elective cesarean delivery if the physician believes that the cesarean delivery promotes the health of the mother and fetus more than a vaginal delivery.[2] Additionally, the number of women attempting a trial of labor after cesarean (TOLAC) has also decreased.[1] The selection of regional or general anesthesia for cesarean delivery depends on the experience of the anesthesiologist, past medical history of the patient, and the indication for and urgency of the cesarean delivery. The anesthetic considerations will be discussed separately for the elective case, where there is little controversy that regional anesthesia is the preferred technique, and the emergent case, where controversy exists.

OPTIONS/THERAPIES

When choosing regional or general anesthesia for cesarean delivery, one must consider both maternal and neonatal outcomes. Maternal outcome studies have primarily focused on maternal mortality, and neonatal outcome studies have focused on umbilical cord pH, Apgar score, the need for ventilatory assistance at birth, and neurobehavioral scores.

EVIDENCE

Elective Cesarean Delivery

Maternal outcomes are better with regional anesthesia than with general anesthesia. In 1997, Hawkins and colleagues[3] found that the case fatality rate for cesarean delivery for the years 1979-1990 was 16 times greater with general anesthesia than with regional anesthesia. The same group reviewed maternal mortality case fatality rate for the years 1991-2002 and again found that the mortality rate was greater when general anesthesia was used, although only by a factor of 1.7.[4] The reason for this difference in anesthetic techniques is primarily related to the respiratory system of the parturient. Difficult tracheal intubation in the parturient is approximately 10 times that of the general population.[5] Furthermore, hypoxemia develops quickly during periods of apnea, and the parturient is at increased risk of pulmonary aspiration. As the incidence of general anesthesia for cesarean delivery decreases, airway experience among trainees is also decreasing. Johnson and colleagues[6] in a study from England found that in 1988 the average trainee was only exposed to four general anesthetics for cesarean delivery during their training. In a follow-up study from the same hospital they found this number decreased further to one general anesthetic per trainee.[7] Hawthorne and colleagues[8] reviewed the incidence of failed tracheal intubation on their maternity unit. They found that the incidence of failed tracheal intubation, defined as the inability to successfully intubate the trachea with one dose of succinylcholine thus necessitating initiation of the failed intubation protocol, increased from 1 in 300 in 1984 to 1 in 250 in 1994. In a recent review of the etiology of maternal mortality, Mhyre and colleagues[9] found that "airway problems" are still a leading cause of maternal mortality but that the problems occurred during emergence or tracheal extubation and not during tracheal intubation as was found in an earlier study.[10]

Neonatal outcomes are also better or unchanged when regional anesthesia is used, although not all studies have demonstrated this. The variables generally measured are umbilical cord pH and clinical variables such as Apgar score and the need for ventilatory assistance. Reynolds and Seed[11] performed a meta-analysis with the primary outcomes of umbilical cord pH and base deficit. They found that spinal anesthesia was associated with a decreased umbilical cord pH and greater base excess than either general or epidural anesthesia. One flaw of their analysis is that both randomized and nonrandomized studies were included as were urgent and nonurgent cases. Also, the choice of vasopressor and degree of hypotension was not controlled. In a second meta-analysis of studies in which patients were randomly assigned to general or regional anesthesia for elective procedures, no differences in umbilical cord pH, Apgar scores, or neurobehavioral scores were found among groups.[12] It should be noted that, even in studies that

found biochemical variables to be better with general anesthesia, clinical variables, such as Apgar scores and the need for ventilatory assistance, were not consistently better.[13]

Spinal anesthesia rather than epidural anesthesia is commonly used for elective cesarean delivery because the speed of onset is quicker and the failure rate is lower. Riley and colleagues[14] found that spinal anesthesia was more reliable and led to a more efficient use of operating room time than epidural anesthesia because the time from entering the operating room until skin incision is faster with spinal anesthesia. In a 2001 survey of obstetric anesthesia trends in the United States, Bucklin and colleagues[15] found that approximately 95% of all elective cesarean deliveries were performed with neuraxial anesthesia and that approximately 80% were performed with spinal anesthesia. The most common complication from spinal anesthesia is hypotension, which should be aggressively treated. Ngan Kee and Lee[16] found in a multivariate analysis that a decrease in systolic blood pressure was an important factor in neonatal outcome.

Numerous techniques for preventing hypotension after spinal anesthesia have been attempted, with varying success. The most important preventive measure is to ensure left uterine displacement so as to avoid supine hypotensive syndrome.[17] Prehydration is not an effective measure to prevent hypotension. Rout and colleagues[18] randomly assigned women to receive no prehydration or 20 mL/kg of a crystalloid solution before cesarean delivery. They found a smaller incidence of hypotension in the prehydrated group (55%) as compared with the control group (71%), but the total amount of fluid, the total amount of ephedrine, and the severity of the hypotension did not differ between groups. Also, the prehydrated group still had a certain amount of hypotension. Park and colleagues[19] randomly assigned women to receive 10, 20, or 30 mL/kg of crystalloid before cesarean delivery. They found less hypotension as the amount of prehydration increased (67% versus 56% versus 47% in the 10, 20, and 30 mL/kg groups, respectively), but it did not reach statistical significance. However, even in those who received 30 mL/kg of crystalloid prehydration, there was almost a 50% incidence of hypotension.

Colloid rather than crystalloid prehydration has also been studied. Ueyama and colleagues[20] were the first to randomly assign women undergoing cesarean delivery to receive either 1500 mL of a crystalloid (lactated Ringer solution) or 500 mL or 1000 mL of a colloid solution (hydroxyethyl starch). The incidence of hypotension was 75% in those who received the crystalloid, 58% in those who received 500 mL of the colloid, and only 17% in those who received 1000 mL colloid. A more recent study confirmed these findings and also found that cardiac output was unchanged between crystalloid and colloid groups.[21] Even in studies that demonstrated that colloid is associated with less hypotension, it has not been shown to improve neonatal outcomes.[22]

Coloading, administering IV fluid rapidly at the time of spinal anesthesia rather than before the anesthetic, has been suggested as an alternative, but this too has not led to decreased hypotension. A meta-analysis of studies comparing preloading with coloading did not find a difference in the incidence of hypotension: 59% in the coloading group and 62% in the preloading group.[23]

Some have recommended prophylactic pressor agents to prevent hypotension. Both ephedrine[24] and phenylephrine have been used, and the most success has been with high-dose phenylephrine infusion along with crystalloid coloading.[25] The problem with this modality is that many of the patients had reactive hypertension. Because most women and their neonates tolerate hypotension without long-term sequelae,[26] the use of the technique has been questioned; it should be used judiciously, and maternal comorbidities should be taken into account.[27] Treatment of hypotension should be aggressive, and the use of phenylephrine has been shown to be better than ephedrine for treating hypotension. This benefit included better hemodynamic control, less maternal nausea and vomiting, and improved acid–base status in the neonate.[28]

Emergency Cesarean Delivery

Maternal outcome is also improved when regional anesthesia is used for an emergent cesarean delivery because of the difficulty with tracheal intubation. Airway concerns during an emergency cesarean delivery are even greater than in the elective scenario. Endler and colleagues[10] reviewed maternal deaths in the state of Michigan from 1972 through 1984. They found that the emergent situation was a risk factor for difficult tracheal intubation and that the inability to successfully intubate the trachea was the principal cause of death in 11 of 15 patients.

Neonatal outcome for the emergent cesarean delivery is also better with regional anesthesia than with general anesthesia. A number of retrospective studies[29-32] but only one prospective study[33] addressed anesthetic technique and its impact on the neonate during urgent cesarean delivery. All the retrospective studies have been fairly consistent and have found that neuraxial anesthesia has an advantage over or is equivalent to general anesthesia in regard to Apgar scores and requirement for assisted ventilation. Bowring and colleagues[30] found that not only were Apgar scores better in those who received regional anesthesia but also the admission rate to the neonatal intensive care unit was lower in the regional anesthesia group.

In the only prospective study, Marx and colleagues[33] evaluated neonatal outcomes for women who underwent cesarean delivery because of fetal distress. The choice of anesthetic—general, spinal, or an extension of an existing epidural catheter—was made by the mother immediately before administration of the anesthetic. There were 126 women in the study of whom 71 chose general anesthesia, 33 chose spinal anesthesia, and 22 chose extension of their epidural anesthetic. The time from decision to perform a stat cesarean delivery until skin incision was less than 20 minutes in all patients. However, the time from decision to perform the cesarean delivery until skin incision was greater in the regional anesthesia groups as compared with the general anesthesia group. Despite this difference in starting time,

they were unable to detect a significant difference in 5-minute Apgar scores or umbilical arterial or venous pH among the three groups; however, the 1-minute Apgar score was greater in the regional anesthesia groups than in the general anesthesia group.

A potential flaw in the Marx study and the retrospective studies is that the definition of what constituted an emergency cesarean delivery was not made clear. Nonetheless, the data support the use of spinal anesthesia for most cases of emergency cesarean delivery. The main concern with choosing spinal anesthesia is the time required for the patient to be anesthetized for the surgery. Obviously, each case should be individualized, but many skilled clinicians can quickly perform spinal anesthesia and are choosing spinal anesthesia for all but the most emergent cases, (e.g., cord prolapse); even in those scenarios, many are choosing spinal anesthesia if the mother has a potential difficult airway or has other comorbidities.

AREAS OF UNCERTAINTY

Most clinicians agree that for elective cesarean delivery, regional anesthesia is safer than general anesthesia for both the mother and the baby and is therefore the preferred technique. The area of uncertainty relates to emergent cesarean delivery. The overriding concern with spinal anesthesia is that the placement may take "too long." However, choosing a general anesthetic should not be taken lightly because the leading cause of maternal morbidity and mortality remains airway catastrophes and aspiration pneumonia.

Obstetricians tend to use the terminology *emergent cesarean delivery* to describe many different scenarios in which there is concern about the fetus. A more useful classification may be to further classify the emergency as either *urgent* or *stat*. An urgent cesarean delivery is one in which there is some concern about the fetus and the baby should be delivered before there is further deterioration, such as the case where there are variable fetal heart rate decelerations with prompt recovery. A stat cesarean delivery is one in which time is of the essence, such as in the case of a cord prolapse with a slow fetal heart rate or maternal hemorrhage. The anesthetic choice may differ based on whether the indication for the emergent cesarean delivery is urgent or stat.

GUIDELINES

There are three guidelines published by ACOG, and one is published in conjunction with the American Society of Anesthesiologists (ASA) in regard to emergency cesarean delivery.[34] The joint guideline states that hospitals should have the availability of anesthesia and surgical personnel to initiate a cesarean delivery within 30 minutes of the decision to perform the procedure.[34] The second guideline asserts in part that (1) failed intubation and pulmonary aspiration is the leading cause of morbidity and mortality for the mother, (2) the obstetrician should be able to identify those factors that place the patient at greater risk of general anesthesia and should request an antepartum anesthesia consultation, (3) strategies to reduce the need for emergency induction of general anesthesia should be developed, including the early placement of an epidural anesthetic, (4) the term *fetal distress* is "imprecise, nonspecific and has little positive predictive value" and, (5) a cesarean delivery for a nonreassuring fetal heart rate pattern does not preclude the use of regional anesthesia.[35] In a further committee opinion, ACOG reiterated their concern with the use of the term *fetal distress* and that it should be replaced with the term *nonreassuring fetal heart rate tracing* followed by a description of the fetal tracing.[36] The ASA has developed Practice Guidelines for Management of the Difficult Airway.[37] These guidelines are an excellent guide to the management of the unanticipated difficult endotracheal intubation, and a plan based on these guidelines is summarized in Figure 64-1.

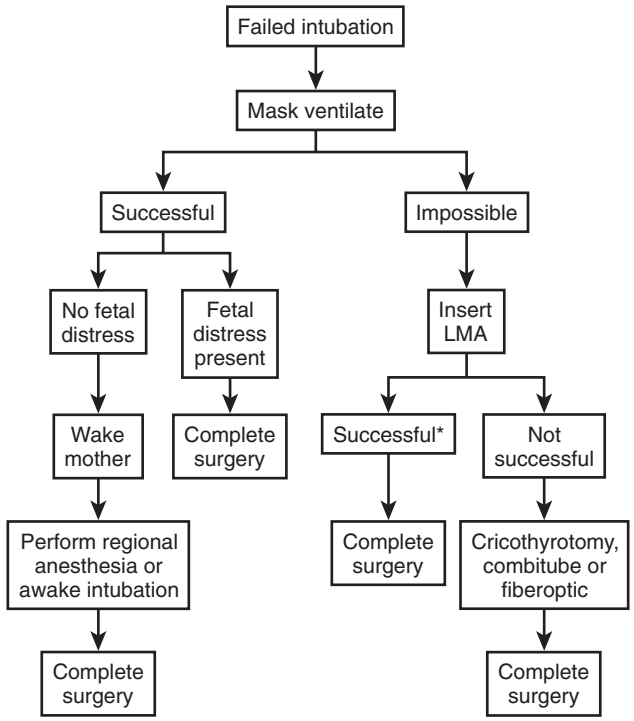

FIGURE 64-1 ■ Management of the Unanticipated Difficult Airway. *LMA,* laryngeal mask airway. *Consider endotracheal intubation through the LMA.

AUTHOR'S RECOMMENDATIONS

Elective Cesarean Delivery

Box 64-1 shows the steps to be taken when regional anesthesia is used for elective cesarean delivery. Spinal anesthesia should be used for the majority of elective cesarean deliveries. Use hyperbaric 0.75% bupivacaine, 1.5 mL, which will reliably give a thoracic-4 level of anesthesia. Preservative-free morphine sulfate, 1 to 2.5 mg, should be added to the spinal bupivacaine. Some opt to use the combined spinal epidural technique for cesarean delivery in case the procedure is prolonged. This decision should be made on an individual basis and should take into account the speed of the surgeon and specific patient factors, for example, repeat cesarean delivery or previous abdominal procedures.

Epidural anesthesia is generally reserved for the parturient who has an epidural in situ, or where there may be a benefit to slow titration of local anesthetic such as a woman with severe hypertension or valvular heart disease. Lidocaine 2% with epinephrine is a commonly used epidural anesthetic regimen. Preservative-free morphine sulfate, 3 to 4 mg, should be given epidurally after delivery of the baby. General anesthesia is reserved for the patient who refuses a regional anesthetic technique or when there is another contraindication to regional anesthesia, such as coagulopathy or infection at the site.

Emergency Cesarean Delivery

When the indication is urgent (not stat), use a spinal anesthetic or an epidural in situ. When a spinal anesthetic is administered for urgent cesarean delivery, the fetal tracing should be continuously monitored in the operating room. Sometimes, the fetal heart rate will improve from the time the patient leaves the operating room until the patient enters the operating room and the urgency will decrease. Do not wait for prehydration before placing the spinal anesthetic but leave the intravenous line running wide open while the spinal is placed. Bupivacaine 0.75% (1.5 mL) will confer adequate and quick analgesia for the cesarean delivery. Early placement of an epidural anesthetic is recommended in a woman likely to require a cesarean delivery or in a woman in whom general anesthesia may be deleterious (history of a difficult airway). Lidocaine 2% with 1:200,000 epinephrine or 2-chloroprocaine 3% can be used to provide safe and rapid anesthesia for the cesarean delivery.

When confronted with a stat cesarean delivery (time is of the essence), the anesthesiologist must accomplish the anesthetic quickly and efficiently and must take into account both the mother and the fetus. Maternal concerns include any preexisting medical condition and a full evaluation of the airway. A nonparticulate antacid should be administered. Airway evaluation should start with an external examination of the head and neck. A receding mandible (micrognathia) and other external anomalies should be noted. Difficulty in neck extension and flexion may predict suboptimal alignment of the oral, pharyngeal, and laryngeal axes. The relation of the size of the tongue to the oral cavity can be estimated using the Mallampati classification. Combining all this information will help the clinician decide if a difficult tracheal intubation is anticipated. Clinical experience is the key to making this decision. If the mother has a known or suspected difficult airway, either an awake tracheal intubation should be performed or a spinal anesthetic should be used. However, under *no* circumstance should the patient receive a general anesthetic before the airway is secured.

If the mother does not have a suspected difficult airway, then either a quickly placed spinal anesthetic or general anesthesia should be used. A spinal anesthetic is not contraindicated in this scenario if it can be accomplished quickly. Some skilled practitioners believe it is quicker to administer a spinal anesthetic then to adequately prepare for a general anesthetic, which requires a rapid sequence induction with preoxygenation. The ultimate decision is based on the skill and experience of the anesthesiologist.

General endotracheal anesthesia must be accomplished in a rapid sequence manner (Box 64-2). After preoxygenation and application of cricoid pressure, general anesthesia proceeds with an induction agent and succinylcholine for paralysis. Although subtle differences exist among induction agents in regard to maternal and neonatal outcomes, they are essentially all safe. Either propofol or etomidate is commonly used. Anesthesia is maintained with either 100% oxygen (emergency cesarean delivery) or 50% oxygen (nonemergent) in N_2O, and approximately 0.5 to 1 minimal alveolar concentration of a potent inhaled anesthetic agent is used to ensure amnesia. The greater concentration of oxygen is chosen for emergency cases to maximize oxygen delivery to the compromised fetus, although this has never been shown to improve outcome.[38]

BOX 64-1 A Suggested Technique for Performing Regional Anesthesia for Elective Cesarean Delivery

1. Check the anesthesia machine. Prepare resuscitative equipment and drugs.
2. Start large-bore intravenous line.
3. Administer a nonparticulate antacid by mouth.
4. Transport to the operating room with left uterine displacement.
5. Place routine monitors including blood pressure cuff, electrocardiogram, and pulse oximeter.
6. Administer oxygen via nasal cannula or face mask.
7. **For spinal anesthesia:** Use small-gauge (25-27) pencil-point needle. Administer 1.5 mL of 0.75% hyperbaric bupivacaine with 0.1-0.25 mg of preservative-free morphine sulfate.
8. **For epidural anesthesia:** After placing epidural catheter, administer 3 mL of 2% lidocaine with epinephrine 1:200,000 as a test dose. Wait 5 minutes, observing for signs of either intravascular or subarachnoid injection. After confirming catheter position, inject same medication in 5-mL increments, no more frequently than every 3-5 minutes, until Thoracic-4 level of anesthesia is achieved. Administer 3-4 mg of preservative-free morphine sulfate after delivery of the baby.
9. Monitor vital signs every 1-2 minutes for the first 10-20 minutes and then every 3-5 minutes thereafter, if stable.
10. If hypotension occurs, administer boluses of crystalloid solution and phenylephrine in 50-100 mcg intravenous doses until blood pressure returns to normal.
11. Monitor fetal heart rate before and after placement of neuraxial anesthetic until surgery starts.
12. After delivery of the baby, administer oxytocin.

BOX 64-2 A Suggested Method for Performing a General Anesthetic

1. Check the anesthesia machine. Prepare resuscitative equipment and drugs.
2. Start large-bore intravenous line.
3. Administer a nonparticulate antacid by mouth.
4. Transport to the operating room with left uterine displacement.
5. Place routine monitors including blood pressure cuff, electrocardiogram, and pulse oximeter.
6. Administer oxygen via face mask.
7. Monitor fetal heart rate before induction of anesthesia, and if it improves, consider spinal anesthesia.
8. After denitrogenation, induce anesthesia with propofol 2 mg/kg or etomidate 0.3 mg/kg followed by succinylcholine, 100 mg, with cricoid pressure. Do not administer a defasciculating dose of a nondepolarizing agent.
9. Maintain anesthesia with 100% O_2, and 0.5-1 minimum alveolar concentration (MAC) potent volatile anesthetic agent until the baby is delivered. After delivery of the baby, administer fentanyl 100 mcg and increase the N_2O concentration to 70%. Keep concentration of halogenated agent below 0.5 MAC to avoid uterine relaxation.
10. Administer neostigmine 0.04-0.07 mg/kg and glycopyrrolate 0.01-0.15 mg/kg to antagonize residual neuromuscular blockade.
11. Tracheally extubate when the patient is fully awake.

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CHAPTER 65

When Should a Combined Spinal–Epidural Be Used?

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INTRODUCTION

The combined spinal–epidural (CSE) technique produces reliable and rapid onset of spinal anesthesia combined with the flexibility to extend the height and duration of a block provided by continuous epidural anesthesia. CSE has become a popular technique in both obstetrics and orthopedic surgery. CSE was originally described in 1979[1,2] as a double-segment technique with the epidural and spinal procedures performed at different interspaces of the lumbar spine. Advances in needle design led to the more popular and practical single-segment technique (SST) in use today. In 1981[3] clinicians described the use of the SST for lower limb surgery and in 1982[4] for cesarean section.

The SST involves locating the epidural space with either a standard or a specialized epidural needle using the loss of resistance technique. Once the epidural space has been identified, a small-gauge spinal needle is introduced via the epidural needle into the cerebrospinal fluid. A spinal dose of opioid or local anesthetic (or both) is given through the spinal needle, and then the spinal needle is removed. An epidural catheter is then inserted through the epidural needle to the appropriate depth. The technique can be performed in the sitting or lateral position.

OPTIONS/THERAPIES

The CSE technique is widely used for labor analgesia, anesthesia for cesarean section, lower-extremity orthopedic surgery, and urologic procedures. Once popular, the role of CSE in lower-extremity vascular procedures has declined secondary to the use of antithrombotic and antiplatelet therapies for the treatment of vascular disease.

CSE produces a rapid onset of analgesia for the woman in advanced labor while simultaneously maintaining the maternal ability to push during the second stage.[5] In early labor, an initial dose of intrathecal opioid alone maintains maternal mobility and may increase the speed of cervical dilation.[6,7] Concurrent placement of the epidural catheter enables additional doses of local anesthetic with or without opioid to produce prolonged labor analgesia or cesarean section anesthesia.

CSE for cesarean section provides the benefit of a quick onset of neuraxial blockade with the ability to use the epidural if the spinal block recedes or the surgery is unexpectedly prolonged. Secondarily, the epidural can be used to provide postoperative analgesia with both low-dose local anesthetics and epidural opioids.

In orthopedic procedures, the CSE technique is used in lower-extremity surgeries, such as total hip and total knee arthroplasties. The technique can be as efficient as a general anesthetic,[8] may reduce the incidence of postoperative deep vein thrombosis,[9] and can be used for postoperative analgesia in the absence of antithrombotic therapy.

The low-dose sequential CSE technique is a modification of the original technique that uses a deliberately subanesthetic intrathecal dose with the expectation of extending the block height by the subsequent epidural injection of either local anesthetic or saline. This technique has been shown to enhance cardiovascular stability in high-risk cases, including pregnant women with severe pre-eclampsia.[10,11]

CONTRAINDICATIONS

Patients receiving a CSE must be appropriate candidates for a neuraxial technique. Contraindications include patient refusal, coagulopathy, and some infections. American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines recommend that a patient have normal coagulation status before undergoing instrumentation of the neuraxis.[12] Aspirin or nonsteroidal anti-inflammatory agent therapy is not a contraindication; however, other antiplatelet therapies such as clopidogrel require cessation 7 days before undergoing the procedure. Patients taking warfarin should go 5 days without therapy or have a current normal prothrombin time (PT) and international normalized ratio (INR). Patients receiving prophylactic doses of low-molecular-weight heparin (LMWH), such as 30 to 40 IU enoxaparin or 5000 IU dalteparin every 24 hours, must wait 12 hours after the last dose before undergoing neuraxial blockade. Patients receiving therapeutic doses of LMWH, such as 1 mg/kg enoxaparin every 12 hours, 1.5 mg/kg enoxaparin daily, 120 U/kg dalteparin every 12 hours, 200 U/kg dalteparin daily, or 175 U/kg tinzaparin daily, must wait 24 hours from the last dose before receiving a neuraxial block. Direct thrombin inhibitors such as argatroban are contraindicated until more data are available. Subcutaneous heparin is not a contraindication to regional anesthesia.[12]

Evaluating the coagulation status of the obstetric patient can present a special challenge. Pregnancy may be complicated by conditions that lower the platelet count or inhibit platelet function such as pre-eclampsia, eclampsia, or the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Given the hypercoaguable condition of pregnancy, the absolute platelet count is less concerning than the trend in platelet numbers. There is no evidence for a specific platelet count below which neuraxial techniques are contraindicated in the obstetric patient. Thus it would seem, as a practical matter, that a risk–benefit assessment should be undertaken for any pregnant woman with a platelet count of less than 75,000/mm^3 or with a sudden, substantial drop from her baseline, and an individualized decision should be reached regarding the safety of a neuraxial technique. Patients with a platelet count less than 75,000/mm^3 should be examined for stigmata of coagulopathy (easy bruising, petechiae, bleeding from the intravenous site or Foley catheter) before instrumentation. A PT, a partial thrombin time, and a platelet count should be reviewed before proceeding. If any of the aforementioned test results are abnormal, a fibrinogen level and a d-dimer level are useful in assessing the patient for the presence of disseminated intravascular coagulation.

Obstetric patients may be receiving anticoagulation therapy for a variety of obstetric or nonobstetric indications. Ideally, women taking long-acting anticoagulants (e.g., for deep vein thrombosis prophylaxis or prosthetic heart valves) should be converted from their long-acting therapies (e.g., LMWH) to subcutaneous heparin at 36 weeks of gestational age. A patient taking therapeutic LMWH who is in labor must wait a minimum of 24 hours from the last dose before undergoing CSE analgesia or anesthesia.

Patients with infection at the needle insertion site, suspected meningitis (bacterial or viral), or sepsis should not undergo neuraxial blockade. Patients with suspected chorioamnionitis can receive regional anesthesia after the administration of appropriate intravenous antibiotics.[13,14] Parturients with a primary herpes simplex outbreak are at increased risk of herpetic meningitis with neuraxial techniques. Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) is not a contraindication to CSE.[12]

EVIDENCE FAVORING THE USE OF COMBINED SPINAL–EPIDURAL TECHNIQUE

Combined Spinal–Epidural Technique for Labor Analgesia

The benefits of CSE for labor analgesia have been described in comparison with either traditional epidural or modern low-dose epidural analgesia. These benefits include faster onset of analgesia, better pain relief in advanced labor, improved maternal mobility, and less chance of an instrumented vaginal delivery. Because no standard drug regimen exists for CSE, traditional, or low-dose epidural analgesia, it is difficult to compare and contrast studies. Nonetheless, a Cochrane Systematic Review, which included data from 19 randomized trials (2658 laboring women), has attempted to assess the evidence behind some of the stated benefits of CSE.[15] This analysis found that analgesic onset is faster with CSE compared with low-dose epidural analgesia, and the likelihood of patient comfort at 10 minutes was nearly twice as high in patients receiving CSE. This finding is important to the laboring woman rapidly approaching the second stage of labor, for whom both comfort and maintenance of adequate motor strength to push are important therapeutic goals.

Two studies have suggested that the CSE technique has no negative influence on obstetric outcome when administered in very early labor. The first, a randomized study of the combination of intrathecal sufentanil and bupivacaine compared with epidural bupivacaine for early (cervical dilation less than 5 cm) analgesia,[5] demonstrated a faster rate of cervical dilation in parturients receiving CSE analgesia (2.1 cm/hr versus 1 cm/hr; $p = 0.0008$).[5] The parturients receiving CSE analgesia also had a quicker analgesic onset and superior pain scores for 110 minutes compared with the women with epidural analgesia. There was no difference in the rate of cesarean section or instrumental delivery between the two groups. A randomized trial of intrathecal fentanyl (25 mcg) compared with systemic hydromorphone (1 mg intravenously and 1 mg intramuscularly) for early (median cervical dilation, 2 cm) labor analgesia followed by epidural analgesia in both groups[6] demonstrated that the CSE group experienced superior analgesia, shorter analgesic onset, and a shorter interval to complete cervical dilation (295 versus 385 minutes; $p = 0.001$) and gave birth to infants with higher Apgar scores ($p < 0.01$). There was no difference in the rate of cesarean section or instrumental delivery between the two groups. The Cochrane analysis compared the likelihood of an instrumental vaginal delivery in patients receiving CSE, traditional epidural analgesia, and low-dose epidural analgesia. There was no difference between CSE and low-dose epidurals, but the relative risk of 0.82 (95% confidence interval, 0.67 to 1.00) was at the border of favoring CSE over traditional epidurals.[15]

Combined Spinal–Epidural Technique for Cesarean Section

The CSE technique has been associated with positive outcomes and low failure rates when used as the anesthetic technique for cesarean delivery. A controlled study of intrathecal bupivacaine compared with epidural bupivacaine[16] demonstrated that 100% of the women receiving a CSE anesthetic had adequate anesthesia compared with 74% of women receiving epidural anesthesia. The total dose of bupivacaine used was three times higher in women with epidural anesthesia (125 mg) compared with those using the CSE technique (40 mg). Maternal and fetal blood concentrations of bupivacaine were higher in the women with epidural anesthesia (604 mg and 186 mg, respectively) compared with the women with intrathecal anesthesia (205 mg and 45 mg, respectively). There was

no difference in Apgar scores, umbilical cord blood gases, or the neonatal neurobehavioral examination between the two groups.[16]

A randomized, prospective study of 120 women comparing CSE with epidural anesthesia assessed both objective outcomes and subjective maternal experience.[17] The women receiving intrathecal bupivacaine and fentanyl had quicker onset of a T4 level of anesthesia (10 versus 16 minutes), a shorter time to surgical incision (29 versus 36 minutes), and more reliable motor blockade (54% versus 11%) than the women receiving epidural lidocaine with epinephrine and fentanyl. Significantly more women in the CSE group reported no pain, lower anxiety, and greater satisfaction than in the epidural group. There were no significant differences in incidence of hypotension, nausea, pruritus, postdural puncture headache (PDPH), or neonatal outcomes between the two groups.[17]

Hypotension can be an important side effect of spinal anesthesia for cesarean section. The CSE technique enables the successful use of small doses of spinal medication coupled with epidural supplementation, if needed.[10,11] A recent study[18] compared the spinal administration of 6.5 mg of hyperbaric bupivacaine combined with 2.5 mcg sufentanil versus 9.5 mg of hyperbaric bupivacaine with 2.5 mcg sufentanil for CSE anesthesia for cesarean delivery. Patients in the high-dose group experienced significantly more hypotension than those in the low-dose group (68% versus 16%, $p < 0.05$), and significantly more patients required treatment. The anesthetic duration was shorter in the low-dose group, which points to the necessity of having an epidural catheter in place.

Combined Spinal–Epidural Technique for Orthopedic Surgery

Patients undergoing orthopedic procedures may also benefit from the CSE technique. A retrospective chart review of 62 total hip arthroplasties found that patients undergoing the CSE technique, single-injection spinal anesthesia, or general anesthesia had the same time interval from anesthesia start to surgical incision (59 minutes), whereas those receiving epidural anesthesia had a longer interval (73 minutes).[8] A randomized controlled study[19] of patients undergoing hip arthroplasty compared time to adequate block and adequacy of muscle relaxation in patients receiving either intrathecal bupivacaine as a single injection, as part of the CSE technique, or through an epidural. Time to adequate block was significantly shorter in the two intrathecal groups: 11 minutes for single-injection spinal and 14 minutes for the CSE technique compared with 36 minutes for the epidural group. Similarly, muscle relaxation was adequate in 100% of those receiving intrathecal bupivacaine compared with 12% of those receiving epidural bupivacaine. Four of the 25 patients receiving epidural bupivacaine were converted to general anesthesia because of inadequate anesthesia, whereas none of the patients receiving intrathecal bupivacaine was. Four of the 25 patients receiving the CSE technique received supplemental bupivacaine via the epidural catheter. There were no differences demonstrated in terms of hemodynamic changes ($p > 0.005$) among the three groups.[19]

CONTROVERSIES

Controversy with the CSE technique has largely centered on the incidence and significance of side effects. For instance, patients who receive a lipid-soluble opioid as part of a CSE technique experience more pruritus than patients who receive a local anesthetic alone or the same opioid by the epidural route.[20] This mu receptor–mediated side effect is not dangerous but can be annoying to the individual patient. The incidence of pruritus can be reduced with lower doses of intrathecal opioid.[21]

Of greater concern is the observation by some authors of an increased incidence of fetal bradycardia after the CSE technique for labor analgesia. A 2002 meta-analysis of studies conducted in the 1990s,[21] administering higher doses of intrathecal opioids than are generally in use today, found an odds ratio of 1.8 for occurrence of fetal bradycardia within the first 60 minutes of intrathecal opioid administration versus neuraxial analgesia without intrathecal opioids. However, these episodes did not result in an increase in the rate of cesarean deliveries. Also reassuring are the results from the 2007 Cochrane Systematic Review,[15] which found no difference in neonatal outcomes, as measured by neonatal Apgar scores or need for neonatal intensive care unit admission, between CSE and epidural techniques. The dose of intrathecal medication appears to have an impact on the incidence of fetal bradycardia. A randomized controlled (low-dose epidural group) study[21] of 7.5 mcg intrathecal sufentanil alone compared with 1.5 mcg intrathecal sufentanil combined with 2.5 mg bupivacaine found that the lower dose combination of sufentanil and bupivacaine was associated with a 12% incidence of fetal bradycardia; the low-dose epidural group had an 11% incidence, and the higher dose sufentanil group had a 24% incidence. There were no differences in maternal pain scores or mobility between the two groups.

Failed epidural is another theoretic concern with the CSE technique. The data from three randomized controlled studies in which epidural failure rates were measured demonstrated an equal or lower failure rate of an epidural when inserted as part of the CSE technique (0.7% to 1.49%) compared with epidural insertion alone (0.7% to 3.18%).[22-24]

The inability to check the level after CSE placement with local anesthetic is another concern. If appropriate (i.e., labor analgesia), intrathecal opioids alone can provide adequate analgesia with the ability to check a level from an epidural-injected local anesthetic. However, if the function of the epidural needs to be 100% (e.g., high risk for cesarean section or morbid obesity), an epidural technique is preferred over CSE.

Meningitis, including viral, bacterial, and aseptic, has been reported after instrumentation of the epidural and intrathecal space. With proper sterile technique, the incidence has been shown to be 0% to 0.04%.[25,26] There are no data that demonstrate an increased rate of meningitis after the CSE technique compared with other neuraxial techniques.[14]

Because the CSE technique requires dural puncture, PDPH is a possible side effect of this technique. The use

of a small-gauge pencil-point needle, however, reduces this risk. In two controlled studies,[27,28] the rate of PDPH after the CSE technique was found to be 0.44% to 1.7%. A 0.65% to 1.6% incidence of dural puncture was seen with the use of a 17-gauge epidural needle; however, that dural puncture was associated with a 38% incidence of PDPH. It appears that puncture with the larger epidural needle is associated with an increased risk of PDPH versus the smaller pencil-point needle used for the actual spinal.

GUIDELINES

Currently, no formal guidelines have been published by national societies that specifically address the indications for CSE. However, broader guidelines from two organizations include information about CSE and many of the issues raised in this chapter. The American Society of Anesthesiologists' "Practice Guidelines for Obstetric Anesthesia" is an excellent resource for best practices in the care of the obstetric patient and supports the use of CSE for both labor analgesia and cesarean delivery.[29] In 2002 the ASRA published the results of a consensus conference, "Regional Anesthesia in the Anticoagulated Patient—Defining the Risks."[12] This document is in the process of being updated from the results of the consensus conference held in 2007. Finally, the ASRA recently published a series of articles based on the 2004 Conference on Infectious Complications of Neuraxial Blockade.[30]

AUTHORS' RECOMMENDATIONS

The combined spinal–epidural (CSE) technique can play a role in any procedure in which rapid onset of analgesia or anesthesia is desirable and the duration of the expected procedure is likely to outlast a single dose of spinal medication or in any procedure in which postoperative pain management with an epidural catheter is warranted. The best evidence supporting the use of CSE is derived from the meta-analysis of numerous, relatively small randomized studies carried out at single institutions. This evidence supports the use of CSE for the following indications. It must be kept in mind, however, that there are inadequate data to demonstrate the difference, if any, between CSE and epidural analgesia for extremely rare events, such as meningitis.

- Labor analgesia: CSE has been shown to be advantageous both very early in labor and in advanced labor. Early in labor, small doses of spinal opioids, with or without local anesthetic, have been associated with excellent maternal pain relief and favorable obstetric outcomes. In advanced labor, CSE reliably produces maternal analgesia while simultaneously maintaining the maternal ability to participate in the second stage of labor. Intrathecal opioids only provide the ability to inject epidural local anesthetic to confirm placement.
- Cesarean section: CSE is advantageous in any setting in which the cesarean section may outlast the duration of a single injection of spinal medication. Low-dose CSE should also be considered for patients in whom hemodynamic stability is a particular concern.
- Orthopedic surgery: CSE can be considered for long procedures, as well as for those patients who would benefit from postoperative epidural analgesia.
- CSE may be associated with an increased risk of fetal bradycardia in the laboring patient. Thus in the situation in which a laboring mother has a fetus already having episodes of fetal bradycardia, an epidural alone may be preferable.

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CHAPTER 66

Does Labor Analgesia Affect Labor Outcome?

Scott Segal, MD, MHCM

INTRODUCTION

In 1847, only months after the first demonstration of anesthesia, James Simpson, an obstetrician, administered ether to a woman in labor for childbirth. He was quite impressed with the analgesia the new drug induced, as was his patient. However, his journal notes on the case indicated his concern over the possible adverse effects of anesthesia on labor and delivery.[1] "It will be necessary to ascertain anesthesia's precise effect, both upon the action of the uterus and on the assistant abdominal muscles; its influence, if any, upon the child; whether it has a tendency to hemorrhage or other complications."

Thus began, more than a century and a half ago, perhaps the longest-lived controversy in the history of obstetric anesthesia, one that continues to this day in both academic and lay circles.

OPTIONS

The modern debate has centered on several main issues:

- Does regional analgesia for labor affect the length of labor or the rate of cervical dilation? In particular, does the timing of initiation of epidural analgesia play a role?
- Does regional labor analgesia increase the risk of instrumental vaginal delivery?
- Does regional labor analgesia increase the risk of cesarean delivery?

No definitive study has adequately addressed any of these questions, and methodologic problems have plagued all available evidence. The principal difficulty is that risk factors for dysfunctional labor also predispose a woman to request an epidural. This chapter will review the available literature, focusing on randomized controlled trials (RCTs) but considering other forms of evidence, and will emphasize the different conclusions reached by observational and prospective randomized designs.

EVIDENCE

Evidence Regarding Rate of Cervical Dilation and Timing of Initiation

Conventional wisdom holds that if started too early in labor (during the latent phase), epidural analgesia may markedly slow or even arrest the progress of labor. Amazingly, this widely accepted clinical dogma has never been proved in carefully performed studies. Its origin can be traced to early case series of caudal or epidural anesthesia for labor, which probably resulted in dense sacral as well as lumbar blocks. In these uncontrolled reports, although some women in whom blocks were initiated very early may not have progressed through labor, it is unclear whether they would have progressed more quickly without the block.[2]

Some nonrandomized studies have found an association between earlier epidural placement and dystocia. Thorp and colleagues[3] compared various groups of nulliparous women defined by their early cervical dilation rate, their cervical dilation at the time of initiation of analgesia, and the choice of epidural or alternative analgesia. Among women with dilation less than 5 cm and a dilation rate less than 1 cm/hr, epidural analgesia was associated with a sixfold increase in cesarean delivery for dystocia. Other comparisons demonstrated smaller relative risks or no difference. In a secondary analysis of the same group's randomized trial,[4] the increased risk of cesarean delivery was greatest in women requesting analgesia earlier, although women were not randomly assigned to dilation at time of initiation of analgesia. Using a case-control methodology, Malone and colleagues[5] identified epidural initiation at less than 2 cm dilation as a significant risk factor for prolonged nulliparous labor (odds ratio [OR], 42.7). In a sophisticated observational study using a variant of multivariate regression (propensity score analysis) to control for multiple simultaneous confounders, Lieberman and colleagues[6] identified both cervical dilation less than 5 cm and station less than 0 at the time of epidural initiation as strong risk factors for cesarean delivery.

Evidence from RCTs has failed to confirm this finding (Table 66-1). Chestnut and colleagues randomly assigned women requesting epidural analgesia to early or late groups (approximately 4 and 5 cm dilation, respectively). No differences in labor outcome were seen in either spontaneous labors[7] or induced labors.[8] However, the early and late groups in these studies were not markedly different in their cervical dilation at the time of epidural placement. Five more recent trials randomly assigned women to early epidural placement or opioids until later in labor[9-11] or to intrathecal opioids followed by later epidural initiation.[12,13] In each case, progress through the first stage of labor was either equivalent or faster[10,12,13] in

TABLE 66-1 **Randomized Trials Comparing Early versus Later Epidural Initiation**

	Cervical Dilation in Centimeters (N)			Results		
Author, Year	Early	Late	Outcome	Early	Late	*p*
Chestnut, 1994[7]*	4 (172)	5 (162)	First stage (min)	329	359	NS
			Second stage (min)	85	88	NS
			CD (%)	10	8	NS
			IVD (%)	37	43	NS
Chestnut, 1994[8†]	3.5 (74)	5 (75)	First stage (min)	318	273	NS
			Second stage (min)	91	77	NS
			CD (%)	18	49	NS
			IVD (%)	43	19	NS
Luxman, 1998[9]	2.5 (30)	4.5 (30)	First stage (min)	342	317	NS
			Second stage (min)	41	38	NS
			CD (%)	7	10	NS
			IVD (%)	13	17	NS
Wong, 2005[12‡]	<4 (366)	>4 (362)	First stage (min)	295	385	<0.001
			Second stage (min)	71	82	0.67
			CD (%)	18	21	0.31
			IVD (%)	20	16	0.13
Ohel, 2006[10]	2.4 (221)	4.6 (228)	First stage (min)	354	396	0.04
			Second stage (min)	95	105	0.12
			CD (%)	13	11	0.77
			IVD (%)	17	19	0.63
Wong, 2009[13§]	2 (406)	4 (400)	Labor duration (min)	528	569	0.047
			Second stage (min)	89	90	0.56
			CD (%)	33	32	0.65
			IVD (%)	14	15	0.63
Wang, 2009[11]	1.6 (6394)	5.1 (6399)	Latent phase (min)	479	485	0.22
			Active phase (min)	111	128	0.68
			Second stage (min)	63	67	0.87
			CD (%)	23	23	0.51
			IVD (%)	12	13	0.10

CD, cesarean delivery; *IVD,* instrumental vaginal delivery; *NS,* not significant.
*Spontaneous labor; cervical dilation given as median.
†Oxytocin-receiving subjects; cervical dilation given as median.
‡Spontaneous labor; subjects randomly assigned at <4 cm to intrathecal fentanyl 25 mcg or intramuscular + intravenous hydromorphone; all subjects received epidural analgesia at second request for analgesia (systemic group) or >4 cm or at third request for analgesia (intrathecal group). Median cervical dilation at first request was 2 cm in both groups, but cervical examination at initiation of epidural analgesia in late group was not reported.
§Nulliparas undergoing induction of labor, with cervical dilation given as median; analgesic protocol similar to Wong 2005. Total labor duration, but not first stage duration, was reported.

the early group than in the later group. No differences in second-stage duration or mode of delivery were found in any of the trials. Two meta-analyses of the RCTs, one performed before and one after the extremely large trial by Wang and colleagues,[11] found no difference in the mode of delivery between early and later epidural initiation.[14,15] The difference between the RCTs and the retrospective studies may be due to selection bias, in that women requesting analgesia earlier in labor may be experiencing pain due to anatomic or physiologic factors predisposing them to dystocia.

The effect of epidural analgesia on cervical dilation in established labor is probably minimal. Some earlier retrospective studies finding slower cervical dilation were probably hampered by selection bias. Meta-analyses of randomized trials of epidural analgesia versus opioid analgesia have concluded that the first stage of labor is not prolonged by epidural analgesia.[16-20]

Evidence Concerning Risk of Instrumental Vaginal Delivery

The incidence of instrumental vaginal delivery may be increased by epidural analgesia, although this practice varies tremendously between obstetricians and hospitals. Table 66-2 shows the results of 21 randomized trials, published in English as full articles, comparing epidural analgesia with systemic opioids. Seven of the trials found a significant difference in rates. However, the overall use of forceps varied from 0% to 55% in the opioid groups and from 2% to 80% in the epidural groups, indicating substantial variation in practice style. Indeed,

TABLE 66-2 **Randomized Trials Comparing Mode of Delivery with Epidural or Opioid Analgesia**

		*Rate of Instrumental Vaginal Delivery**			*Rate of Cesarean Delivery for Dystocia†*		
Author, Year	**Parity**	**Epidural Group**	**Opioid Group**	***p***	**Epidural Group**	**Opioid Group**	***p***
Robinson, 1980[67]	Nulliparas	17/28 (51%)	8/30 (27%)	<0.02	0	0	—
	Mulitparas	5/17 (30%)	1/18 (6%)	NS			
Philipsen, 1989[68]	Nulliparas	1/57 (2%)	0/54 (0%)	NS	10/57 (17%)	6/54 (11%)	NS
Thorp, 1993[4]	Nulliparas	4/48 (8.3%)	3/45 (6.7%)	NS	8/48 (16.7%)	1/45 (2.2%)	<0.05
Ramin, 1995[23‡]	Mixed	41/432 (10%)	13/437 (3%)	<0.0001	43/664 (6%)	37/666 (6%)	NS
Bofill, 1997[22]	Nulliparas	39/49 (80%)	28/51 (55%)	0.004	4/49 (4%)	3/51 (3%)	NS
Sharma, 1997[63]	Mixed	26/358 (7%)	15/357 (4%)	NS	13/358 (4%)	16/357 (5%)	NS
Clark, 1998[69]	Nulliparas	24/156 (15%)	20/162 (12%)	NS	15/156 (9.6%)	22/162 (14%)	NS
Gambling, 1998[70§]	Mixed	51/616 (8%)	34/607 (6%)	0.08	39/616 (6%)	34/607 (6%)	NS
	Nulliparas	37/336 (13%)	32/314 (13%)	NS	30/336 (10%)	25/314 (9%)	NS
Loughnan, 2000[71]	Nulliparas	88/304 (29%)	81/310 (26%)	NS	36/304 (12%)	40/310 (13%)	NS
Howell, 2001[72]	Nulliparas	55/184 (30%)	36/185 (19%)	0.03	13/184 (7%)	17/185 (9%)	NS
Lucas, 2001[73‖]	Mixed	51/372 (14%)	27/366 (7%)	0.005	46/372 (12%)	54/366 (15%)	NS
Dickinson, 2002[74¶]	Nulliparas	169/493 (34%)	148/499 (30%)	NS	85/493 (17%)	71/499 (14%)	NS
Sharma, 2002[62]	Nulliparas	26/226 (12%)	7/233 (3%)	<0.001	13/226 (6%)	17/233 (7%)	NS
Head, 2002[75‖]	Mixed	3/56 (5%)	3/60 (5%)	NS	7/53 (13%)	6/52 (12%)	NS
Jain, 2003[76]	Nulliparas	12/43 (28%)	8/83 (10%)	<0.01	9/45 (20%)	12/83 (14%)	NS
Long, 2003[77]	Mixed				1/30 (3%)	6/50 (12%)	NS
Halpern, 2004[78]	Nulliparas	36/124 (29%)	25/118 (21%)	NS	6/124 (5%)	10/118 (5%)	NS
Nafisi, 2006[79#]	Nulliparous	4/197 (2%)	4/198 (2%)	NS	8/197 (4%)	8/198 (4%)	NS
Evron, 2008[80]	Mixed	9/148 (6%)	1/44 (2%)	NS	19/148 (13%)	4/44 (9%)	NS
Volmanen, 2008[81]	Mixed	1/21 (5%)	4/24 (17%)	NS	1/21 (5%)	1/24 (5%)	NS
El-Kerdawy, 2010[82‖]	Mixed	3/15 (20%)	0/15 (0%)	NS	4/15 (27%)	3/15 (20%)	NS

NS, not significant.
*Total forceps rate (outlet + "low") when separately reported, includes vacuum delivery when reported.
†Cesarean delivery rate for dystocia if separately analyzed, otherwise total cesarean delivery rate.
‡Ramin and colleagues was originally reported in 1995 only as a protocol compliant analysis, which is inappropriate in primary analysis of randomized trials. The data given in the table are taken from the authors' 2000 published reanalysis by intention-to-treat, the correct method, for cesarean delivery.[24] Only protocol-compliant analysis has been reported for forceps.
§Combined spinal–epidural versus opioid.
‖Patients with pregnancy-induced hypertension.
¶Control group received continuous midwifery care and a variety of nonepidural analgesics; crossover to epidural group was 61.3%.
#Epidural lidocaine versus opioid.

meta-analysis of randomized trials has found the total instrumental delivery rate to be 1.38 to 2.19 times more likely in patients receiving epidural analgesia but with very broad confidence intervals indicative of the variation between studies.[16-21] Moreover, there is strong evidence that many instrumental deliveries in epidural patients are done for reasons other than dystocia, perhaps for teaching purposes.[22] Indeed, two meta-analyses[16,17] concluded that instrumental delivery for the indication of dystocia was not increased by epidural analgesia, and another[21] concluded "non-elective" instrumental delivery was likely not increased (OR, 1.56; 95% CI, 0.99 to 2.46).

Evidence Concerning Risk of Cesarean Delivery

Evidence regarding cesarean delivery represents the most important aspect of the issue of the effect of epidural analgesia on labor. Both RCTs and an important type of observational study have been reported. Data from 21 randomized trials reported in English as full articles in which epidural analgesia was compared with systemic opioids are given in Table 66-2. Only one trial, when analyzed on an intent-to-treat basis, has found a difference in the risk of cesarean delivery.[4] One other, by Ramin and colleagues,[23] was originally reported on a protocol-compliant basis, after excluding from the analysis approximately one third of the randomized patients. In this form, a significant difference in cesarean delivery rates was observed. Unfortunately, the reasons for noncompliance were not given. It is likely that some excluded patients in the epidural group were low-risk patients who delivered quickly without the need for analgesia. Conversely, some patients receiving opioids probably demanded epidural analgesia because of inadequate analgesia during a protracted, painful labor (i.e., high risk). Therefore the protocol-compliant analysis probably overemphasized the difference between groups. Indeed, the authors published a revised analysis (see Table 66-2) on an intent-to-treat basis that found no difference in cesarean delivery.[24]

Several meta-analyses of various groups of these RCTs, which sometimes included studies reported only as

abstracts or in languages other than English, are shown in Table 66-3. Despite inclusion of different studies, these analyses have consistently shown no difference in the total rate of cesarean delivery or the rate of cesarean for dystocia.[16-21]

Another body of evidence concerns studies in which the availability of epidural analgesia in an institution has suddenly changed.[25-35] The results of 11 such studies are given in Table 66-4. None has found an association between higher use of epidural analgesia and a higher rate of cesarean delivery. Not surprisingly, a meta-analysis showed no association between greater availability of epidural analgesia and cesarean delivery.[36] Although nonrandomized, these "sentinel event" or "natural experiment" studies offer some unique insights. The investigations span two decades and studied widely varying practice settings. All patients in the hospital are included, so external validity is not a problem as it may be with the RCTs. An assumption of these studies is that the patient population and obstetric practice styles are likely to change little, or at least slowly, when compared with the sudden availability of epidural analgesia. This assumption has generally proved valid, but not all sentinel event studies have addressed it directly; some documented subtle changes in the patient population.[28,33-35]

Obstetric Practice Style

As evidence has accumulated discounting the direct effect of epidural analgesia on labor, greater emphasis has been placed on the role of the obstetric caregiver as the primary determinant of the risk of cesarean delivery. One early study demonstrated that after nulliparity, the greatest risk factor for cesarean delivery among a cohort of women was the identity of the individual obstetrician.[37] Other investigators have reported variation in cesarean delivery

TABLE 66-3 **Meta-Analysis of Randomized Controlled Trials Comparing Epidural with Nonepidural Analgesia**

Author, Year	No. of Trials	Outcome	No. of Subjects (Epidural/ Nonepidural)	Epidural	Nonepidural	OR, RR, or WMD (95% CI) Epidural versus Nonepidural
Halpern, 1998[16]	5	First stage (min)	524/555			+42 min (17-68)*
	6	Second stage (min)	581/609			+14 min (5-23)*
	7	CD (%)	1183/1186	8.2	5.6	1.50 (0.81-2.76)
	9	IVD (%)	1155/1164	15.5	8.9	2.19 (1.32-7.78)*
	2	IVD dystocia (%)	106/105	12.2	17.1	0.68 (0.31-1.49)
Zhang, 1999[18†]	4	First stage (min)	397/409			1.19 (1.01-1.39)*
		Second stage (min)				1.37 (1.07-1.76)*
		CD (%)				1.66 (0.59-4.68)
		CD dystocia (%)				1.75 (0.58-5.30)
		IVD (%)				1.57 (0.92-2.68)
Liu, 2004[21]	4	Second stage (min)	479/491	64.5	49.3	+15 min (2.1-28.2)*
	7	CD (%)	1473/1489	12.1	11.3	1.18 (0.71-1.48)
	6	IVD (%)	1276/1300	27.8	22.2	1.63 (1.12-2.37)*
	4	IVD nonelective (%)	1071/1087	27.3	22.2	1.56 (0.99-2.46)
Leighton, 2002[17]	7	First stage (min)	1012/1050			+26 min (–8-60)
	8	Second stage (min)	1068/1103			+15 min (9-22)*
	14	CD (%)	2161/2136	7.7	8.0	1.0 (0.77-1.28)
	12	IVD (%)	1813/1840	19.0	12.3	2.08 (1.48-2.93)*
	3	IVD dystocia (%)	538/542	7.2	4.2	1.53 (0.29-8.08)
Anim-Somuah, 2005[19‡]	9	First stage (min)	1165/1163			+24 min (–19-67)
	11	Second stage (min)	1796/1784			+16 min (7.5-24)*
	20	CD (%)	3326/3308	11.0	10.2	1.07 (0.93-1.23)
	11	CD dystocia (%)	2311/2295	6.3	7.0	0.90 (0.73-1.12)
	17	IVD (%)	3044/3118	19.3	14.2	1.38 (1.24-1.53)*
Anim-Somuah, 2011[20]	11	First stage (min)	1422/1559			+19 min (–13-50)
	13	Second stage (min)	2053/2180			+14 min (7-21)*
	27	CD (%)	4223/4194	10.8	9.8	1.10 (0.97-1.25)
	12	CD dystocia (%)	2508/2493	6.1	6.7	0.90 (0.73-1.12)
	23	IVD (%)	3981/3954	17.0	12.4	1.42 (1.28-1.57)*

CD, cesarean delivery; *CI,* confidence interval; *IVD,* instrumental vaginal delivery; *OR*, odds ratio; *RR*, relative risk; *WMD,* weighted mean difference.

*Statistically significant difference at 0.05 level.

†Also analyzed observational studies and comparisons of epidurals continued or discontinued during second stage. Only randomized trials comparing epidural with nonepidural analgesia are included in the table. Pooled estimates of various parameters were not reported; labor duration was tested as ratio in epidural to nonepidural group. 99% CI reported.

‡Replaced an earlier meta-analysis also by the Cochrane Collaborative from 2000 examining 11 studies published through 1997.[83]

TABLE 66-4 **Sentinel Event Studies Comparing Cesarean Delivery Rate before and after a Rapid Change in Epidural Availability**

	Rate of Cesarean Delivery (Epidural Rate)		
Author, Year	Low Epidural Use Period	High Epidural Use Period	*p*
Bailey, 1983[25]	7.1% (0%)	9.3% (27%)	NS
Gribble, 1991[27]	9.0% (0%)	8.2% (47%)	NS
Larson, 1992[30]	27.5% (0%)	22.9% (32%)	NS
Mancuso, 1993[32]	14.9% (19%)	12.3% (67%)	NS
Johnson, 1995[29]	18.4% (21%)	17.2% (71%)	NS
Lyon, 1997[31]	11.8% (13%)	10.0% (59%)	NS
Fogel, 1998[26]	9.1% (1%)	9.7% (29%)	NS
Yancey, 1999[34]	19.4% (1%)	19.0% (59%)	NS
Impey, 2000[28]	3.8% (10%)	4.0% (57%)	NS
Zhang, 2001[35]*	14.4% (1%)	12.1% (84%)	NS
Vahratian, 2004[33]*	18% (2%)	18% (92%)	NS

NS, not significant.
*Zhang and Vahratian studied the same institution at slightly different time periods, and Vahratian confined the analysis to nulliparas admitted in spontaneous labor and who received epidural analgesia at <4 cm dilation.

rates between indigent patients and those with private health insurance, despite similar rates of epidural analgesia use.[38,39] Three studies have reported 50% decreases in hospital-wide cesarean rates by peer review, physician education, and publishing individual obstetricians' rates of operation, while simultaneously doubling the rate of epidural analgesia use.[40-42] Another found no correlation between 110 individual obstetricians' rates of cesarean delivery and the rates of epidural analgesia use among their patients.[43] Two others have documented no relationship between epidural rates and cesarean rates across hospitals in Belgium and Sweden.[44,45]

However, indirect effects of the presence of a regional analgesic block may affect obstetric decision making on the mode of delivery. For example, it is well-known that patients with epidural blocks will experience a gradual rise in temperature and more clinical fever during the course of labor.[46] Maternal fever or its consequences (e.g., fetal tachycardia) may be one of the factors leading an obstetrician to decide to perform a cesarean delivery.[47] Similarly, most anesthesiologists request that patients remain in bed, usually supine or semisitting, after an epidural block is initiated. There is common belief among some obstetric caregivers (but limited objective evidence even in women without epidural analgesia[48]) that upright posture or ambulation speeds the progress of labor; therefore the presence of an epidural block could indirectly slow the rate of cervical dilation. Controlled trials have also failed to confirm a beneficial effect of walking in labor, in both patients with and without regional analgesia.[49-51] Finally, it has also been suggested that a patient who desires epidural analgesia may be one who is more amenable to a more interventional management of her labor, including assisted vaginal or cesarean modes of delivery.[52]

CONTROVERSIES

General Methodologic Difficulties

It is generally agreed that the ideal clinical study is prospective, randomized, double-blind, and placebo-controlled. No study of epidural analgesia's effect on labor and delivery has met this standard, and none probably ever will. By far, the majority of studies meet none of these criteria but are instead retrospective comparisons of women who self-selected epidural analgesia with those who did not. Such comparisons introduce selection bias. Bias is introduced by comparing two groups of patients who do not share equivalent risk of the outcome being studied. In this case, the outcomes of interest may include the duration of labor, the need for oxytocin, or the risk of cesarean delivery.

Indeed, investigators have identified many characteristics of patients requesting epidural analgesia that independently predict longer labor and nonspontaneous delivery. They are more frequently nulliparous, tend to come to the hospital earlier in labor and with higher fetal station, have slower cervical dilation before analgesia, more frequently are already receiving oxytocin for induction or augmentation of labor, deliver larger babies, and may have received epidural analgesia because of other perceived risk factors for operative delivery such as poor fetal status or maternal systemic disease.[3,53-55] Floberg and colleagues[56] used radiographic pelvimetry to demonstrate that women requesting epidural analgesia have smaller pelvic outlets, an obvious risk factor for operative delivery.

Another important and often overlooked difference is the pain of labor itself. Pain in early labor is associated with slower labor and forceps or cesarean delivery.[57] Of course, more pain in labor is associated with a higher likelihood of selecting epidural analgesia. Investigators have also related the ongoing analgesic requirements of patients who are already receiving epidural analgesia to dysfunctional labor. These studies suggest that women who require denser blocks or more "top-up" doses of local anesthetic have slower labors and are at increased risk of operative vaginal or cesarean delivery.[58] Panni and Segal[59] further extended this observation by demonstrating a greater local anesthetic requirement in nulliparous women in early labor who later went on to require cesarean delivery for dystocia than in those who delivered vaginally. Others have demonstrated similar findings in women receiving patient-controlled intravenous meperidine for labor analgesia.[60]

Several randomized, prospective trials comparing epidural analgesia with an alternative (usually parenteral opioids) have appeared (see Table 66-2). Although these studies represent a far better approach than retrospective comparisons, there are still potential problems with them. First, in none was a placebo control used. Performing randomized prospective trials with placebo controls may raise ethical concerns, or, at least, it may be very difficult to get patients to give their consent and minimize crossover between groups. Because parenteral opioids may themselves affect the course of labor,[61] these trials cannot specifically define the influence of epidural

analgesia relative to natural childbirth. Nonetheless, the pain control is consistently better with epidural than with systemic opioid analgesia. Consequently, a second, essentially insurmountable problem is posed by the practical impossibility of blinding patients and obstetricians, nurses, and anesthesiologists to the presence or absence of a functional epidural block. Because the decision to proceed with operative delivery is ultimately a subjective clinical one made by the obstetrician, the absence of blinding may be very important. Obstetricians and midwives may not treat their patients with epidural analgesia the same way they treat those without it. For example, forceps-assisted delivery may be more common among patients with epidural analgesia partly because obstetricians know their patients will be comfortable and have relaxed pelvic musculature for the procedure.[22]

Third, several of the randomized trials have been severely underpowered. Detecting a moderate difference in typical cesarean delivery rates of 10% to 20% requires several hundred patients per group. Many of the trials that have concluded that epidural analgesia does not affect the rate of cesarean delivery have studied only a small fraction of this number. Hence, their conclusions could at least theoretically be due to the small sample sizes involved.

Fourth, protocol noncompliance has been a persistent problem. Approximately one third of patients in most randomized trials do not ultimately receive the randomly assigned treatment. Analysis of only protocol-compliant patients introduces bias because patients excluded from an epidural group may be low-risk patients progressing easily through labor with minimal pain, whereas those excluded from an opioid group may be high-risk patients experiencing slow, painful labor. Analysis by intent-to-treat, although correct, is complicated when such large numbers of patients fail to receive their assigned analgesic and, at the very least, further reduces the statistical power of the study. One group has conducted sufficiently powered studies that achieved low crossover (8%).[62,63]

Finally, it may not be easy to extrapolate the findings of even well-conducted randomized trials to the general labor and delivery population (i.e., external validity). Most parturients have strong opinions about their desire for labor analgesia. Patients who do consent to randomized trials (in which they have a 50% chance of being assigned to not receive epidural analgesia) may make up a subset of patients who are ambivalent about labor analgesia and thus not representative of the general labor and delivery population. Unfortunately, this may be the case with the studies from the group at Parkland Hospital in Dallas, which achieved low crossover but also demonstrated very low cesarean rates.[62,63]

GUIDELINES

The American College of Obstetricians and Gynecologists (ACOG) has periodically revised its guidelines for obstetric anesthesia services. Previously, ACOG had suggested that epidural analgesia be delayed until a cervical dilation of 4 to 5 cm is reached. Anesthesiologists were not well-represented in the formation of these guidelines, and the evidence cited in support of them was incomplete.[64] More recently, ACOG updated this statement, no longer endorsing a delay and explicitly disavowing consideration of fear of increasing the risk of cesarean delivery.[65] ACOG and the American Society of Anesthesiologists have also jointly endorsed a statement that "maternal request is a sufficient medical indication for pain relief during labor" and that epidural analgesia is usually the preferred method.[66]

AUTHOR'S RECOMMENDATIONS

- Methodologic problems are likely to continue to make definitive answers to the controversies of the effects of epidural analgesia on labor elusive.
- Earlier administration of epidural analgesia does not cause longer labor or an increase in operative delivery. In the absence of a contraindication, women should be offered an epidural whenever labor pain is intensive enough to elicit a request for analgesia.
- Epidural analgesia minimally affects the progress of established labor. The second stage is prolonged approximately 15 minutes; the first stage may not be prolonged at all.
- Instrumental vaginal delivery is probably increased by effective epidural analgesia. Variation in obstetric practice style, however, makes it difficult to assess the magnitude of this risk for any given patient.
- The risk of cesarean delivery is not increased by epidural analgesia.
- Appreciation of indirect effects of the presence of an epidural on the practice style of obstetricians or the decision-making process of patients may further our understanding of the possible effects of epidural analgesia on labor outcomes.

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CHAPTER 67

Does Anesthesia Increase the Risk to the Parturient Undergoing Nonobstetric Surgery?

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INTRODUCTION

It is estimated that 0.75% to 2% of pregnant women in developed countries undergo nonobstetric surgery during the course of parturiency; approximately 42% undergo surgery in the first, 35% in the second, and 23% in the third trimesters.[1,2] Nonobstetric surgery during pregnancy accounts for approximately 75,000 to 80,000 procedures per year in the United States alone.[3,4] Procedures for appendicitis, cholelithiasis, traumatic injuries, ovarian torsion, cervical incompetence, and breast disease are the most prevalent in this patient population.[2-4] Often, these procedures are indicated. According to Buser,[5] complications from appendicitis during pregnancy include preterm labor, maternal morbidity, and early fetal delivery or loss in which fetal loss ranges between 3% and 5% without perforation but up to 36% with perforation. Rarely, major surgeries including cardiac, vascular, and neurologic procedures are indicated during pregnancy.[6]

Despite overall favorable results, there is a strong aversion to the use of drugs and the performance of procedures during pregnancy.[6] Of ultimate concern to both patients and health care providers is the effect of anesthetic agents on fetal development. For more medically astute individuals, other issues of concern include the maintenance of uterine perfusion and fetal well-being during surgery; the need for fetal monitoring during surgery; and the prevention of preterm labor or delivery postsurgery. This chapter explores the current evidence on the effect of anesthesia on the parturient undergoing nonobstetric surgery with special emphasis on recent data focusing on the effect of general anesthesia on apoptosis-mediated neurodevelopment as evident in animal studies.

OPTIONS

Virtually all surgical procedures performed during pregnancy are either urgent or emergent. Key options or alternatives revolve around the timing of surgery (i.e., should surgery be delayed until later in gestation considering the risk and benefits of the surgery) and the agents used.

EVIDENCE

Both the American Society of Anesthesiologists (ASA) and the American College of Obstetricians and Gynecologists (ACOG) agree that the paucity of data does not allow for specific recommendations regarding nonobstetric surgery during pregnancy. This can be attributed to the inability to conduct large randomized clinical trials in this patient population. Several important issues, however, deserve attention and a review of the literature for insight on the existing consensus and standard of clinical practice.

Anesthetic Toxicity to the Fetus: Teratogen or Not?

The human embryo is most vulnerable to the teratogenic effects of a drug between the third and eighth weeks of gestation.[3,4] However, no anesthetic agents have been shown to be teratogenic at any gestational age when used in the normal standard concentrations for surgery. Opioids, local anesthetics, intravenous induction agents, and inhalational anesthetic agents have been consistently associated with safety in pregnancy.[6] Although benzodiazepines were initially associated with an increased risk of cleft palate in the first trimester, subsequent studies have been unable to demonstrate similar results.[3,6-10] Nitrous oxide has been labeled a teratogen in rodents because of an increased incidence of fetal resorption and skeletal and visceral anomalies.[11] It has also been shown to increase adrenergic tone in animal studies, leading to vasoconstriction of the uterine vessels and a possible decrease in uterine blood flow when administered alone[6] or a decrease in central vascular tone leading to possible intracranial hemorrhage in preterm fetuses.[12] In addition, nitrous oxide inhibits methionine synthetase and could theoretically affect DNA synthesis in the developing fetus.[1,2] Nevertheless, despite the aforementioned theoretical concerns, no adverse effects have been demonstrated with the use of nitrous oxide in humans. Large studies in this population show no increase in congenital abnormalities but a greater risk of abortion, growth restriction, and low birth weight attributable to primary disease and the surgical procedure rather than anesthetic exposure.[1,3,13,14]

Teratogenicity has never been conclusively demonstrated in humans.[6] Most clinicians, however, avoid the repetitive use of benzodiazepines or nitrous oxide in the first trimester[15] because of its questionable safety profile in animal studies. The inability to adequately test new drugs for safety in this population before release makes extra caution a necessity.

With recent studies[16,17] showing widespread apoptotic neurodegeneration in animals with fetal or newborn exposure to general anesthetics and the concern of subsequent learning or memory impairments, the use of general anesthesia in pregnancy and newborns has become a hot topic of debate. Palanisamy and colleagues[16] demonstrated abnormal neurobehavioral performance in adult male rats exposed to clinically relevant concentrations of isoflurane in utero. According to the authors, these behavioral changes were attributed to direct effects because maternal physiology and variables were maintained during these experiments. The equivalent of the second trimester (14 days for fetal rats) was identified as the period of highest risk for nonobstetric surgery or fetal interventions because of the appearance of gamma-aminobutyric acid (GABA) receptor subunits. Most anesthetics act by potentiation of $GABA_A$ receptors, and it is this mechanism of action that is thought to induce widespread neuronal apoptosis when given during periods of synaptogenesis (brain growth spurt).[17] Animal studies are, however, plagued by several limitations. Rats have a relatively brief brain developmental process, and it is difficult to extrapolate changes induced by a single anesthetic in a rodent to the long, more gradual development of the human brain.[18] Even though a previous study in guinea pigs,[18,19] an animal with a more gradual brain developmental process, did show an induction of neuroapoptosis with a 4-hour exposure to isoflurane during synaptogenesis, more consistent data are needed. Most are behavioral studies with no insight into causative mechanisms.[16] Parallel measures of histopathology and behavior would be more informative.[18] These studies are also often underpowered in that male rats are sometimes used for experiments instead of female rats.

The substantial and prolonged use of volatile anesthetics (VA) in the fetus is probably more concerning in ex utero intrapartum treatment (EXIT) procedures in which the parturient is often exposed to high concentrations of VA, mostly exceeding 2 minimum alveolar concentration (MAC) to maintain uterine relaxation.[20,21] EXIT procedures are very rare but are designed to allow partial delivery of the fetus with a potentially difficult airway (e.g., large fetal neck mass) with subsequent management of the neonatal airway while oxygenation is maintained via the placenta.[20-22] The high concentration of VA provides surgical anesthesia for the mother, tocolytic effects on the gravid uterus, and intraoperative anesthesia for the fetus.[20,23,24] More extensive prospective studies assessing the effects of high concentrations of VA on cognition and learning in children who required EXIT procedures in utero need to be performed for more definite conclusions on the effect of neuroapoptosis on cognition.

The appearance of recent epidemiologic studies showing the lack of an increased incidence of learning disabilities in children exposed to general and regional anesthesia for cesarean and vaginal deliveries compared with those unexposed to any anesthetics has reduced the recent concern about early anesthesia exposure to a certain degree.[25-27] Nevertheless, the use of epidemiologic studies alone to study the association between general anesthesia and learning disabilities remains suboptimal because of the possibility that fetuses of mothers who needed general anesthesia may already be at an increased risk of learning difficulties compared with the general population.[18] In addition, surgery can induce an inflammatory process that can subsequently induce changes in the central nervous system.[18] The need for randomized clinical trials cannot be overemphasized.

Fetal Monitoring during Surgery

Although fetal homeostasis is maintained by avoiding maternal hypotension and hypoxemia, maternal hemodynamic stability does not always guarantee adequate placental perfusion and fetal oxygenation during surgery.[28,29] Is fetal heart rate (FHR) monitoring needed during surgery to effectively monitor these variables? Unfortunately, the false-positive rate for performing a cesarean section with the use of electronic FHR monitoring is 99.8%,[30,31] and the use of FHR monitoring has still not been shown to be superior to intermittent fetal auscultation.[30,32,33] Such lack of a definite measure of fetal well-being during surgery has led to the recommendation of specific guidelines by both the ASA and ACOG for fetal monitoring during surgery. If a fetus is considered previable (less than 23 to 24 weeks of gestation), it is generally sufficient to obtain FHR by Doppler before and after the procedure. At a minimum, if the fetus is viable, simultaneous electronic FHR and contraction monitoring should be obtained before and after the procedure to assess for fetal well-being and the absence of contractions.[34,35] Intraoperative electronic fetal monitoring (EFM) may be appropriate if all the following apply: the fetus is viable, intraoperative EFM is possible, an obstetric provider is available and willing to intervene for fetal indications, and the parturient has consented to emergency cesarean delivery if necessary.[34-37] Intraoperative EFM may also be considered for previable fetuses to facilitate positioning and oxygenation interventions. Nevertheless, the decision to use fetal monitoring should be individualized and necessitates a multidisciplinary team approach. Skilled personnel should be available to accurately interpret the FHR and uterine contraction tracing.[34,35] The goals of FHR monitoring during surgery are to maintain adequate uterine perfusion and identify fetal compromise or preterm labor (PTL).[30] Although the actual use of FHR monitoring to achieve such goals is flawed, early detection of a change in a trend could lead to possible therapeutic interventions such as position changes, increasing maternal oxygenation, improving placental blood flow by increasing maternal blood pressure, changing the site of surgical retraction, and tocolysis by increasing maternal depth of anesthesia to decrease uterine tone,[4,6,30] all of which could be considered before delivery of the fetus. Transvaginal probes have been used for abdominal surgeries in which access via a transabdominal approach remains a challenge. With continuous monitoring under

general anesthesia and the use of sedatives, loss of beat-to-beat variability is expected.[6,36,37] Fetal bradycardia and decelerations are not normal and may indicate the need for intervention, as already indicated. Nonetheless, monitoring has still not been shown to improve fetal outcomes (Figure 67-1).[6,29,37]

Preterm Labor after Nonobstetric Surgery

The prevention of preterm labor or delivery (PTL/D) remains one of the greatest concerns of anesthesiologists in the postoperative parturient.[6] Most epidemiologic

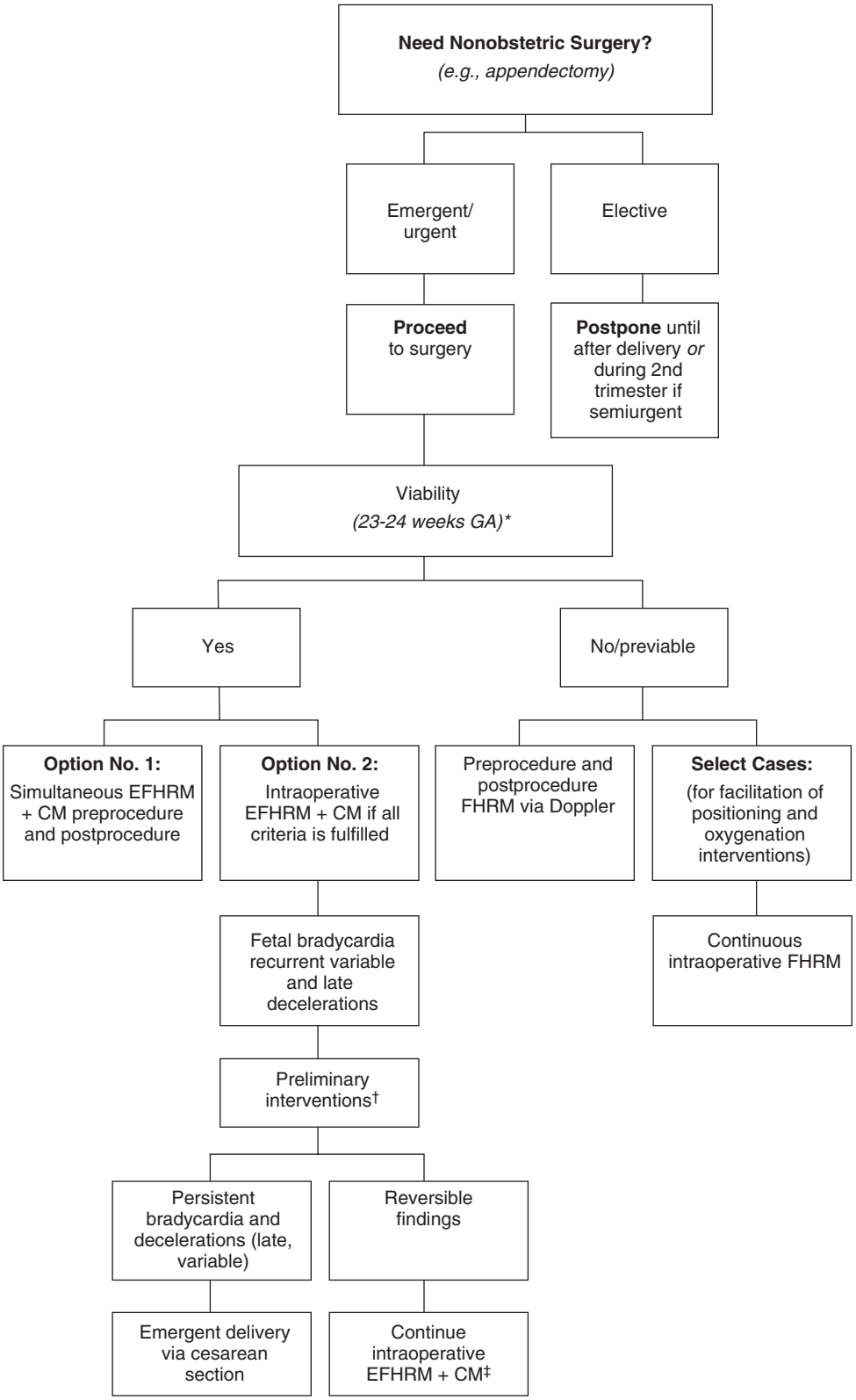

FIGURE 67-1 ■ Algorithm with Recommendations for Fetal Monitoring during Nonobstetric Surgery in a Parturient following ASA and ACOG Guidelines. At all stages, it is important to note that decision should be made by a multidisciplinary team approach (anesthesia, obstetric care providers, surgery, pediatrics, and nursing) for optimal safety of the woman and the fetus.

*Three prerequisites for proceeding to surgery with any fetal heart rate monitoring *(FHRM):* (1) institution must have neonatal and pediatric services, (2) availability of obstetrician with C-section privileges, and (3) availability of qualified staff to interpret FHR and contraction patterns. *GA,* gestational age.

†Preliminary interventions: position change (left uterine displacement), increasing maternal oxygenation, improving placental blood flow, changing site of surgical retraction, and tocolysis (increasing depth of anesthesia to decrease uterine tone).

‡Five criteria for performing intraoperative/continuous electronic fetal heart rate monitoring *(EFHRM)* and contraction monitoring *(CM):* (1) viable fetus, (2) physically possible to perform EFHRM and CM, (3) availability of health care provider with obstetric surgery privileges who is willing to intervene during surgery for fetal indications, (4) informed consent from parturient for emergency cesarean delivery if possible, and (5) ability to safely interrupt surgical procedure for emergency delivery.

studies of nonobstetric surgery during pregnancy demonstrate an increased incidence of PTL/D and abortion with unclear conclusions about the etiology. Manipulations of the uterus, the particular surgery (specifically intra-abdominal procedures), and underlying maternal disease have all been considered possible culprits.[1,4,6,38] Anesthetic management has not been shown to be a causative factor.[4,6] In addition, no evidence has currently associated any anesthetic agents with an increased risk of PTL/D.[4] According to Mazze and Kallen,[39] second trimester procedures and those not involving uterine manipulation carry the lowest risk of PTL/D. Prophylactic tocolytic therapy is controversial and has not been shown to be effective in preventing PTL/D but is, instead, associated with an increased risk of maternal adverse effects.[1,4,37]

Although prior studies have shown both the risk of teratogenicity and spontaneous labor or PTL to be less in the second trimester,[6,35] Palanisamy and colleagues[16] describe the second trimester as the period of highest risk for nonobstetric surgery or fetal interventions in light of apoptotic neurodegeneration and subsequent learning impairments. More studies are needed to reconcile these issues and identify the least vulnerable period for performing emergent nonobstetric surgeries during pregnancy by weighing the risk–benefit ratio.

Use of Laparoscopy during Pregnancy

Most of the abdominal surgeries prevalent in pregnancy are amenable to the use of the laparoscopic surgical approach. The use of laparoscopy has therefore remained a relevant topic in this patient population. In a cohort study[5] of 2783 pregnancies with an operative incidence of 1.3%, the majority of the cases were conducted for gallbladder disease with a 3 to 1 ratio of cholecystectomy to appendectomy (the second most frequent procedure). The use of laparoscopy has been demonstrated to be safe in pregnant patients in any trimester and is no longer considered a contraindication in pregnancy.[3,5,30,40,41] A Swedish study of more than 2 million deliveries favored laparoscopic surgery to an open procedure.[42] Other studies have shown laparoscopy to be no more dangerous than laparotomy to either the mother or the fetus.[43,44] Although several studies have outlined clear maternal benefits of minimal invasive surgery, fetal outcomes have been shown to be similar irrespective of the surgical approach.[6,45] Advantages of laparoscopy include less fetal exposure to anesthetics, smaller incisions, decreased blood loss, decreased postoperative analgesia requirements, shorter hospital stays, and an earlier return to activities of daily living. Disadvantages, however, include a decrease in venous return and cardiac output with a subsequent decrease in uteroplacental perfusion due to increased intra-abdominal pressure from pneumoperitoneum and aortocaval compression; alterations in maternal and fetal blood gases due to absorption of CO_2 or hypoventilation; and direct uterine or fetal injury from trocar insertion.[1,2,30] Theoretically, the risk of hypercarbia, hypoxemia, and hypotension is increased.[42] However, animal studies in near-term sheep demonstrate that CO_2 pneumoperitoneum does not cause hypoxia or significant fetal hemodynamic changes but can induce fetal respiratory acidosis.[6] On the other hand, work in preterm animals indicates that laparoscopically induced hypercapnia and acidosis are accompanied by prolonged fetal hypoxia and cardiovascular depression, even after insufflation is discontinued.[6] The exact clinical significance as it relates to the developing human brain is still unknown.[6] A major limiting factor to the laparoscopic approach as described by Buser[5] was the skill of the surgeon and the awareness of one's own capabilities and limitations. Guidelines to prevent adverse effects from laparoscopy include an open technique to enter the abdomen to avoid uterine or fetal trauma; low insufflation pressures of less than 12 to 15 mm Hg; cautious and limited use of the Trendelenberg and reverse Trendenlenberg positions; and gradual position changes while maintaining left uterine displacement to minimize uterine compression of the great vessels.[2,4,6,28,36] Vasopressors (e.g., phenylephrine and ephedrine) may also be needed to treat hypotension as well as pneumatic stockings to promote venous return.[1,2,36] FHR and uterine activity is monitored through the transvaginal route when necessary. The uterus is protected with lead shielding during radiation.[1,2,6]

CONCLUSION

In summary, no study has shown the type of surgery, type of anesthetic, length of anesthesia, trimester in which surgery is performed, length of surgery, or estimated surgical blood loss to significantly affect pregnancy outcomes.[6,36] Nevertheless, elective surgery is not performed during pregnancy. Most women who undergo general anesthesia during pregnancy do so because of necessity. Reassurance of the mother by the anesthesiologist while educating her about the safety of anesthesia during pregnancy is important. Fetal monitoring should be used as per ASA and ACOG guidelines and should be approached as a medical issue not a medicolegal one![6,36] The decision to use fetal monitoring should be individualized and warrants a multidisciplinary team-based approach to ensure the optimal safety of the mother and fetus.[6,34-36] New research continues to emerge. Simply put, the clinical relevance of animal findings to their human counterparts is unclear, and more studies are obviously needed to translate these findings into human clinical practice.

AREAS OF UNCERTAINTY

The most recent area of hot debate and controversy, with new findings published as recently as 2011 by Palanisamy and colleagues,[16] is the increased risk of subsequent learning impairment with fetal or newborn exposure to general anesthesia due to widespread apoptotic neurodegeneration. Of note is the existence of prior similar findings by Jevtovic-Todorovic et al[17] in 2003, also showing an increased risk of learning deficits and widespread neurodegeneration in developing rat brain due to early exposure to common anesthetic agents. Both studies are animal studies and are therefore plagued by several

limitations as already described. Validation is still lacking in humans.

Simultaneously, the appearance of recent epidemiologic studies showing the lack of an increased incidence of learning disabilities in children exposed to general anesthesia for cesarean section compared with those unexposed to any anesthetics brings this association between early exposure to general anesthesia and cognitive impairment into question.[25-27] The need for additional studies, especially those strictly performed in humans, cannot be overemphasized. Nevertheless, the use of epidemiologic studies to study the association between general anesthesia and learning disabilities remains suboptimal because of the possibility that fetuses of mothers that needed general anesthesia may already be at an increased risk of learning difficulties compared with the general population.[18] In addition, surgery can induce an inflammatory process that can subsequently induce changes in the central nervous system.[18] The need for randomized clinical trials therefore remains the optimal choice. Palanisamy and colleagues[16] also describe the second trimester as the period of highest risk for nonobstetric surgery or fetal interventions in light of apoptotic neurodegeneration and subsequent learning impairment. Prior studies, however, indicate second trimester procedures to carry the lowest risk of PTL/D.[39] More studies are needed to reconcile these issues and identify the least vulnerable period for performing semiurgent nonobstetric surgeries during pregnancy by weighing the risk–benefit ratio. Prospective studies assessing the effects of high concentrations of VA on cognition and learning in children who required EXIT procedures in utero may also provide more definite conclusions.

Unfortunately, performing large-scale trials in this patient population will always remain a challenge, and several questions may never be adequately addressed in this population.

GUIDELINES

There are currently no evidence-based guidelines for anesthesia for nonobstetric surgery, but recommendations and expert opinions exist on this issue. A joint statement incorporated in "Practice Guidelines" from the ASA and ACOG[34,35] was developed to address issues of concern to both specialties. Because of the difficulty of conducting large-scale randomized clinical trials in this patient population, no definite data allow for specific recommendations or guidelines; however, the expert consensus from both committees has been incorporated in Figure 67-1 and is also extensively described in the section on fetal monitoring under surgery. In summary, both committees agree that a pregnant woman should never be denied indicated surgery, regardless of the trimester. Elective surgery should be postponed until after delivery. If possible, nonurgent surgery should be performed in the second trimester when preterm contractions and spontaneous abortion are least likely. The decision to use fetal monitoring should be individualized[34,35] and should follow the recommended guidelines in Figure 67-1. Ultimately, each case warrants a team approach (anesthesia, obstetric care providers, surgery, pediatrics, and nursing) for optimal safety of the woman and the fetus.

In addition to the ASA and ACOG guidelines, one must rely on the comprehensive chapters in the major texts and take into account the normal physiologic changes of pregnancy to determine the risk of anesthesia for the parturient undergoing nonobstetric surgery.[30]

AUTHOR'S RECOMMENDATIONS

- Reassure and counsel the parturient preoperatively, specifically concerning the safety of anesthetic agents during pregnancy. Despite the concern of many, no anesthetic agent has been shown to be teratogenic in humans when used in standard concentrations. Even with recent animal studies showing widespread neuroapoptosis with general anesthesia and subsequent learning impairment, validation is still lacking in humans. Moreover, epidemiologic studies fail to show similar results in patients exposed to general anesthesia via cesarean section.
- Nevertheless, when appropriate and possible, avoid general anesthesia and err toward regional anesthesia in the parturient because of a constellation of benefits. Extra caution is always a necessity because of the paucity of data in this patient population.
- Fetal heart rate (FHR) and uterine contraction monitoring can be useful before, after, or during nonobstetric surgery but because of its high false-positive rate, its use should be guided by the specific recommendations of both the American Society of Anesthesiologists and American College of Obstetricians and Gynecologists (see Figure 67-1). FHR monitoring should be used for early detection of a change in trends that could lead to possible therapeutic interventions. The decision to use FHR monitoring should be individualized and done from a multidisciplinary approach.
- With the increasing use of the laparoscopic approach during nonobstetric surgery, the anesthesiologist should be aware of the possible complications and physiologic derangements seen with laparoscopy. Of more importance is understanding how to counteract these effects and their implications. Reassuringly, laparoscopy has been shown to be safe in pregnancy when used during any trimester.

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CHAPTER 68

How Young Is the Youngest Infant for Outpatient Surgery?

Lucinda L. Everett, MD

INTRODUCTION

Outpatient surgery accounts for a significant percentage of anesthetics delivered annually in the United States. Many pediatric procedures, such as hernia repair, circumcision, endoscopy, and heel cord tenotomy, are performed in infants and may occur on an outpatient basis.

Apnea is the most common serious adverse event after general anesthesia in an infant. Premature and former premature infants are at higher risk of apnea than healthy term babies; furthermore, there is little evidence regarding apnea risk in term patients. In addition, infants (younger than 1 year) are at higher risk of intraoperative anesthetic cardiac arrest and other complications[1] and require careful anesthetic management by practitioners with training and ongoing experience in this population.

PATHOPHYSIOLOGY

Apnea of prematurity is found in 50% of premature infants and is almost universal in infants who are 1000 g at birth. Clinically significant apnea in infants is defined as breathing pauses of 20 seconds or pauses of 10 seconds with bradycardia or oxygen desaturation. However, no consensus exists as to what is pathologic in terms of the duration of apnea, degree of change in oxygen saturation, and severity of bradycardia, and the relationship with conditions such as gastroesophageal reflux is unclear.[2]

In the perioperative setting, 1982 brought Steward's publication[3] of a small series of infants having herniorrhaphy, which showed that preterm infants were more prone to apnea and other airway complications. A larger prospective study of infants having general anesthesia for a variety of procedures found that a much higher proportion of premature infants required postoperative ventilation.[4] The authors postulated that "anesthetics may unmask a defect in ventilatory control of prematurely born infants younger than 41 to 46 weeks conceptual age with preanesthetic history of idiopathic apnea." Apnea of prematurity and postoperative apnea are primarily central in nature, although a minority of children have an obstructive or mixed pattern.

EVIDENCE

Overall Risk in Pediatric Anesthesia

Few studies specifically address risk in infants for outpatient surgery. Patel and Hannallah[5] assessed anesthetic complications in a large series of pediatric outpatients and did not note any specific issues in approximately 350 patients younger than 6 months.

Further evaluation of overall risk requires extrapolation from studies of particular patient populations or from adverse outcomes in infants who are not necessarily outpatients. Several studies have demonstrated an increased incidence of complications in infants (younger than 1 year) compared with other pediatric age groups. A prospective survey of 40,240 anesthetics in infants and children from 1978 to 1982 found an overall complication rate of 4.3% in infants compared with 0.5% in children 1 to 14 years of age; the cardiac arrest rate was 1.9% in infants compared with 0.2% in the older patients.[6] Risk increased with increasing American Society of Anesthesiologists (ASA) status and in emergency procedures; the majority of "accidents" in the infant group occurred during the maintenance of anesthesia and were initiated by respiratory events. Analysis of anesthetics conducted in more than 29,000 children from 1982 to 1987 found a high incidence of adverse events in very small infants (younger than 1 month), but patients were more likely to have a higher ASA status or be undergoing major cardiac or intra-abdominal surgery.[7] A large prospective French audit reflecting currently available drugs and monitoring techniques showed that respiratory events accounted for 53% of all intraoperative events and that there remains a higher risk of adverse events in infants compared with older children.[8]

Analysis of closed claims information as published in 1993[9] showed that pediatric claims were more often related to respiratory events and that the mortality rate was greater than in adults. The complications in pediatric cases were more frequently thought to have been preventable with better monitoring. Analysis of pediatric closed claims from 1990 to 2000[10] showed a decrease in the proportion of respiratory claims, particularly those for inadequate oxygenation and ventilation, compared with pediatric claims from the earlier period.

The initial observations from the closed claims data led to the creation of the Pediatric Perioperative Cardiac Arrest (POCA) Registry.[1] Basic demographic information from participating institutions was submitted along with case reports of cardiac arrest. Although overall denominator data are available, more specific information such as breakdown of anesthetic agents in all cases or qualifications of the anesthesia caregivers is not. The incidence of cardiac arrest for the institutions studied for the first report (1994 to 1997) was 1.4 per 10,000 anesthetics, with a mortality rate of 26%. Cardiac arrest occurred most often in patients less than 1 year of age and in patients with severe underlying disease. Patients with concurrent diseases and those having emergency surgery were most likely to have fatal outcomes. In patients whose ASA status was 1 or 2, 64% of the cardiac arrests were medication related; two thirds of the medication-related arrests were due to cardiovascular depression from halothane alone or in combination with other drugs. Cases from the POCA registry for the years 1998 to 2004 demonstrated a declining proportion of cardiac arrests related to medications, in parallel with the transition from halothane to sevoflurane in clinical practice.[11]

Apnea Risk

Term Infants

There is relatively little specific evidence about apnea risk after anesthesia in term infants. Some evidence exists for individual procedures, but it is not generalizable; however, it may help in setting limits for outpatient surgery. Infants with pyloric stenosis require admission because of the need for preoperative fluid resuscitation and the risk of postoperative apnea (related to metabolic abnormalities). Data from 60 full-term neonates and infants undergoing pyloromyotomy showed a significant incidence of apnea (27% preoperatively and 16% postoperatively), and some instances were in patients with normal preoperative pneumograms.[12] Although currently cleft lip repair is not considered appropriate for outpatient surgery because of associated airway concerns, Stephens and colleagues[13] reported a retrospective analysis of 50 neonates (3 to 56 days old; 11 former premature infants of less than 45 weeks' postconceptual age) having cleft lip repair who had minimal respiratory complications. Ongoing reassessment of practice and refinement of techniques, however, continue to lead to additional procedures being done in a short-stay or day-surgery setting in selected patients: 23-hour admission has been described for otherwise healthy, nonsyndromic patients having primary cleft palate surgery at ages from 6 to 20 months.[14] Large population studies are needed to truly evaluate the risk.

Premature Infants

The bulk of evidence regarding apnea risk after anesthesia relates to former premature infants rather than term babies. A number of small case series tried to more accurately define risk; the data from several of these were pooled into a "combined analysis" in 1995 by Coté and colleagues.[15] The combined series contains data from 255 former preterm infants having general anesthesia for inguinal hernia repairs; infants receiving caffeine were excluded. Using a standardized definition of apnea (greater than 15 seconds without bradycardia or less than 15 seconds when accompanied by bradycardia), they looked for associated risk factors to better define the population at risk. Variation was considerable between institutions in the reported incidence, which was thought to be related to differences in monitoring techniques. The combined analysis showed that apnea was strongly and inversely related to both gestational age and postconceptual age and that continuing apnea at home and anemia were also risk factors. No association was found with a number of other historical factors or anesthetic variables, but this may have been due to the relatively small numbers.

The Coté combined analysis does not define a strict cutoff age for all patients but rather defines confidence intervals for the risk of apnea at various combinations of gestational and postconceptual ages. For nonanemic infants free of recovery room apnea, the probability of apnea was not less than 1% until postconceptual age 56 weeks with gestational age 32 weeks or postconceptual age 54 weeks with gestational age 35 weeks. The authors note that individual clinicians must decide on acceptable risk in a given practice setting.

Some question the clinical relevance of apnea detected only by sophisticated monitoring techniques. One group has published a series of 124 former preterm infants, including 67 patients younger than 46 weeks of postconceptual age; those having uncomplicated anesthetics were discharged after an average recovery room stay of 94 minutes with no apparent adverse consequences.[16] One episode of apnea, responsive to stimulation, was noted in an infant on an apnea monitor at home. A retrospective review of respiratory complications in 57 former premature infants having hernia repair noted that all instances of postoperative apnea/bradycardia and laryngospasm occurred within the first 4 hours postoperatively.[17] Caution is urged in generalizing these findings without larger studies to demonstrate the safety of outpatient care in this patient population. A recent "classification and regression tree analysis" identified five factors as predictive of postanesthesia care unit duration of stay after herniorrhaphy in infants: postconceptual age younger than 45 weeks, prematurity, general anesthesia, postoperative opioid administration, and the use of intraoperative regional analgesia.[18]

Methylxanthines. A prospective randomized trial of caffeine versus placebo for apnea of prematurity in 2006 infants with birth weights of 500 to 1250 g showed that fewer caffeine-treated infants required supplemental oxygen (36% versus 47%) and that treated infants had positive airway pressure discontinued, on average, 1 week earlier.[19] The follow-up phase of the same study showed a modest improvement in survival rate and a modest decrease in the incidence of cerebral palsy and cognitive dysfunction in caffeine-treated very-low-birth-weight infants at 18 months but not at 5 years of age.[20] Economic analysis suggests that caffeine treatment leads to both improved outcomes and a slightly lower cost of care.[21]

Caffeine has been shown to decrease the risk of apnea in former premature infants undergoing general anesthesia, but studies are relatively small. Welborn and colleagues[22] randomly assigned 32 former preterm infants (37 to 44 weeks' postconceptual age) to receive either 10 mg/kg caffeine or placebo in conjunction with general anesthesia for inguinal hernia repair. No patients in the caffeine group had postoperative bradycardia, prolonged apnea, periodic breathing, or postoperative oxygen saturation less than 90%; 81% of patients in the control group had prolonged apnea at 4 to 6 hours postoperatively. Systematic review of the available studies concluded that evidence supports that caffeine reduces apnea risk but that, because of small numbers and questionable clinical significance of apneic episodes in clinical trials to date, caution should be used in applying these results to routine clinical practice (Table 68-1).[23]

Anesthetic Technique and Apnea Risk. In a prospective comparison by Welborn and colleagues,[24] spinal anesthesia alone had a lower incidence of postoperative apnea and bradycardia in former preterm infants when compared with spinal anesthesia plus sedation or general anesthesia. Other studies have confirmed a lower incidence of oxygen desaturation and bradycardia,[25] although Krane and colleagues[26] did not find a difference in the incidence of central apnea, suggesting that airway obstruction may also play a role in postoperative clinical events. The incidence of apnea after unsupplemented spinal anesthesia in former premature infants is low[27]; however, cardiopulmonary events occur frequently enough in this population[28] to warrant postoperative observation similar to general anesthesia. A Cochrane review analyzed four small trials comparing spinal with general anesthesia in the repair of inguinal hernia in former preterm infants (Table 68-2).[29] The authors found no significant difference in the proportion of infants having postoperative apnea/bradycardia or oxygen desaturation. Meta-analysis supported a reduction in postoperative apnea in infants having spinal anesthesia without sedation, as well as a borderline significant decrease in the use of postoperative assisted ventilation.

The majority of studies of spinal anesthesia in former preterm infants used comparison with older volatile agents, primarily halothane; however, a comparison with sevoflurane still showed a lower incidence of postoperative cardiorespiratory complications with spinal anesthesia.[30] Because both groups received supplemental caudal analgesia, this study actually examined whether a "light" general anesthetic with caudal block would lower the risk to the same level as with unsupplemented spinal anesthesia and found that it did not.

Clonidine has good safety and efficacy in children for caudal block, but several case reports have suggested that it is associated with postoperative apnea. A prospective series of term and preterm infants having spinal anesthesia with bupivacaine and clonidine found a significant increase in apneic episodes postoperatively but no change in the incidence of desaturation[31]; there was not a study group without clonidine.

Regarding general anesthetic agents, one study comparing halothane with remifentanil for infants undergoing pyloromyotomy found that none of the 38 patients receiving remifentanil developed new pneumogram abnormalities after anesthesia, whereas three of 22 infants receiving halothane did.[32] Coté and colleagues[15] did not find a specific influence of opioids on postoperative apnea but noted that very few of the infants in their study received opioids. In a comparison of general anesthetic techniques in term and former preterm infants less than 60 weeks of postconceptual age having hernia repairs, patients having thiopental or halothane induction with desflurane maintenance had significantly shorter times to extubation than those having the entire anesthetic with either halothane or sevoflurane. None of the 40 infants in this study had significant postoperative apnea.[33] A prospective comparison of sevoflurane and desflurane in former premature infants having hernia repair found no difference in the incidence of respiratory events, and no difference was found between the preoperative and postoperative incidence of apnea in either group.[34]

TABLE 68-1 **Summary of Meta-Analysis on Prophylactic Caffeine to Prevent Postoperative Apnea following General Anesthesia in Former Preterm Infants**

Study, Year	No. of Trials	No. of Subjects	Intervention	Control	Outcomes
Henderson-Smart, 2001[23]	3	78	Caffeine (10 mg/kg in two studies, 5 mg/kg in one)	Placebo	Apnea/bradycardia occurred in fewer treated infants. In two studies, oxygen desaturation was evaluated; fewer episodes occurred in the treatment group.

TABLE 68-2 **Summary of Meta-Analysis on Regional versus General Anesthesia in Preterm Infants**

Study, Year	No. of Trials	No. of Subjects	Intervention	Control	Outcomes
Craven, 2003[29]	4	108	Spinal anesthesia (local anesthetic only)	General volatile plus muscle relaxant	Significant reduction in postoperative apnea for unsupplemented spinal anesthesia

Expertise of Anesthesia Providers

Although not extensively studied, some evidence suggests fewer adverse outcomes in the hands of anesthesiologists with frequent ongoing experience in anesthetizing children. Keenan and colleagues[35] found a lower incidence of bradycardia in infants when a pediatric anesthesiologist was present. Mamie and colleagues[36] showed a lower incidence of respiratory complications in the hands of pediatric anesthesiologists. Both the exact definition of a pediatric anesthesiologist and how to best balance adequate ongoing practice with broad availability remain controversial.[37] The American Academy of Pediatrics Section on Anesthesiology[38] has stated that anesthesiologists "providing or directly supervising the anesthesia care of patients in categories designated by the facility's Department of Anesthesia as being at increased anesthesia risk should be graduates of an ACGME pediatric anesthesiology fellowship training program or its equivalent or have documented demonstrated historical and continuous competence in the care of such patients."

CONTROVERSIES

Current evidence does not define an exact "safe" age for former premature infants to be discharged after general anesthesia, nor does it completely delineate the appropriate length of postoperative monitoring for general anesthesia with or without caffeine or for spinal anesthesia. Consensus is lacking on what constitutes a "significant" postoperative apneic event, and different studies report apnea in different ways (i.e., absolute number of episodes versus change from preoperative). Although evidence supports an advantage to the use of spinal anesthesia in former premature infants, the optimal anesthetic and analgesic regimen for all infants is not known.

In addition, the overall postoperative risk in healthy term infants having outpatient surgery is not well delineated, although apneic risk after minor procedures appears to be low.

GUIDELINES

There are no formal practice guidelines from major anesthesia or pediatric organizations regarding outpatient surgery in infants. However, many individual hospitals have developed such guidelines, particularly for expremature infants. These frequently establish a cutoff age of 50 to 56 weeks of postconceptual age in infants born before 37 weeks and may also consider factors such as anemia, prior apnea, and coexisting disease. Postoperative monitoring recommendations range from 12- to 24-hour admission for cardiorespiratory monitoring to include oxygen saturation, heart rate, and impedance pneumography. Some facilities also restrict the lower age for day-surgery procedures to older than 44 to 46 weeks of postconceptual age in term infants or require a longer observation period (e.g., 4 hours) in phase II recovery.

A practice guideline from the American Academy of Pediatrics Section on Anesthesiology does have implications for facilities providing anesthesia care for infants. The document "Guidelines for the Pediatric Perioperative Anesthesia Environment" makes recommendations for facilities, equipment, and provider considerations in caring for various classes of pediatric patients and recommends that patients considered by the facility to be at "high risk," including small infants, be cared for by anesthesiologists with fellowship training or expertise based on ongoing experience.[38] The ASA has made similar recommendations.

AUTHOR'S RECOMMENDATIONS

Key Findings Based on Data

- Postoperative apnea in former premature infants is inversely proportional to both gestational age and postconceptual age.
- Caffeine decreases the risk of postoperative apnea in former premature infants.
- Spinal anesthesia without sedation has a lower incidence of postoperative apnea in premature infants than general anesthesia or spinal with sedation.
- No specific general anesthetic agent or regimen has been shown to be superior in minimizing complications in former premature infants.
- Anesthesia for healthy term infants having simple surgical procedures appears to be safe on an outpatient basis, although few data exist.

Specific Clinical Recommendations

- Appropriate short-acting anesthetic agents may facilitate emergence and discharge.
- Where possible, regional anesthetic techniques and nonopioid analgesics should be used instead of opioids.
- A loading dose of 20 mg/kg caffeine citrate may decrease postoperative apnea in former premature infants.
- If the surgical procedure is suitable, consider spinal anesthesia without sedation in former premature infants; however, postoperative monitoring is still recommended in the at-risk age range.
- Former premature infants should be admitted for observation unless they are older than 54 to 56 weeks of postconceptual age (depending on degree of prematurity) and are without anemia, ongoing apnea, or other significant medical problems. Infants meeting these criteria also need to have had an uneventful anesthetic and recovery room course to allow consideration of discharge. More refined recommendations regarding exact postconceptual age and gestational age can be made on an individual patient basis using data from the combined analysis of Coté and colleagues.[15]
- Term infants can undergo outpatient procedures provided that they are otherwise healthy, the procedure is not likely to result in significant physiologic changes or postoperative pain requiring opioid medications, and the anesthetic proceeds uneventfully. It may be prudent to monitor these patients in the recovery area for several hours postoperatively (Figure 68-1).
- All infants should be cared for in a facility with adequate and appropriately sized equipment and medical and nursing staff with appropriate expertise and adequate ongoing experience in caring for this age group.

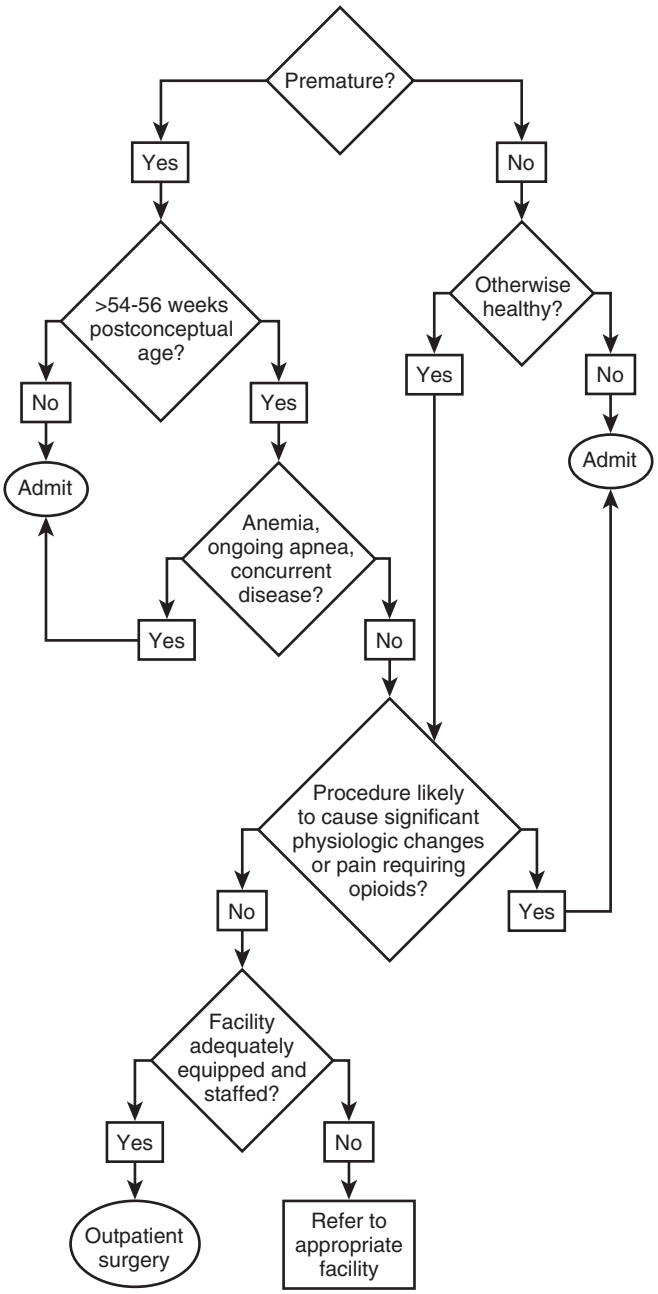

FIGURE 68-1 ■ Algorithm for Infants Younger Than 6 Months of Age Having Outpatient Surgery.

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CHAPTER 69

Should a Child with a Respiratory Tract Infection Undergo Elective Surgery?

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INTRODUCTION

Acute respiratory infections are one of the leading medical causes of surgery cancellation in children.[1] Anesthesiologists are often confronted with patients demonstrating symptoms of upper respiratory tract infections (URIs) (e.g., runny nose, congestion, and coughing) and lower respiratory tract infections (LRIs) (e.g., crackles, rales, wheezing, and sputum production) on the day of surgery. Additional pressures to proceed with anesthesia and surgery despite respiratory symptoms often involve nonmedical issues, which may be social, emotional, and even financial in nature, and these pressures can come from the patient's family, the surgeon, and the hospital.[1]

What is the evidence regarding the risk of proceeding with anesthesia and surgery in the face of acute URI or LRI symptoms? Many large retrospective studies have shown an increased risk of adverse intraoperative and perioperative events such as croup, laryngospasm, and bronchospasm.[2,3] Physiologic experiments in animals and humans have shown increased small airway reactivity during and after viral respiratory tract infections.[4-7] Although the exact mechanisms are unknown, it appears that the airways are affected for up to 6 weeks after a viral respiratory infection.

Another confounding issue in dealing with respiratory tract infections in children is the frequency with which they occur. The average child less than 5 years of age is reported to have from five to six URIs per year with a duration of 7 to 10 days of active symptoms and residual pulmonary effects of 2 to 6 weeks.[8] This creates a practical problem of children becoming reinfected as often as every 2 weeks, especially during the winter months. Adverse respiratory events such as bronchospasm and laryngospasm have been shown to occur more frequently in all pediatric patients, even in the absence of respiratory infections, especially in children younger than 1 year of age. Pediatric patients have an incidence of laryngospasm of 17.4 per 1000 in the age group of 0 to 9 years, which increases in patients with reactive airways disease to 63.9 per 1000. The ratio rises to 95.8 per 1000 when children have a history of respiratory tract infections.[3] Children with underlying chronic pulmonary diseases (e.g., reactive airways disease, asthma, cystic fibrosis, and lung disease of prematurity) have been shown to have an increased risk of perioperative events such as prolonged intubation, reintubation, hypoxemia, bronchospasm, and laryngospasm.[9-13] There is some evidence that the risk of airway events is also increased in children who are exposed to secondhand smoke even in the absence of a history of reactive airways disease or infection.[14]

OPTIONS

Although there is a great deal of anecdotal information in the literature concerning adverse events in children with respiratory infections,[15,16] the clinical dilemma of managing those patients who are demonstrating symptoms of URI or LRI persists for many practitioners. Numerous studies have attempted to elucidate the risks of anesthesia in children with respiratory infections. The following studies and their results are reviewed to better understand the current state of anesthetic care for infants and children with respiratory tract infections.

EVIDENCE FOR PERIOPERATIVE RISK IN CHILDREN WITH RESPIRATORY INFECTIONS

No randomized prospective studies have evaluated the different management options and the relationship to perioperative respiratory complications in children who are currently symptomatic or in those who are recovering from a respiratory tract infection. Other than one study of the risks of URI in children undergoing cardiac surgery, no studies evaluating children with URI who undergo prolonged or invasive procedures have addressed the possibility of benefit from delaying versus proceeding with nonurgent surgery. Therefore one must rely on cohort studies for determining the clinical evidence that exists for management of children with symptomatic and resolving respiratory tract infections (Table 69-1).

Appropriately Identifying Children with Respiratory Tract Infections

The diagnosis of a respiratory tract infection is made based on symptoms. There are no laboratory tests or radiographic findings that make the diagnosis more or

TABLE 69-1 **Overview of Study Design and Findings of Major Studies Involving Risk of General Anesthesia in Children with Upper Respiratory Tract Infection**

Study	Design	No. of Patients Studied	No. of Children with URI	No. of Children with Recent URI	Intubation	LMA	Facemask	Adverse Events	Conclusions
Tait (1987)[18]	Retrospective	3585	122	133	Yes	Yes		L, B, S, A	No increased risk if URI; no difference between ETT versus facemask; if recent URI, had a three times higher rate of bronchospasm
Tait (1987)[20]	Prospective	489	78	84	No	Yes		L, Dy, A	No increased rate of complications in groups with acute or recent URI
DeSoto (1988)[22]	Prospective	50	25	—	Yes	Yes		D	If URI present, increased risk of desaturation
Cohen (1991)[26]	Prospective	22,159	1283	—	Yes	Yes	Yes	L, B, S, A	If URI, then two to three times more likely to have event; 11 times more likely if URI and ETT
Rolf (1992)[24]	Prospective	402	30	—	Yes	Yes	Yes	L, B, D	If URI, then increase in minor desaturation; if URI and ETT, then higher frequency of bronchospasm
Kinouchi (1992)[23]	Prospective	61	20	—	No	Yes		D, A	Desaturation occurs more frequently in young children and is of longer duration
Levy (1992)[21]	Prospective	130	22	28	No	Yes		D	If acute or recent URI, then an increased risk of desaturation
Schreiner (1996)[25]	Case control	15,183	30	17	Yes	Yes	Yes	L	Laryngospasm was more likely to occur in patients with URI, younger children; no correlation between mask versus ETT versus LMA
Skolnick (1998)[14]	Prospective	602	?	?	Yes	Yes		L, B, S, A	Increased risk of adverse events if URI; smoking exposure increase airway complications
Tait (1998)[27]	Prospective	82	82	?	Yes	Yes	Yes	C, A, L, B, D	LMA suitable alternative to ETT
Homer (2007)[28]	Prospective	335	?	?	Yes	Yes	Yes	D, C	Specific preoperative symptoms were not predictive of specific adverse respiratory events
Tait (2001)[50]	Prospective	1078	407	335	Yes	Yes	Yes	B, L, A, C, D	Child with active or recent URI at increased risk of adverse events, but most can be safely anesthetized
von Ungern-Sternberg (2007)[29]	Prospective	831	223	223	No	Yes	No	B, C, D, L	LMA use in child with recent URI associated with higher rate of complications compared with healthy children

A, apnea/breath holding; *B,* bronchospasm; *C,* coughing; *D,* desaturation; *Dy,* dysrhythmia; *ETT,* endotracheal tube; *L,* laryngospasm; *LMA,* laryngeal mask airway; *S,* stridor; *URI,* upper respiratory tract infection.

less accurate. As mentioned earlier, symptoms can involve the upper respiratory tract, the lower respiratory tract, or both (Table 69-2). Unfortunately, other chronic conditions such as a nasal foreign body or allergic rhinitis can occur with symptoms similar to a respiratory tract infection. There are no published guidelines on diagnosing a child with a respiratory tract infection. Studies have used varying definitions ranging from rigid criteria to simply asking parents, "Does your child have an upper respiratory tract infection?" An early study by Tait and Knight[18] used two symptoms of the following list for the diagnosis of URI. These were sore or scratchy throat, sneezing, rhinorrhea, congestion, malaise, cough, fever (higher than 38.3° C), or laryngitis. The most prevalent and statistically significant symptoms for URI were sneezing (24.4%, $n = 78$), congestion (53.8%, $n = 78$), and a nonproductive cough (76.9%, $n = 78$) that were more common when compared with asymptomatic control subjects. In a later study, Tait and colleagues[19] surveyed 212 pediatric anesthesiologists and found the following symptoms being used by anesthesiologists in diagnosing respiratory tract infections. The single symptoms used as contraindications to surgery were fever (64%, $n = 125$), productive cough (62.4%, $n = 121$), wheezing (80.3%, $n = 163$), and rales and/or rhonchi (78.2%, $n = 151$). Further, the most frequently cited combination of symptoms resulting in cancellation of the case were fever and a productive cough (45.4%) or fever and yellow/green rhinorrhea (40.5%). Of note, the average temperature cutoff for cancellation of surgery was 100.8° F (38.3° C). After deciding if a patient is currently symptomatic, one must also consider how to manage a "recently" symptomatic child. The following studies often use a 1- to 2-week period after resolution of acute symptoms as having a "recent" or "resolving" URI. This is one of the confounding elements in dealing with these studies.

Evidence to Proceed with General Anesthesia in Children Not Requiring Endotracheal Intubation with Symptoms of Acute and Resolving Respiratory Tract Infection

A prospective cohort study by Tait and Knight[20] of 489 patients investigated the prevalence of respiratory complications in children with URI or recent URI undergoing general anesthesia by facemask. No increased rate of complications (i.e., laryngospasm, dysrhythmia, or apnea) was found in the children with URIs ($n = 243$) when compared with the control group.[20]

Tait and Knight[18] also retrospectively evaluated the prevalence of adverse perianesthetic respiratory events (i.e., stridor, laryngospasm, and bronchospasm) in 3585 children; 122 had active URIs, and 133 had recent URI symptoms. No increased rate of respiratory complications during and after anesthesia was noted in the symptomatic group when compared with historical control subjects, but a threefold increase in bronchospasm and laryngospasm was demonstrated in the patients with a history of recent URI, regardless of intubation requirement.[18]

Levy and colleagues[21] prospectively studied 130 children undergoing general anesthesia by facemask with either acute or recently resolved URI symptoms. They demonstrated an increased incidence of hypoxemia (despite oxygen administration) during transport to the postanesthesia care unit (PACU) in both the actively infected and recently infected groups when compared with children without URIs. Increased rates of desaturation persisted in the actively infected group during their stay in the PACU.

Although some respiratory events still occur in children with URIs undergoing general anesthesia by facemask, the risk for laryngospasm and bronchospasm does not appear to be significantly increased; however, the incidence of desaturation intraoperatively and postoperatively may be higher. It would seem that the decision to proceed with elective surgery can be made with caution, but the risk of adverse respiratory events is less if endotracheal intubation of children with URI symptoms is avoided.

Evidence to Proceed with General Anesthesia in Children Requiring Endotracheal Intubation with Symptoms of Acute and Resolving Respiratory Tract Infection

Endotracheal intubation in patients with acute or recent URI symptoms has been shown in a variety of studies to be associated with a higher incidence of adverse

TABLE 69-2 **Signs and Symptoms of Respiratory Tract Infections in Children with Upper or Lower Respiratory Tract Infection**

	Mild URI	Severe URI	LRI	Allergic Rhinitis
History	No fever Minimal cough Clear runny nose Sneezing	Malaise Fever Purulent coryza Sneezing Cough	Severe cough Sputum production Wheezing ± fever	Atopy Seasonal history Sneezing
General examination	Nontoxic appearance Clear runny nose	Toxic appearance Malaise Fever	± Toxic appearance Tachypnea ± irritability	No fever Allergic shiners
Pulmonary examination	Clear lungs ± upper airway congestion	Maybe clear lungs Upper airway congestion	Rales Rhonchi	

LRI, lower respiratory tract infection; *URI,* upper respiratory tract infection; *±,* may be present or absent.

respiratory events such as perioperative hypoxia, bronchospasm, and laryngospasm. An increased incidence of intraoperative and postoperative hypoxemia in children with an acute URI has been well-studied and demonstrated in children.

DeSoto and colleagues[22] prospectively studied 50 children (25 with URIs) ages 1 to 4 years who underwent general anesthesia and found that 20% ($n = 5$) of the URI group had postoperative hypoxemia (defined as $SpO_2 < 95\%$) ($p < 0.03$). Of note, no supplemental oxygen was administered in the recovery period unless desaturation was noted. Another study of hypoxemia in children with URIs by Kinouchi and colleagues[23] found that the time period for desaturation to 95% SpO_2 in preoxygenated children was 30% shorter during induction in those with an acute respiratory infection.

Rolf and Cote[24] conducted a prospective study of 402 children who were either asymptomatic ($n = 372$) or symptomatic with nonpurulent coryza URI ($n = 30$) undergoing general anesthesia. They compared perioperative events such as desaturation, laryngospasm, and bronchospasm between the two groups and found a higher frequency of minor desaturations ($SpO_2 < 95\%$ for 60 seconds or more) and a higher frequency of bronchospasm in patients with URIs who had endotracheal tubes (ETTs) placed for surgery.[24] Schreiner and colleagues[25] performed a case-control study to examine whether children who experienced laryngospasm were more likely to have a URI on the day of surgery. URI symptoms were evaluated by questionnaire in 15,183 children. Laryngospasm was found to occur more often in children with active URIs, in children of young age (less than 1 year of age), and in children whose anesthetics were supervised by less experienced attending anesthesiologists.[25]

Cohen and Cameron[26] conducted a large prospective study involving 22,159 children. URI symptoms were present in 1283 of these children with a two to seven times higher incidence of respiratory events intraoperatively and postoperatively when compared with asymptomatic children. They also found that the use of an ETT in a child with URI symptoms increased the risk of adverse respiratory events by elevenfold.[26]

Based on these studies and the strong correlation demonstrated between adverse events and URI symptoms in the setting of endotracheal intubation, the decision to delay elective surgery that requires general anesthesia with endotracheal intubation seems prudent until the adverse effects of the infection have resolved.

Evidence to Proceed with General Anesthesia in Children Using a Laryngeal Mask Airway with Symptoms of Acute and Resolving Respiratory Tract Infection

Some surgical procedures that require endotracheal intubation may be amenable to airway management using a laryngeal mask airway (LMA). In a series of 82 patients, Tait and colleagues[27] in an observational study demonstrated that the use of an LMA ($n = 41$) in place of endotracheal intubation ($n = 41$) was associated with a significantly lower incidence of mild bronchospasm (12.2% versus 0%, $p < 0.05$). No significant difference was seen in larygnospasm, coughing, breath holding, or oxygen desaturation.[27] The coughing observed on emergence after LMA usage was subjectively thought to be less severe than with ETT use in this study. Further, the authors demonstrated no difference in the incidence of complications with endotracheal extubation under deep anesthesia versus awake, although the incidence of complications was higher for the ETT groups compared with LMA (adverse events: 40.5% ETT versus 24.2% LMA; $p < 0.05$). There are no randomized controlled trials comparing the effects of deep versus awake endotracheal extubation in patients with URIs.

Homer and colleagues,[28] using data collected from several prospective studies, showed that airway management had an impact on postanesthetic respiratory complications, such as laryngospasm, desaturation, and coughing ($p = 0.003$). When compared with LMA removed at a deep level of anesthesia, deep endotracheal extubation had a higher incidence of adverse respiratory events (odds ratio [OR], 2.39). The protective effect of LMA was minimized when the airway device was removed with the patient awake. This same study showed that the use of a facemask alone decreased such events (OR, 0.15).[28]

A 2007 prospective observational study by von Ungern-Sternberg and colleagues[29] compared the use of LMA in healthy children with those with recent URIs (within 2 weeks of surgery). They found a higher overall incidence of respiratory events in the recently infected group (OR, 1.981). The difference in intraoperative adverse respiratory events between the groups did not reach statistical significance. However, compared with healthy children, recently infected children were found to have a significantly higher incidence of coughing and laryngospasm in recovery (ORs, 3.401 and 5.561, respectively). Multivariate analysis showed URI and age to be independent risk factors for adverse respiratory events. No difference in outcomes was found for the removal of an LMA in awake patients versus those deeply anesthetized.

On the basis of available evidence, the use of LMA anesthesia may have a role in children with URI symptoms. In patients in whom mask anesthesia would be cumbersome, LMA may be a suitable alternative. Although it does carry more risk of laryngospasm, bronchospasm, and desaturation when compared with a facemask, LMA appears to have a lower incidence in comparison with endotracheal intubation, regardless of the circumstance (whether removed awake or during deep anesthesia).

Evidence for Delaying Surgery 2 to 6 Weeks following an Acute Respiratory Infection

The majority of anesthesiologists who choose to delay an elective surgery will establish a period of time that must pass before they believe the child will be "safe" or at a

"lower risk" to undergo anesthesia. The exact duration of time is unknown. Physiologic studies examining respiratory infections and anesthesia performed in animals demonstrate alterations in arterial oxygen tension, distribution of ventilation and perfusion, shunting, and functional residual capacity before and after viral infection. The exact mechanism is unknown. Perhaps it is a convergence of multiple processes such as changes in airway secretions,[30] smooth muscle responsiveness to tachykinins,[31] and altered muscarinic receptors.[32] Studies in adults evaluating pulmonary function tests before and after a respiratory tract infection have shown changes in small airway hyperreactivity that persist for up to 7 weeks[33] and general respiratory muscle weakness for up to 12 days.[34] Similar pulmonary function test changes have been demonstrated in children ages 6 years and older with URIs.[6]

Skolnick and colleagues[14] prospectively studied 499 children, of whom 26.8% had some history of passive smoke exposure, who received general anesthesia. Adverse respiratory events or complications were identified as severe coughing on induction or emergence, desaturation to SpO_2 less than 95% in the operating room, breath holding, severe coughing in the recovery room, and laryngospasm. The incidence of respiratory complications was 44% in smoke-exposed children compared with 25.5% in children not exposed to smoke. However, children with active URIs were not found to have an increased risk of events, whereas patients with a recent URI and passive smoke exposure had a higher incidence of events. The presence of a URI in this study was determined only by parental survey. As mentioned earlier, Tait and Knight[18] found a threefold increase in bronchospasm and laryngospasm in patients with a recent history of URI, regardless of intubation requirement. These findings would suggest that waiting would eliminate the higher risk of these adverse events. Unfortunately, no study has determined a correlation between duration of surgical delay, severity of respiratory tract symptoms, and a decreased incidence of respiratory complications.

In summary, these studies fail to generate a consensus.[17,35-40] They do suggest a higher risk of developing laryngospasm, bronchospasm, and desaturation events with ETT placement in actively and recently infected children. Also, both physiologic and patient-based studies provide evidence that supports the decision to delay surgery for 2 to 6 weeks after a respiratory tract infection in children, especially in the presence of high risk factors (e.g., reactive airways disease and the presence of increased nasal congestion or sputum).

Evidence Pertaining to the Use of Adjunct Medicines for Children Undergoing General Anesthesia with a Recent Upper Respiratory Tract Infection

The use of adjunct medicines to specifically minimize perioperative respiratory adverse events in children with recent or active URIs is not well-documented in the literature. Elwood and colleagues[41] studied the effects of ipratropium and albuterol on otherwise healthy children with recent URIs undergoing general anesthesia compared with children without URIs. In the first phase of the study, 58 children were given ipratropium, aerosolized saline placebo, or no intervention. No difference was found in respiratory adverse events between ipratropium and nonintervention groups. The placebo was found to significantly increase coughing on emergence ($p = 0.03$) and was eliminated from the second phase of the study. In the second phase of the study, 51 children were given albuterol versus no intervention. Again, the study results showed no significant difference between the two groups when the incidence of adverse respiratory events was evaluated.

Tait and colleagues[42] proposed that antisialogogues might minimize the incidence of respiratory events, given the evidence showing a correlation between such events and copious secretions. In their study, 130 children with recent URIs undergoing a general anesthetic for elective surgery were randomly assigned to receive glycopyrrolate or placebo after induction of anesthesia. The authors showed that there were no differences in the incidence of adverse respiratory events between the two groups. They did show that intraoperative secretions in either group correlated with an increase in adverse respiratory events.

A small randomized study of 15 mg/kg magnesium given by infusion over 20 minutes after intubation in children having adenotonsillectomy showed a significant reduction in laryngospasm after deep extubation compared with those who received saline.[43] Hypomagnesemia has been linked to perioperative laryngospasm.[44] A study from the otorhinolaryngologic literature compared the effects of levobupivacaine or levobupivacaine and magnesium infiltration with saline placebo on postoperative analgesia and laryngospasm in tonsillectomy patients.[45] No patients who received magnesium experienced laryngospasm. This result did not, however, achieve statistical significance. Both experimental groups did demonstrate lower pain scores than the control group, and the magnesium group had significantly lower scores than the other two groups.

The most recent study of the use of adjunct medications in this patient population was in 2009 by von Ungern-Sternberg.[46] The investigators studied the role of albuterol in the prevention of adverse respiratory events in children with URIs undergoing general anesthesia. Four hundred children with a recent history of URI were equally divided into two groups. One group received preoperative albuterol 10 to 30 minutes before surgery. The other group received no premedication. A third group of 200 children with no history of URI symptoms in the 4 weeks before anesthesia were used as a control group. The albuterol group had significantly lower instances of bronchospasm (5.5% versus 11%, $p = 0.0270$) and severe coughing (5.5% versus 11.5%, $p = 0.0314$) than did the nonintervention group. The children without recent URIs had the lowest rates of adverse respiratory events in all categories.

The aforementioned studies provide a confusing picture for the use of adjunctive medications in children with URIs. Given these findings, it is difficult

to recommend a single therapeutic course. Perhaps bronchodilator therapy should be given routinely to children with URI symptoms before an anesthetic. Clearly, further evidence is needed before a definitive recommendation can be made.

CONTROVERSIES

One area of controversy raised by these studies is defining and differentiating symptoms for acute and recent respiratory tract infections. Attempting to define the condition is easy; however, the particular symptoms used to make the diagnosis and the assignment of severity to those symptoms is difficult within a single study. Importantly, the definition of *respiratory tract infection* and *resolving respiratory tract infection* differed greatly between studies and makes comparison difficult.

A criticism that exists for all the aforementioned studies is their failure to identify alternative causes of *runny nose* and *coughing*. Children can have other underlying diseases that mimic the symptoms of an acute URI. For instance, either allergic rhinitis or a foreign body can cause a runny nose and should be sought as possible etiologies before an incorrect diagnosis of URI is made.

Although many texts and articles cite an increased incidence of pulmonary complications in children with underlying concomitant chronic medical disease and URIs, there are no data in the literature to support this notion. Children with conditions such as congenital heart disease, asthma, and cystic fibrosis are commonly identified as being at increased risk of anesthetic complications. Whether the presence of an acute or recent respiratory tract infection further increases anesthetic risk has not been well-studied. One study in children with asthma and URI symptoms undergoing anesthesia with and without ETT placement demonstrated no increased incidence of adverse events.[10] Another study in children with congenital heart disease undergoing cardiac surgery who had URI symptoms evaluated the incidence of adverse respiratory events compared with asymptomatic children undergoing similar procedures and found no increased incidence and even an improvement in symptoms.[17] Further studies need to be performed to better understand whether anesthetic risk is increased in children with chronic diseases such as asthma, cystic fibrosis, and congenital heart disease who experience URIs. However, current biases and perceptions in anesthetic practice may make such studies difficult.

GUIDELINES

There are no formal practice guidelines regarding management of patients with respiratory tract infections from any major pediatric or anesthesia society. The difficulty of providing a consensus statement or practice guideline is perhaps substantiated in a survey by Tait and colleagues,[19] who sent 400 questionnaires to members of the Society for Pediatric Anesthesia. Of the 212 respondents, 35% reported seldom canceling cases secondary to URI symptoms versus 20% indicating they usually canceled in the event of a URI. Factors considered to be of major importance were urgency of surgery, underlying asthma, procedure requiring intubation, fear of perioperative complications, and past experience anesthetizing patients with URIs. The delay in surgery was up to 4 weeks for URI symptoms and longer than 4 weeks for LRI symptoms. The single symptoms identified as contraindications to surgery were fever, productive cough, wheezing, and rales and/or rhonchi. Currently, the only published "guidelines" are for general pediatric practitioners when evaluating children immediately before surgery, but these "guidelines," for reasons stated earlier, are not evidence based.[41]

AUTHORS' RECOMMENDATIONS

The following suggestions have been derived from the aforementioned studies. These recommendations are neither clinical guidelines nor a consensus statement and should not replace clinical judgment, but they should serve as a guide to help anesthesiologists make a rational decision with parents, surgeons, and patients. As with all children, the preoperative evaluation can serve as an important time to screen children for risk factors for anesthetic complications and to begin educating parents about the anesthetic and operative process.[47-51] However, the absence of a visit for preoperative evaluation does not eliminate the need for an exchange of information between families and the center, which should occur before the day of surgery. Efforts should be made to make parents aware of the problems with respiratory tract infections and anesthesia, and parents should be encouraged to call before the day of surgery to discuss the symptoms and possible need for delay with the anesthesiologist and surgeon. There may be a role for pediatricians and other primary care practitioners to play in the process of preoperative evaluation and education.

Although it is clear that emergency surgery must proceed regardless of the presence or absence of respiratory symptoms, a current or recent upper respiratory infection (URI) or lower respiratory infection (LRI) should be taken into consideration when planning airway management in patients requiring emergency surgery. Such considerations may include preoperative nebulization of albuterol, ensuring adequate anesthetic depth for intubation, and preparation for possible intraoperative bronchospasm and suctioning of pulmonary secretions.

In patients undergoing elective (nonurgent) surgery, initial consideration should be directed at the severity of respiratory tract symptoms (Figure 69-1). Acute symptoms, such as a runny nose and cough, must be differentiated from chronic symptoms related to underlying diseases such as allergic rhinitis (clear runny nose) and asthma (cough). Often, careful questioning of parents can differentiate acute from chronic

AUTHORS' RECOMMENDATIONS (Continued)

symptoms. Patients with severe symptoms such as a fever higher than 38.4° C, malaise, productive coughing, wheezing, or rhonchi should be considered for delay of elective surgery. A reasonable period of delay would be 4 to 6 weeks. If mild symptoms are present, such as nonproductive coughing, sneezing, or mild nasal congestion, surgery could proceed for those having regional or general anesthesia without endotracheal tube (ETT) placement. The intraoperative plan should include early use of pulse oximetry, decision of a facemask or laryngeal mask airway use, and careful suctioning of the nasal and oropharynx under deep anesthesia before emergence. Additional management considerations for patients with URIs or LRIs undergoing anesthesia include hydration status, use of airway humidification, and the potential benefit of pharmacologic agents to help with airway hyper-reactivity (e.g., beta-agonists). Conditions during induction and emergence should be optimized to minimize the risk of laryngospasm, and the anesthesiologist should have a clear treatment plan if laryngospasm does occur.[51] However, for those patients who require ETT placement for anesthesia, especially children younger than 1 year, it is important to identify risk factors such as passive smoke exposure and underlying conditions (e.g., asthma and chronic lung disease) because these children may benefit from a slight delay of 2 to 4 weeks. Finally, those patients with resolving respiratory tract infections with severe symptoms or mild symptoms should have the same relative waiting periods fulfilled to minimize risks of proceeding with surgery (i.e., 2 to 4 weeks after resolution of a minor URI and 4 to 6 weeks after resolution of a severe URI or LRI).

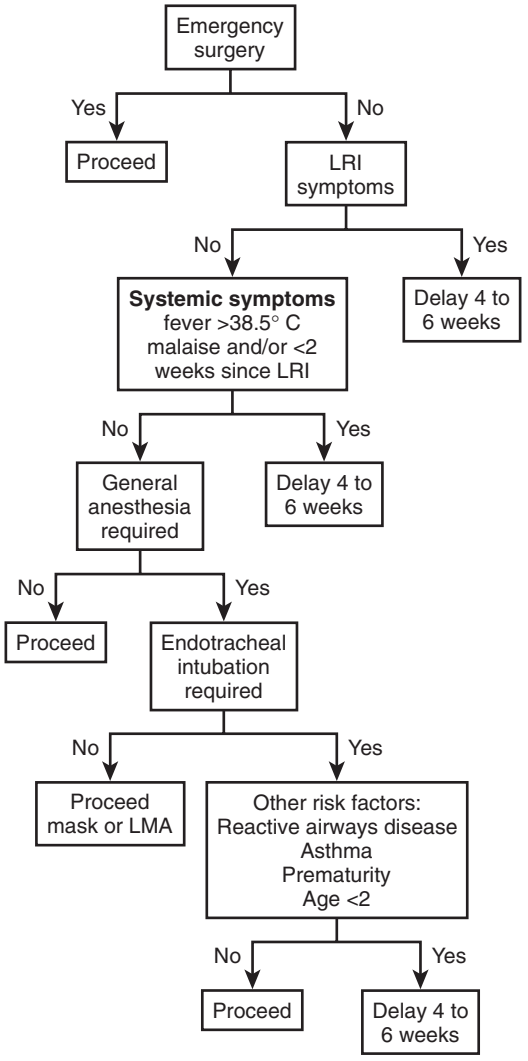

FIGURE 69-1 ■ Clinical Decision Tree for Proceeding with Surgery in Children with Respiratory Tract Infections. *LMA,* laryngeal mask airway; *LRI,* lower respiratory tract infection.

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CHAPTER 70

When Should Regional Anesthesia Be Used in Pediatric Patients?

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INTRODUCTION

The role of regional anesthesia in adult practice is well-established. Some of the benefits of regional anesthesia include improvement in postoperative respiratory function and bowel function and a decrease in the hormonal stress response.[1-3]

Regional anesthesia can be safely and effectively used in children of all ages. The use of regional anesthesia in the pediatric population has been gradually evolving and expanding beyond a few centers.[4-6] Providing adequate analgesia in children during the perioperative period is critically important for patient and parental satisfaction and may improve surgical outcomes.[7-9] Prevention of pain should be our goal in all possible patient care scenarios.[10]

OPTIONS

Regional anesthesia for the pediatric patient can be classified into central neuraxial blocks and peripheral nerve blocks (PNBs). Central neuraxial blocks include the single injection caudal block, which provides analgesia for 4 to 6 hours, or a continuous epidural block in which a catheter is placed for providing continuous delivery of local anesthetic and adjuvants (e.g., clonidine or opioids) into the epidural space. PNBs can be further classified, based on the location, into upper extremity nerve blocks, truncal blocks, and lower extremity nerve blocks. The selective nature of PNBs has made them an attractive option instead of the caudal technique. The increasing use of ultrasound in the perioperative setting has helped in performing these PNBs and in increasing their success rate.

EVIDENCE

Anand and colleagues[1] in their seminal study demonstrated that neonates could mount a hormonal and metabolic stress response in the immediate postoperative period. They found that this stress response correlated with the degree of surgical stress and affected postoperative morbidity and mortality rates. They further showed that blocking this stress response resulted in less patient morbidity in the postoperative period. Another study looking at neonatal circumcision revealed that performing a dorsal penile nerve block reduced the pain related behavior in neonates compared with application of lidocaine/prilocaine (EMLA) cream or no treatment to the site.[11]

Evidence supporting the use of regional anesthesia in children has been accumulating since the 1980s.[12,13] There has been particular interest in the use of regional anesthesia for decreasing the incidence of postoperative apnea in expremature infants after surgery.[14] Early reports were of the use of epidural analgesia (caudal approach) as a supplement to general anesthesia for decreasing the use of opioid medications in these infants.[15] A Cochrane review analyzed evidence regarding improvement in perioperative apnea, bradycardia, and oxygen desaturation between a purely regional (spinal or epidural) anesthetic technique and general anesthesia.[16] They did not find a statistically significant difference in the proportion of infants having postoperative apnea or bradycardia (relative risk [RR], 0.69; confidence interval [CI], 0.4, 1.21) or postoperative desaturation (RR, 0.91; CI, 0.61, 1.37). When infants sedated preoperatively were excluded from the analysis, the difference reached statistical significance (RR, 0.39; CI, 0.19, 0.81). In the conclusion, the authors noted that their review was based on analysis of only 108 patients and recommended that larger randomized controlled trials be performed to determine whether there was a difference between regional and general anesthesia. The authors also noted the limitations of the spinal anesthesia technique, including its high failure rate (about 10%) and the limited time of surgical anesthesia (50 to 60 minutes).

A prospective randomized study using general anesthesia and a caudal block in former premature infants having inguinal hernia repair did not show any difference in outcomes between the use of sevoflurane and desflurane.[17] The authors recommended a light general anesthesia with an inhalational agent and a caudal blockade for pain relief for expremature infants having inguinal hernia repair. Currently, no consensus exists regarding the use of regional anesthesia only (spinal or caudal), general anesthesia only, or a combined regional anesthesia and general anesthesia technique for this common procedure in a very vulnerable population.

Caudal block is the most commonly performed regional anesthetic technique in children because it is easily learned, reliable, and effective. Caudal block is

adequate for all lower extremity and many lower abdominal surgeries. It is not recommended for surgeries above the T9 dermatome (umbilical cord). It is commonly performed in anesthetized children in the lateral decubitus position but can also be performed in the prone position. A short bevel hypodermic needle of the smallest diameter (22- to 25-G needle) is typically used for this block. Specially designed caudal needles with a short bevel and a stylet are available. The sacral hiatus is palpated, and the needle is placed in the most proximal part of the sacral hiatus at a 45- to 60-degree angle to the skin. After the needle pierces the sacrococcygeal membrane, the needle is advanced a further 2 to 5 mm to ensure epidural location. Advancing the needle further may increase the risk of vascular puncture or intrathecal placement. The French-Language Society of Pediatric Anesthesiologists (ADARPEF) study prospectively examined their experience with 24,409 regional anesthetics in the early 1990s.[12] Caudal blocks accounted for about 60% of the procedures performed, all other peripheral blocks accounted for about 20%, and local infiltration accounted for 20%. They reported a complication rate for all blocks to be 0.9 per 1000, and all the complications were minor. A follow-up to this initial report[18] found that, of the nearly 30,000 regional blocks, caudal blocks accounted for 34% of blocks, whereas PNBs accounted for the other 66%. This highlighted the increasing use of peripheral nerve techniques in children. Complications were again noted to be minor with a rate of 1.2 per 1000 blocks; central blocks had a higher complication rate. Fifteen patients developed cardiac toxicity from the local anesthetic, 10 had inadvertent spinal taps, and five developed temporary nerve injuries. In another audit of all 10,163 epidurals placed in the United Kingdom over a 1-year period, 56 complications were noted in this cohort, yielding an incidence of 1 in 189. Five of these were graded as serious (incidence of 1 in 2000), and one was persistent at 12 months (incidence of 1 in 10,000).[19] Two patients developed an epidural abscess, one developed a postdural puncture headache requiring a blood patch, one developed meningism, and another one developed cauda equina syndrome secondary to an incorrectly administered dose (three times the intended bolus) of local anesthetic.

Eyres and colleagues[20] were the first to measure blood levels of bupivacaine after caudal administration in children. Recent data show that blood levels are within safe limits when 1 mL/kg of 0.25% bupivacaine or 0.2% ropivacaine are used for caudal block placement.[21,22] Both 0.2% ropivacaine and 0.125% or 0.25% bupivacaine have been extensively used to perform the caudal block. Ropivacaine has a lower incidence of motor blockade and a safer profile compared with bupivacaine in case of accidental intravascular injection.[21,23] A dose of about 1 mL/kg to a maximum of 25 mL is adequate for most indications.

Bosenberg and colleagues[24] were the first to describe successful placement of a thoracic epidural catheter via the caudal route. Subsequent studies showed this technique to be reliably successful when a styleted epidural catheter was used.[25] The technique has a higher success rate when performed in children younger than 1 year of age. Bosenberg and colleagues also studied the pharmacokinetics of 0.2% ropivacaine infusion in neonates and infants and found that the plasma levels of ropivacaine were below the suggested toxic level of 0.375 mgL.[26] However, neonates did show a higher concentration than the infants for unbound ropivacaine levels. On the basis of their observation, the authors advocate the use of a dose of 0.2 mg/kg/hr for infants younger than 180 days old and 0.4 mg/kg/hr for infants older than 180 days (Figure 70-1). Meunier and colleagues[27] evaluated the pharmacokinetics of bupivacaine during an epidural infusion in neonates and infants. They looked at an infusion rate of 0.375 mg/kg/hr for 48 hours and found two infants to have a blood level greater than 0.2 mg/L (Figure 70-2). On the basis of this observation, they recommended a dose of 0.3 mg/kg/hr for infants younger than 4 months of age and a dose of 0.375 mg/kg/hr for infants older than 4 months of age.

As demonstrated by the French study, PNBs are gaining in popularity in the pediatric population, and increasing data are emerging to demonstrate feasibility, efficacy, and safety in this population.[4,19,28] Several studies in children have demonstrated the safety, feasibility, and efficacy of PNBs.[2,4,29-31] The advantages of PNB include efficient, site-specific analgesia, a decrease in the need for opioids, and consequently, a decrease in opioid-related side effects. Early reports of regional anesthesia in pediatric practice used the fascial clicks (pops) technique to deposit the local anesthetic in the desired plane.[15] This was followed by the use of peripheral nerve stimulators to elicit a motor response when the needle was in close proximity to the nerve.[32] This technique is limited to the major motor nerves (e.g., femoral and sciatic) and was not applicable to blocks such as the ilioinguinal block and penile block, which are commonly performed in children. The problem with the anatomic and nerve stimulator–based approaches was that they did not provide any information regarding the relation of the nerve to the adjoining structures, location of other important neurovascular structures in the region, or provide any feedback regarding the spreading of local anesthetic in relation to the

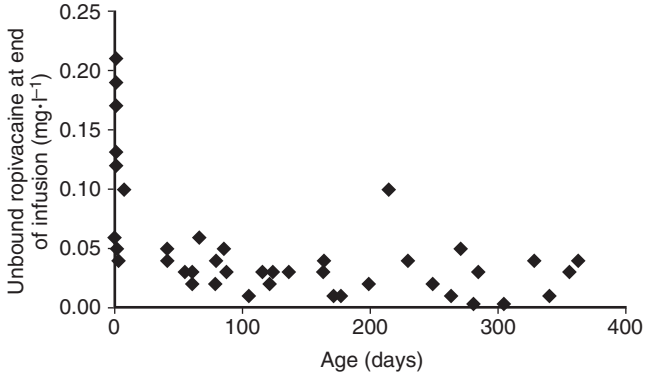

FIGURE 70-1 ■ Plasma Concentrations of Unbound Ropivacaine at the End of a 48- to 72-Hour Epidural Infusion of Ropivacaine. (From Bösenberg AT, Thomas J, Cronje L, Lopez T, Crean PM, Gustafsson U, et al. Pharmacokinetics and efficacy of ropivacaine for continuous epidural infusion in neonates and infants. Paediatr Anaesth 2005;15:739–49.)

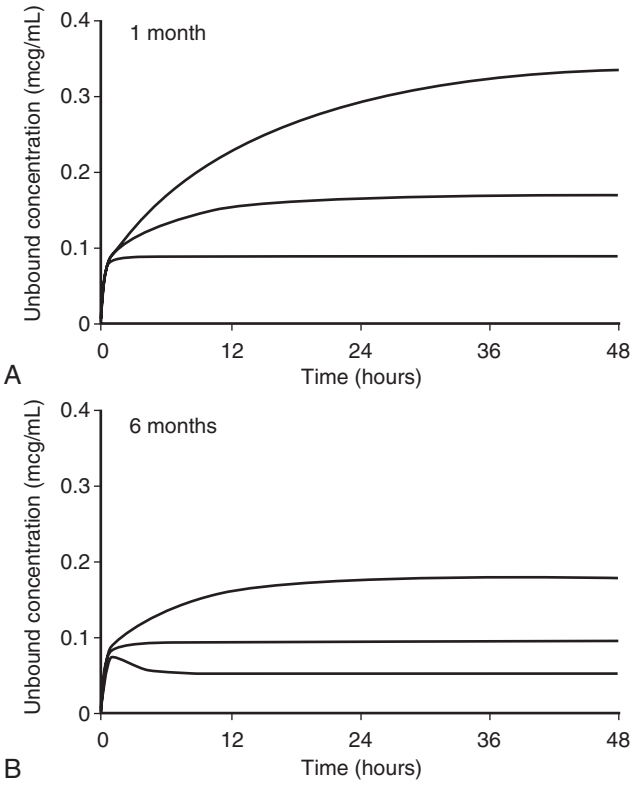

FIGURE 70-2 ■ Simulation of Unbound Bupivacaine Concentration during 48-Hour Infusion in Infants Aged 1 Month **(A)** and 6 Months **(B)**. (From Meunier JF, Goujard E, Dubousset AM, Samii K, Mazoit JX. Pharmacokinetics of bupivacaine after continuous epidural infusion in infants with and without biliary atresia. Anesthesiology 2001;95:87–95.)

nerve.[33,34] The use of ultrasound to perform PNB has permitted the practitioner to have a clear visualization of the nerve and surrounding structures and provides visual confirmation of the spreading of local anesthetic relative to the nerve.[34-36]

ULTRASOUND GUIDANCE

Ultrasound is becoming an important aspect of modern medicine. It is providing practitioners with a tool to directly visualize structures within the body and helps diagnose pathology or direct therapy. It is noninvasive and has minimal potential side effects. Compared with the other techniques in modern radiology, it is very portable. Ultrasound helps in localizing the neural structures and in guiding the needle to the intended target. It increases success rates, increases the speed of onset of the block, and lowers the volume of local anesthetic needed for PNB.[37] Ultrasound machines are cheaper and simpler to use than before, the user interface has been simplified, and many are preprogrammed to optimize visualization of nerves and vasculature.[38] Despite its ease of use, basic training is necessary to ensure safety and increase efficacy.[39] Higher frequency settings improve the image resolution (the ability to distinguish two adjacent objects). However, as the frequency increases, more of the ultrasound beam is absorbed by the medium, and the beam cannot penetrate deeper structures. For this reason, higher frequencies (e.g., 7.5 to 15 MHz) are used to provide good detail of superficial structures such as the interscalene brachial plexus and the femoral nerve, whereas lower frequencies (3 to 7.5 MHz) are useful in imaging deeper structures like the sciatic nerve and the infraclavicular brachial plexus.[40] In children, because of their smaller size, the higher frequency transducers can be used to image the sciatic nerve and the infraclavicular brachial plexus and will provide better resolution images.

ROLE OF REGIONAL ANESTHESIA TECHNIQUE BY ANATOMIC REGION

Abdominal Wall Blocks

Ilioinguinal/Iliohypogastric Nerve Block

The most common block that has been studied in pediatric regional anesthesia is the ilioinguinal/iliohypogastric (IL/IH) nerve block for inguinal hernia repair. The original technique described was the single or double pop technique in which the local anesthetic was placed in a plane between the internal oblique muscle and the transversus abdominis muscle medial to the anterior superior iliac spine. Despite some modifications, the landmark-based technique of needle placement has been associated with bowel injury and does have a high failure rate.[40-42] One study[43] used ultrasound to assess the placement of local anesthetic by the landmark-based technique. The authors found that the local anesthetic was placed in the correct plane between the internal oblique and transversus abdominis muscles only 14% of the time. Another finding in the same study was that 86% of the IL/IH blocks were rated as clinically adequate. The same group found that, by using ultrasound guidance, the exact location of the needle tip in relation to the IL/IH nerve in the correct fascial plane could be identified, and the volume required to produce a clinically significant block was considerably small (0.075 mL/kg of local anesthetic).[44,45] On the basis of these studies, it is our recommendation that ultrasound guidance be used to increase the efficacy and safety of the IL/IH block in the pediatric population.

Rectus Sheath Block

The rectus sheath block provides analgesia for umbilical surgeries and other midline abdominal procedures. Local anesthetic is placed around the terminal branches of the ninth, tenth, and eleventh intercostal nerves. One approach is to place the local anesthetic in a plane between the rectus abdominis muscle and the posterior rectus sheath.[46] Ultrasound guidance facilitates placement of the local anesthetic in this plane.[47,48] In a prospective randomized study comparing ultrasound-guided rectus sheath block with local anesthetic infiltration,[29] our group found a statistically significant decrease in the amount of opioid medication used in the rectus sheath block group. Two techniques, the out-of-plane technique and the in-plane technique for needle placement have

been described for this block. Anesthesiologists can choose from either of these techniques based on their comfort level with a particular approach. We would recommend ultrasound guidance for performing rectus sheath block, as the risk of injuring the epigastric vessels or entering the peritoneal cavity does exist with the blind approach.

Transversus Abdominis Plane (TAP) Block

The TAP bock provides analgesia for the anterior abdominal wall. The classic TAP block is performed by placing the local anesthetic in a plane between the internal oblique muscle and the transverse abdominis muscle in the lumbar triangle of Petit (a space bound by the iliac crest, latissimus dorsi muscle, and the external oblique muscle). Evidence regarding the efficacy of TAP block for providing analgesia after abdominal surgery has been variable: some trials have shown superior analgesia compared with a placebo TAP block, whereas others have failed to show additional analgesic efficacy.[49,50] In the pediatric population, one prospective randomized trial showed a decrease in opioid use in patients who received a TAP block compared with a placebo injection in patients undergoing open appendectomy.[51] Another prospective randomized trial in children found that the IL/IH block provides better analgesia compared with the TAP block for surgery in the inguinal region.[50] No pediatric study has compared the TAP block to epidural analgesia, which is a common technique used for postoperative analgesia for open abdominal procedures.

A recent study points to the need for performing a upper intercostal TAP block in addition to the classic TAP block to cover T7 to T12 dermatomes.[52] In this study, the classic TAP block was seen to provide a sensory block in the T10 to T12 dermatomes. A cadaver study of infiltration of aniline dye using ultrasound guidance as in a classic TAP block found good coverage of segmental nerves at the T10 to L1 level.[52a]

Lower Extremity Nerve Blocks

Orthopedic procedures are the most common procedures performed on the lower extremity. Regional anesthesia for lower extremity procedures sometimes requires the performance of more than one nerve block to achieve adequate analgesia depending on the location of the surgery. For knee surgery and procedures above the knee joint, a femoral nerve block is required. Additionally, a sciatic nerve block is required for procedures involving the posterior aspect of the thigh, whereas an obturator nerve block is recommended for procedures involving the medial thigh.[53] For procedures below the knee area, the sciatic nerve block covers most of the area, except the cutaneous area over the medial aspect of the shin, which requires a saphenous nerve block.

Femoral Nerve Block

A femoral nerve block is typically performed just caudad to the inguinal ligament. The femoral artery is located by palpation or with ultrasound guidance, and the femoral nerve is located lateral to the artery. The femoral nerve lies underneath two fascial layers, the superficial fascia lata and the deeper fascia iliaca. The nerve typically lies over the iliacus and psoas muscles, but anatomic variations have been documented where the nerve lies underneath muscular slips from the iliacus muscle.[54] As the nerve passes into the thigh, it divides into an anterior and a posterior division and quickly arborizes. Using the origin of the lateral circumflex femoral artery, a branch of the femoral artery, as a guide for placement of the femoral block may help in the performance of the femoral nerve block before it ramifies and may avoid risk of injury to this branch of the femoral artery.[55,56] Using ultrasound compared with nerve stimulation to place the femoral nerve block in pediatric patients has been shown to increase the mean duration of analgesia provided by the block (508 versus 335 minutes) and decrease the volume of local anesthetic (0.2 mL/kg versus 0.3 mL/kg) required for the block.[28] For procedures where prolonged analgesia (beyond 10 to 12 hours) may be beneficial (e.g., anterior cruciate ligament repair and tumor excisions), a catheter can be placed in the proximity of the femoral nerve to infuse local anesthetic continuously for 48 to 72 hours postoperatively.[31] Our group reported the role of patient and family education and continued follow-up in successful implementation of a continuous PNB program in the pediatric population.[4]

Lumbar Plexus Block

A few pediatric studies have reported that the lumbar plexus block provides excellent postoperative analgesia after hip and femoral shaft surgeries.[57] The duration of analgesia provided by the lumbar plexus block was greater than that of a caudal block.[57] The use of ultrasound guidance to aid in placement of this nerve block has been described in children. An observational study[58] evaluated the landmarks for placing lumbar plexus block in pediatric patients. In this study, the authors found that the point at three quarters of the distance from the midline of a line connecting the L4 vertebrae to a paramedian line through the posterior superior iliac spine to be feasible for placing a lumbar plexus block.[58] With the use of ultrasound guidance, the lumbar plexus appears as an ovoid structure consisting of hypoechoic dots (fascicles) within the posterior part of the psoas major muscle.[37] Complications related to the lumbar plexus block include renal hematomas, epidural placement, intrathecal placement, and injury to intra-abdominal structures. These should be considered in the risk–benefit analysis when the lumbar plexus block is selected.

Saphenous Nerve Block

Saphenous nerve block is useful as a supplement to the sciatic nerve block for foot and ankle surgery. In a study comparing saphenous nerve blocks performed using a perifemoral approach, transsartorial approach, block at the medial femoral condyle, and below-the-knee field block, the perifemoral and trans-sartorial approaches were seen to be superior.[59] In the trans-sartorial method the sartorius muscle is identified, and the saphenous

nerve is located underneath it.[59] The femoral artery runs with the saphenous nerve in the proximal thigh and should be avoided. We prefer to perform the block at a more distal location to avoid the femoral artery.

Sciatic Nerve Block

The sciatic nerve block is used for procedures involving the posterior aspect of the lower extremity and for most procedures below the knee in children.[28,32] Recent reports in adult and pediatric patients have shown the feasibility of ultrasound guidance for this technique.[60-62] One prospective study in pediatric patients showed that the use of ultrasound guidance increased the duration of postoperative analgesia by 30%.[28] In addition, the amount of local anesthetic needed in the ultrasound group was decreased. Another study has shown that ultrasound guidance decreases the time to completion of the nerve block and is associated with fewer needle passes for block completion.[63] The sciatic nerve block can be performed at gluteal, subgluteal, midthigh, or popliteal regions on the basis of the area involved in the surgery. Sciatic nerve block has been associated with a higher incidence of motor block.[64] For this reason, a lower concentration of local anesthetic is preferred if a motor block is undesirable. Popliteal sciatic nerve blocks placed under ultrasound and nerve stimulation guidance with the use of a current of less than 0.5 mA (2 Hz, 0.1 msec) to place the nerve block resulted in intraneural injection in 16 of the 17 patients studied.[65] Postoperative follow-up with the use of electrophysiologic testing revealed no injury to the sciatic nerve secondary to the intraneural injection. These data, although limited because of a small sample size, highlight the risk of intraneural and subepineural injection; a possible increased risk of injury exists when low-current intensity (less than 0.5 mA) is used in the placement of a sciatic nerve block with the popliteal approach.

Upper Extremity Nerve Blocks

PNBs along the brachial plexus are used to provide postoperative analgesia for upper extremity procedures. Commonly used techniques in children are the interscalene, infraclavicular, and axillary blocks, depending on the location of the surgery.

Interscalene Brachial Plexus Block

A case series of severe neurologic complications after interscalene blocks performed under general anesthesia[66] led to recommendations against performing this block in patients under general anesthesia.[67] As almost all regional anesthesia in pediatric patients is performed under deep sedation or general anesthesia, this created a safety concern regarding performance of this block in children. Ultrasound guidance has been seen in recent reports to be superior to nerve stimulation in performance of the interscalene block and provides a means of visualizing the spread of the local anesthetic.[35,36] The use of ultrasound guidance may allow us to safely perform this block in a pediatric population.

Supraclavicular Nerve Block

The ultrasound-guided supraclavicular nerve block has been described in pediatric patients for upper extremity surgery.[68] In the supraclavicular region, the brachial plexus is identified medial to the clavicle, posterolateral to the subclavian artery, and superficial to the first rib.[69] In a prospective study in pediatric patients, infraclavicular nerve block and supraclavicular nerve blocks had similar efficacy and duration of block.[68]

Infraclavicular Nerve Block

The infraclavicular nerve block has been described in the pediatric population for elbow surgery. An advantage of this block is that all the branches of the brachial plexus are still together. The use of ultrasound guidance was seen to help in successful placement of this block in pediatric patients.[70,71] The use of ultrasound guidance for this block has been shown to have a better success rate compared with the nerve stimulation technique.[72] Continuous perineural infusion with the use of the infraclavicular approach was seen to provide superior postoperative analgesia compared with a supraclavicular approach for distal upper extremity surgery.[73]

Axillary Nerve Block

The axillary nerve block has been described for distal arm and hand procedures. Studies have found the ultrasound-guided axillary nerve block to have a similar or improved success rate compared with nerve stimulation–guided axillary nerve block.[74,75] One study of the ultrasound-guided axillary nerve block found that the ability to detect needle-to-nerve contact was 74.5% with the nerve stimulation technique and 38.2% with the use of a paresthesia technique.[76] The authors concluded that the low sensitivity of either technique might increase the number of attempts needed to successfully place an axillary nerve block.

AREAS OF UNCERTAINTY

The techniques used to place PNBs in pediatric patients have evolved from a landmark-based technique to a nerve-stimulation based technique to an ultrasound-guided technique. The advantages of the ultrasound-guided technique include visual confirmation of the needle position in the proximity of the nerve and visualization of the spreading of the local anesthetic around the nerve.[33] One of the risks of the nerve stimulation–guided technique is the risk of subepineural or intraneural injection of the local anesthetic with currents (0.3 to 0.5 mA, 2 Hz, 0.1 msec) that are currently used for placement of PNBs. This has been documented with the popliteal sciatic block.[65] Ultrasound guidance has the potential to detect an increase in the size of the nerve, which indicates a subepineural injection. However, the current resolution of most ultrasound equipment used in operating rooms does not allow for differentiation between an extrafascicular subepineural injection

(less potential for nerve injury) and a intrafascicular subepineural injection (increased potential for nerve injury).

GUIDELINES

There are currently no practice guidelines by a national or international society on the use of specific regional anesthesia techniques in specific procedures for pediatric patients. The American Society of Regional Anesthesia and Pain Medicine (ASRA) Practice Advisory on Neurologic Complications in Regional Anesthesia and Pain Medicine includes a section on regional anesthesia in pediatric patients. The authors state "A child may be unable to communicate symptoms of potential peripheral nerve injury. Any uncontrolled movements may increase the risks of an injury. Therefore the placement of peripheral nerve blocks in children undergoing general anesthesia may be appropriate after duly considering individual risk to benefit ratio." The authors did caution against performing interscalene nerve blocks in patients under general anesthesia, as the risks of a severe neurologic injury with these procedures does exist. In January 2012, a themed issue of the journal *Paediatric Anaesthesia* was published, which provided review articles on various pediatric regional anesthesia–related topics.[77]

TABLE 70-1 **Recommended Regional Anesthesia Technique by Area of Surgery**

Area/Type of Surgery	First Choice
Upper extremity: shoulder, upper arm	Interscalene block
Upper extremity: elbow, forearm, hand	Infraclavicular block/ supraclavicular block
Thoracic surgery: neonates, infants	Caudally placed thoracic epidural
Thoracic surgery: older children	Thoracic epidural
Major abdominal surgery	Low thoracic or high lumbar (depending on surgical field)
Umbilical hernia repair	Rectus sheath block
Inguinal hernia repair	Ilioinguinal nerve block
Penile surgery (circumcision)	Penile block
Hypospadias repair	Caudal block
Hip surgery	Lumbar epidural, lumbar plexus block
Above knee and knee procedure (anterior thigh)	Femoral block
Bilateral leg procedures	Lumbar epidural block.
Above-knee (posterior) procedures	Sciatic nerve block (gluteal/ subgluteal approach)
Below-knee procedures	Sciatic nerve block (popliteal approach)

AUTHORS' RECOMMENDATIONS

The role of regional anesthesia in pediatrics has expanded from a few centers performing a limited number of techniques to a wider application of a larger variety of techniques. The advent of ultrasound guidance has provided an additional means of improving the success of regional techniques and may improve the safety of these techniques in the pediatric population. We recommend the use of ultrasound guidance for all peripheral nerve blocks in pediatric patients. In Table 70-1, we have compiled a list of recommended regional anesthesia techniques by area of surgery.

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CHAPTER 71

Optimal Postoperative Analgesia

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INTRODUCTION

Postoperative pain management in the United States was fairly standardized before the 1980s. Mild-to-moderate pain was treated with acetaminophen or a nonsteroidal antiinflammatory drug (NSAID), and moderate-to-severe pain was treated with intermittent, intramuscular opioids, as needed. In the 1980s, the options for managing postoperative pain expanded. When endogenous opioids and their receptors were identified in the late 1970s, the value of neuraxially administered opioids was realized, and epidural analgesia became popular. During the 1980s, infusion pump technology improved dramatically and intravenous patient-controlled analgesia (PCA) became a viable option for the treatment of acute pain. More recently, interest in regional anesthesia for the management of postoperative pain has increased, especially with the use of ultrasound guidance for the performance of these procedures.[1]

Ready and colleagues[2] introduced the concept of a formalized acute pain service to provide coordinated, interdisciplinary acute pain care. This prompted widespread use of integrated, interdisciplinary teams to provide inpatient acute pain services, as well as increased efforts to improve the process of patient care, thus improving pain-related patient outcomes.[3] The importance of multimodal analgesia was recognized, and as a result, there was increased interest in the impact of nonopioid analgesics on acute pain control. This opened the door to further investigations into the use of nonopioid analgesics, including NSAIDs, acetaminophen, and gabapentin, in the perioperative period.[4] The goal of therapy was not necessarily to replace opioids with these medications but rather to improve acute pain control, lower the incidence and severity of treatment-related adverse effects, and perhaps lower the incidence and severity of chronic pain after selected surgical procedures.

When the era of evidence-based medicine dawned at the end of the twentieth century, most existing trials of postoperative pain management compared newer approaches (e.g., epidural analgesia, PCA, and adjunctive use of NSAIDs) with conventional analgesia, often defined as systemic opioids. Therefore early attempts at formulating an evidence-based approach to postoperative pain management focused on assessing whether these new approaches offered superior analgesia or a better effect on surgical outcome compared with conventional analgesia. As a result, first attempts at providing evidence-based recommendations focused on assessing the outcomes associated with the use of a single approach to postoperative pain management.[5]

There are many factors, some of which are not obvious, that can affect the results observed in clinical trials. The decisions made by health care providers throughout the surgical period can affect outcomes in a number of ways, from patient selection for the surgical procedure, to the performance of anesthesia and surgery, to the care provided in the immediate postoperative period. Therefore variability exists within and outside the context of pain care, and this variability can have an impact on the outcomes of pain-related clinical trials. This variability may also make it difficult to document the outcomes related only to the pain therapy of interest.

Many experts advocate the use of perioperative rehabilitation, often defined as the use of an integrated, interdisciplinary process of care for patients undergoing the same kind of surgical procedure.[6] With perioperative rehabilitation, a team approach is advocated. Pain management is integrated into this care and is often multimodal, no longer relying only on a single pain therapy technique. Therefore the manner in which pain therapy is applied may well be another treatment variable to consider when the outcomes associated with pain therapy are evaluated.

OPTIONS

It is hard to imagine that 20 years ago patients undergoing major surgery would stay in the hospital for up to 2 weeks (sometimes longer); would stay immobile in bed, unable to move because of severe pain; and would not be given water or food until the bowel function was regained. Not surprisingly, the incidence of thrombosis, embolus, infarction, and infection was much higher than seen today. Improvements in pain care have contributed to the recent improvement in surgical outcomes.

Postoperative care has evolved from passively waiting for recovery to actively encouraging a return to normal function. Although pain control is critical to rapid recovery, the clinician must balance the risk of harm associated with pain therapy with the potential for benefit. Although uncontrolled pain can, indeed, delay a return to normal function by making patients afraid to move, breathe deeply, or cough, systemic opioids may delay recovery by causing adverse gastrointestinal effects, increased sedation, and (rarely) compromise of ventilation.

An important role of postoperative pain management is to maximize pain relief while minimizing adverse side effects. Treatment options should be evaluated not only according to their ability to provide satisfactory pain control but also by their ability to promote recovery and

rehabilitation. The choice of postoperative analgesia should be procedure-specific because analgesic efficacy is contingent on the specific type of surgery.[7] In this chapter, we consider the evidence supporting the use of epidural analgesia, intravenous PCA, NSAIDs, and continuous peripheral nerve blocks (CPNBs).

EVIDENCE

Epidural Analgesia

Epidural analgesia can be accomplished by infusing a variety of medications (typically a combination of low-dose local anesthetics and opioids) into the epidural space. Epidural *analgesia* must be distinguished from epidural *anesthesia*, which implies dense epidural local anesthetic blockade that can be used as the primary anesthetic for surgery. Conceptually, the provision of epidural analgesia is an attractive means of minimizing the opioid requirement while providing excellent analgesia (especially with movement), thereby promoting recovery after surgery. Epidural opioid doses are much smaller than those required systemically (in the order of one tenth), and low-dose epidural local anesthetics, apart from producing analgesia without overt sensory/motor blockade or opioid-associated adverse effects, can have additional beneficial effects on bowel mobility. Does the evidence support the superior analgesic efficacy of epidural analgesia and its ability to promote recovery after surgery?

It is important to note that patient outcomes may vary based on how and when epidural analgesia is administered. When used during surgery, the benefit of epidural anesthesia likely relates to the impact on outcomes of profound neural blockade (e.g., lower incidence of thromboembolic events, lower incidence of graft failure in the case of major vascular surgery, less blood loss, lowering of the metabolic stress response, and a lower incidence of chronic pain). The timing of the administration of epidural analgesia relative to surgery (i.e., starting analgesia before, during, or after completion of surgery) may also affect patient outcomes, but the impact of timing on outcomes has not been clearly documented. This chapter concentrates on the benefits likely to pertain specifically to postoperative epidural analgesia.

Many of the early trials of epidural analgesia (during the 1970s and early 1980s) were small randomized studies that attempted to confirm the clinically apparent superior analgesia of postoperative epidurals compared with systemic opioid analgesia, and some of these studies assessed the impact of epidural analgesia on postoperative recovery. These early trials (and meta-analyses) overwhelmingly supported the superior analgesic efficacy of epidural analgesia compared with systemic opioid administration.[8] Assessment of postoperative recovery focused on a variety of outcome measures including pulmonary function, bowel function, and patient mobility.[9-11]

A goal of epidural analgesia is to restore normal physiologic function as rapidly as possible so that adverse outcomes presumed to be associated with prolonged immobilization and hospital stay can be avoided. As evidenced by small randomized controlled trials (RCTs) and subsequent meta-analysis (and, in some cases, confirmed by the large RCTs), epidural analgesia fulfills this goal extremely well. Epidural analgesia has been shown to promote early mobilization and reduce rehabilitation time, particularly after joint surgery.[12-14] In addition, it has been shown to reduce pulmonary morbidity,[10,15-18] reduce time to extubation after major thoracic and vascular procedures,[15-17,19-22] reduce cardiac ischemia and dysrhythmia in high-risk patients,[19,23] and reduce postoperative ileus,[24] thereby reducing length of the hospital stay.[25-28] The overall benefit of epidural analgesia on patients undergoing cardiac surgery remains controversial. A meta-analysis by Beattie and colleagues[23] found a reduction in the incidence of myocardial infarction (MI) associated with the use of postoperative epidural anesthesia (odds ratio [OR], 0.56; confidence interval [CI], 0.30 to 1.03). However, another recent meta-analysis by Svircevic and colleagues[28a] demonstrated a statistically significant reduction in supraventricular arrhythmias and respiratory complications but failed to show any benefit in MI, stroke, or mortality.

Several clinical trials have been conducted to evaluate the impact of epidural analgesia on mortality rate and major morbidity (including major cardiac morbidity, pulmonary embolus, and stroke). Early results suggested that combined epidural and general anesthesia followed by postoperative epidural analgesia had a favorable effect on major morbidity and possibly also on mortality rate.[29,30] The findings of Yeager and colleagues[30] were particularly striking because they showed remarkable decreases in surgical morbidity and mortality rates attributed to epidural analgesia in high-risk patients undergoing major surgical procedures. Interestingly, this study was stopped after the completion of 53 patients by the monitoring committee because the committee believed that the observed outcomes favored the epidural treatment so strongly that it would be unethical to continue the trial. This study certainly contributed to the belief among many pain physicians that epidural analgesia improves surgical outcomes, particularly in sick patients.

It is important to note, however, that the validity of the results of the Yeager study has been called into question.[31] Indeed, two large RCTs have now been published that failed to confirm the positive outcomes associated with the use of epidural analgesia reported earlier by Yeager.[15,16] Both studies provided strong evidence regarding the efficacy of epidural analgesia. However, although both studies were designed and appear to have been powered adequately to confirm the results reported by Yeager, neither study demonstrated a reduction in major morbidity and mortality rates in high-risk patients after the use of epidural analgesia.

Epidural analgesia may play an important role after abdominal surgery. In this setting, epidural analgesia has been reported to lower the incidence of MI, stroke, and death in patients undergoing abdominal aortic surgery.[15] A meta-analysis evaluated the impact of epidural analgesia versus systemic opioids after abdominal aortic surgery.[32] This analysis included 13 studies involving 1224 patients. The epidural analgesia group showed significantly improved pain control on movement up to the third postoperative day. In addition, the postoperative

duration of tracheal intubation and mechanical ventilation was significantly shorter by about 20%. The overall incidence of cardiovascular complications, MI, acute respiratory failure, gastrointestinal complications, and renal insufficiency were all significantly lower in the epidural analgesia group, especially in trials that used thoracic epidural analgesia. The incidence of mortality, however, was not reduced.

Another study provided indirect evidence that epidural analgesia may lower mortality rates after major surgery.[33] This study examined a cohort of 3501 patients who underwent lung resection. These patients represented a 5% random sample of patients who underwent lung resection procedures between 1997 and 2001 and who were listed in the Medicare claims database. Multivariate regression analysis showed that the presence of epidural analgesia was associated with a significantly lower odds of death at 7 days (OR, 0.39; 95% CI, 0.19 to 0.80; $p = 0.001$) and 30 days (OR, 0.53; 95% CI, 0.35 to 0.78; $p = 0.002$). Interestingly, this study reported no difference in major morbidity rates.

It is easy to forget that the evolution of epidural analgesia has occurred alongside the evolution of postoperative management in general and that differences in serious morbidity and mortality rates that might be expected to emanate from the benefits outlined earlier may not be obvious because of improvements in postoperative care in general. A policy of early oral fluid administration, early nasogastric tube removal, and forced early mobilization, in combination with optimized pain management, has resulted in earlier hospital discharge and a decrease in the postoperative mortality rate when compared with that 20 years ago. It may be impossible to show the benefit of postoperative epidural analgesia in isolation; instead, studies of this mode of analgesia used with regard to its specific effects on certain outcomes (e.g., postoperative ileus); with attention to appropriate level of catheter placement, drug choice, and drug dose to achieve the desired outcome; and its combination with other aspects of postoperative care are needed before we can discount the value of epidural analgesia in terms of major morbidity and mortality rates.[34] At the same time, major morbidity and mortality rates have become so low that very large numbers of patients will have to be enrolled to be able to detect a difference in morbidity between study groups.[16]

In summary, the superior analgesic efficacy of epidural analgesia compared with conventional analgesia seems very clear, and benefits in terms of morbidity and length of hospital stay (by contributing to an accelerated return to normal physiologic function) have been demonstrated. Although epidural analgesia appears to have a positive impact on the incidence of a number of major complications related to surgery, it remains unclear whether epidural analgesia has a role in reducing perioperative mortality.

Patient-Controlled Analgesia

The use of sophisticated infusion pumps to enable patients to self-deliver doses of analgesic medications (PCA) was popularized in the 1980s when microprocessors became small enough to be incorporated into portable pumps. A majority of patients and nurses prefer PCA to nurse-administered "as needed" opioid administration: patients prefer it because of the greater control they achieve over their analgesic dosing, and nurses prefer it because of the convenience of this mode of analgesia. PCA is now available in most hospitals in the United States,[35] and it has become an important tool to aid hospitals' compliance with mandated pain assessment and treatment standards. PCA is most often used for the systemic delivery of opioids (intravenous PCA), but this method of drug delivery has also been used to deliver opioids, local anesthetics, and other drugs (often in combination) via other routes, such as via an epidural catheter or a regional nerve block catheter.

Intravenous PCA differs from conventional analgesia in two important ways: (1) provided the technique is used appropriately, peaks and troughs in serum analgesic level are less extreme, and analgesic administration is better matched to analgesic need; and (2) patients report a greater sense of control over their pain care. The questions to be asked are, do these factors result in improved pain control, lower opioid requirements, superior patient satisfaction with treatment, fewer side effects, and better surgical outcome? Intravenous PCA is compared here with conventional analgesia; the use of patient-controlled epidural analgesia (PCEA) in the management of postoperative pain is also increasing in popularity,[36] but this use will not be addressed.

Three meta-analyses of PCA versus conventional analgesia have been published, one in 1993,[37] the second in 2001,[38] and the third in 2006.[39] Apart from updating the first analysis, the second incorporated trials in which control group opioids were given by the subcutaneous and intravenous as well as the intramuscular route. Fifteen trials (787 patients) were included in the first analysis, 32 (2072 patients) in the second, and 55 (3861 patients) in the third. All but one trial (which used meperidine) in the first analysis used morphine in both experimental and control group patients (699 patients). In the second and third analyses, morphine was used in the majority of studies, but other opioids were also used, including hydromorphone, meperidine, piritramide, nalbuphine, and tramadol.

The first meta-analysis demonstrated that patients prefer PCA to conventional analgesia and that PCA had slightly better analgesic efficacy. The mean difference in satisfaction was 42% ($p = 0.02$), whereas the mean difference in pain score on a scale of 0 to 100 was 5.6 ($p = 0.006$). However, there was no difference in opioid use, side effects, or length of hospital stay.

Despite the passing of almost 10 years and the addition of 12 trials (1000 patients) to the first meta-analysis, the results of the second analysis differ very little from those of the first. Patients' preference for PCA was confirmed, as was slightly better analgesic efficacy. In three morphine trials and one meperidine trial, PCA was preferred (relative risk [RR], 1.41; CI, 1.1 to 1.80). Combined data on pain intensity and relief from one piritramide, one nalbuphine, and eight morphine trials also demonstrated a preference for PCA (RR, 1.22; CI, 1.00 to 1.50). There was no difference in opioid use or side effects and no convincing evidence of a difference in surgical outcome,

although the limited data (152 patients) available on pulmonary function did suggest an improvement.

The third meta-analysis included yet more studies (55) and patients (2023 receiving PCA and 1838 receiving conventional analgesia).[39] Even with an increase in the number of trials and patients, the results were again similar, in that PCA was demonstrated to provide better pain control and patient satisfaction than conventional analgesia. However, patients using PCA consumed higher amounts of opioids than the control subjects and had a higher incidence of pruritus but had a similar incidence of other adverse effects. There was no difference in the length of hospital stay.

Another meta-analysis evaluated PCA compared with conventional analgesia after cardiac surgery.[40] This study used patient-reported pain intensity as the primary outcome and cumulative opioid use, intensive care unit and hospital length of stay, postoperative nausea and vomiting, sedation, respiratory depression, and all-cause mortality rate as secondary outcome measures. The authors identified 10 RCTs involving 666 patients. Compared with conventional analgesia, PCA significantly reduced the visual analog scale at 48 hours but not at 24 hours after surgery. PCA increased cumulative 24- and 48-hour opioid consumption. Ventilation times, length of intensive care unit stay, length of hospital stay, patient satisfaction scores, sedation scores, and incidence of postoperative nausea and vomiting, respiratory depression, and death were not significantly different.

Do these meta-analyses represent the best evidence about the utility of intravenous PCA compared with conventional analgesia? Certainly, the meta-analyses help by providing a quantitative summary of existing data. However, because many of the trials contributing to these meta-analyses were small, treatment effects may have been distorted because of deficiencies inherent in small trials, including type I error, distortions that can possibly be compounded in meta-analyses.[41-45] Another problem encountered here (and, indeed, in many epidural trials) is that neither patients nor assessors were blinded to treatment; thus there is a high likelihood of assessor bias, which might be expected to exaggerate treatment effects.[38,46] One should also be concerned with the degree of differences observed in the analysis. Some meta-analyses have demonstrated a small improvement in analgesic efficacy and possibly pulmonary function with PCA use. However, the clinical significance of these findings needs to be questioned not only because of the small effect size but also because of the weakness in the design of the contributing studies as a result of blinding.

It is also worth noting that in real life there are wide variations in factors such as patient education and nursing workload that have a profound effect on the doses of analgesic actually received and thus on the efficacy of either method.[47] In addition, there may be significant differences in outcomes in patients participating in clinical trials evaluating pain outcomes when compared with patients receiving routine postoperative care outside the context of an analgesic trial. Thus the efficacy of PCA compared with conventional analgesia is likely to differ among trials and real life, individual patients, and institutions.

Patients' preference for PCA seems to be an important reason that PCA has been established as the standard of care for routine management of moderate-to-severe postoperative pain. In view of the lack of evidence of any other real advantage to PCA, other than a slight improvement in analgesic efficacy, it seems that the reason that patients prefer PCA is that it provides them with a sense of autonomy and control over their own analgesic management.[48,49] In today's health care climate, patient preference is an important and valid reason for a treatment choice.

Given the lack of evidence of other benefits, one has to ask whether the cost of PCA is justified. Preliminary cost–benefit analyses suggest that postoperative analgesia with PCA is more expensive than conventional analgesia,[50-52] despite the hope that nursing involvement would be reduced and reduced nursing costs would offset the increase in equipment costs. However, the results of cost-effectiveness studies are often based on cost data specific to one institution at a specific time; therefore they may not be valid at other institutions or at different times.

Nonsteroidal Antiinflammatory Drugs

NSAIDs have been demonstrated to be effective analgesics for the treatment of pain after surgery. This has been proven in single-dose studies in mild-to-moderate pain,[53] as well as in multiple-dose studies in moderate-to-severe pain.[54] NSAIDs have clearly been demonstrated to have an opioid-sparing effect.[55,56]

When the use of NSAIDs are considered in the postoperative period, several issues are key. First, does the addition of an NSAID improve pain control, lower the incidence of opioid-induced adverse side effects, or both? Second, does the addition of an NSAID present new risk of harm to the patient? Third, are there any benefits to the use of cyclooxygenase-2 (COX-2) selective agent in this setting?

After major surgery, NSAIDs alone cannot provide effective pain relief. Therefore they are added to other pain therapy, such as systemic opioids. When given in combination with other opioids after surgery, NSAIDs result in better pain relief and lower opioid consumption.[57,58] A 2005 meta-analysis evaluated the administration of NSAIDs on morphine PCA.[59] This analysis included 33 trials with 1644 patients. In the trials evaluating multiple-dose regimens of NSAIDs, the average reduction in 24-hour morphine consumption was 19.7 mg, which was equal to a 40% opioid-sparing effect. In addition, the use of an NSAID lowered pain intensity from approximately 3 to 2 on the 10-cm visual analog scale when compared with morphine PCA alone.

The addition of an NSAID with the resultant reduction in opioid consumption may not lower the overall incidence of adverse events.[55] It seems clear that the incidence and degree of respiratory depression is reduced,[58,60,61] but improvements in pulmonary function (less opioid-induced hypercapnic responses) have not been convincingly demonstrated.[57] The adjunctive use of NSAIDs reduces the incidence of nausea in several studies, although an equal number of studies do not show any benefit.[57] The literature is equivocal about whether opioid sparing by

NSAIDs promotes rapid recovery. A limited number of studies demonstrate accelerated recovery in association with less nausea and sedation, improved mobility, and earlier return of bowel function,[62,63] but others fail to show any benefit in terms of recovery.[58,64,65]

A meta-analysis evaluated the effect of NSAID administration on PCA morphine side effects.[66] This study included 22 randomized, double-blind clinical trials published between 1991 and 2003, with 1316 patients receiving NSAIDs and 991 patients receiving PCA morphine only. This study demonstrated that NSAIDs significantly decreased the incidence of postoperative nausea and vomiting by 30%, and the incidence of sedation by 29%. Pruritus, urinary retention, and respiratory depression were not significantly decreased by NSAIDs.

NSAID use may be associated with a number of potential adverse events, including inhibition of platelet function, alteration in renal function, peptic ulceration, and alterations in bone healing.[67-71] However, it appears that short-term use of NSAIDs around the time of surgery may not be associated with a compromise of bone healing.[72] The risk of NSAID-induced adverse events is higher with higher doses and longer durations of therapy. In addition, the risk of harm is higher in the elderly.

A meta-analysis evaluated the effects of NSAIDs on postoperative renal function in adults with normal renal function.[73] This analysis included 23 trials with 1459 patients. Perioperative administration of NSAIDs reduced creatinine clearance by 16 mL/min (95% CI, 5 to 28) and potassium output by 38 mmol/day (95% CI, 19 to 56) on the first day after surgery compared with placebo. However, no significant difference was seen in serum creatinine level on the first day (0 mmol/L; 95% CI, −3 to 4). No significant reduction in urine volume during the early postoperative period was found, and no cases of postoperative renal failure required dialysis. Other studies have demonstrated that the risk of adverse renal effects is increased in patients with pre-existing compromise of renal function, hypovolemia, hypotension, or the concomitant use of other nephrotoxic drugs.[74]

Concern has developed over the last several years about the cardiovascular consequences of NSAID administration.[75] This concern was triggered by evidence that the COX-2 inhibitors may lack the thrombotic-protective and cardioprotective effects of aspirin and other standard NSAIDs but now extends to the demonstrated deleterious effects of NSAIDs in general on cardiac function and blood pressure, especially in susceptible patients. A meta-analysis that included 55 trials with 99,087 patients evaluated the impact of COX-2 selective agents on the risk of MI.[76] The overall pooled OR for MI risk for any coxib compared with placebo was 1.46 (95% CI, 1.02 to 2.09). This study concluded that celecoxib, rofecoxib, etoricoxib, valdecoxib, and lumiracoxib were all associated with higher MI risk compared with placebo. The pooled OR for any coxib compared with other NSAIDs was 1.45 (95% CI, 1.09 to 1.93). Another meta-analysis reported that all NSAIDs increase the risk of MI and cerebrovascular accidents, and COX-2 selective agents confer the highest risk.[77]

In summary, perioperative NSAID administration is associated with significant opioid-sparing effects and a resultant reduction in several opioid-induced side effects. Other than the differences in the effect on platelet function, there appears to be little advantage to the use of COX-2 selective agents, and the use of these agents may be associated with an increased risk of cardiovascular adverse events.

Continuous Peripheral Nerve Block

Interest in CPNBs in the perioperative setting has increased within the past few decades. Similar to epidural analgesia, peripheral nerve block catheters are an attractive means of minimizing opioid requirements while providing excellent analgesia, thereby promoting increased mobility and rapid recovery after surgery. First described in 1946, the peripheral nerve catheter has evolved from a needle inserted through a cork attached to a patient's chest to percutaneous insertion of a catheter directly adjacent to a peripheral nerve.[78] The peripheral nerve catheter serves to continuously provide analgesia (typically local anesthetics) to the affected region postoperatively. Single-injection peripheral nerve blocks are also useful in the postoperative setting, but they are limited in their duration, usually lasting less than 24 hours.[79] As with PCA administration, a discussion of CPNBs must involve the following questions: do these regional interventions result in better analgesia, lower opioid requirements, increased patient satisfaction, fewer side effects, and better surgical outcome?

Previous RCTs have shown that the addition of a CPNB greatly decreases postoperative pain, as well as opioid requirements. Unfortunately, these studies have included a relatively small sample size and have failed to show statistical significance in the reduction of pain in all time periods.[80]

A meta-analysis[80] evaluating the efficacy of CPNBs in the reduction of postoperative pain, undesired side effects (including nausea, vomiting, sedation, and motor/sensory blockade), opioid use and patient satisfaction reviewed 19 RCTs involving 603 patients. CPNB provided superior postoperative pain control when compared with systemic opioids ($p < 0.001$), as well as a lower incidence of side effects (i.e., nausea, vomiting, and sedation). Total opioid consumption was also significantly less ($p < 0.001$) with the peripheral catheter (20.8 mg morphine; 95% CI, 18.5 to 23.1; $n = 165$ patients) compared with opioid analgesia (54.1 mg morphine; 95% CI, 50.8 to 57.4; $n = 174$ patients). This meta-analysis demonstrated that, compared with opioid analgesia, CPNB provides superior postoperative analgesia, decreased opioid requirement, and decreased side effects such as nausea and vomiting. Further investigation is needed to determine the role of CPNBs in the postoperative setting, including questions regarding optimal catheter placement, technique, and equipment used in placement (i.e., stimulating-catheter versus ultrasound), as well as the different types of infusions and their relationship to toxicity and adverse effects.

AREAS OF UNCERTAINTY

The focus of postoperative pain trials has been on assessing new modes of analgesia with particular regard to both their analgesic efficacy and their ability to improve surgical outcomes. In this chapter, trials assessing epidural analgesia, PCA, CPNBs, and NSAIDs used as adjuncts were reviewed. The studies leave no doubt that these modes of analgesia are effective, and in the case of epidurals and adjunctive NSAIDs, pain relief is better than that achieved by systemic opioids alone.

The opioid-sparing effects of epidural analgesia and adjunctive NSAIDs are confirmed. The incidence of some opioid-induced adverse side effects is also lower. It is not clear, however, whether opioid sparing per se actually improves recovery, and the evidence from the literature regarding this outcome is equivocal.

Epidural analgesia offers a number of distinct benefits and appears to hasten recovery (largely because of its favorable effects on the bowel). However, although improvements in morbidity have been demonstrated in select patient populations, analysis of current trials suggests that epidural analgesia offers no clear benefit in terms of decreased major morbidity and mortality associated with surgery.

Despite the apparent certainty of these stated findings, many questions remain unanswered. It is unknown whether the marked improvements in surgical morbidity and mortality rates that have occurred over the last few decades are due to improvements in postoperative care in general or to improved postoperative pain control provided by some pain therapy modalities. Trials have tended to segregate treatments and have not assessed pain treatments as part of a multimodal approach or in terms of their integration into accelerated recovery programs. Issues such as choice of drug, dosage, and site of administration, and their relationship to specific benefits, have largely been ignored, particularly in epidural and PCA trials, and as a result it is difficult to use evidence to select the "best" method of providing specific pain therapy modalities. It is hoped that future studies will examine the role of analgesia in rehabilitation after surgery. Uncertainty about the benefits of various types of pain therapy will remain until the importance of pain control is understood in the context of the overall goal of restoring normal physiologic function as rapidly as possible.

GUIDELINES

Guidelines on acute and postoperative pain management abound. One of the first comprehensive evidence-based guidelines was published by the Agency for Health Care Policy and Research (AHCPR) in 1992, but this guideline is now clearly out of date. Anesthesia and pain societies around the world have published their own guidelines on acute pain management.[3,25,81-84] The American Society of Anesthesiologist (ASA) recently updated practice guidelines for the treatment of acute pain. These guidelines, which are unchanged from those previously published in 2004, provide new evidence-based support for the management of acute pain during the perioperative period.

Key features of the ASA guidelines include:

- Continued education and training of health care personnel in the management of acute pain
- Around-the-clock availability of an anesthesiologist in the perioperative setting
- Performance of a thorough history and physical examination, including pain assessment and evaluation
- Preparation and education of patients on postoperative care planning for PCA, PCEA, or epidurals
- Acknowledgment and consideration of different treatment options in specific subpopulations (e.g., geriatric, pediatric, critically ill patients)
- Use of a dedicated acute pain service
- Development of a multimodal approach, including around-the-clock NSAIDs, coxibs, or acetaminophen unless contraindicated, to help manage pain[81]

One of the best clinical practice guidelines available to guide management of acute pain has been prepared by the Australian and New Zealand College of Anaesthesia and Faculty of Pain Medicine.[85] These guidelines are evidence based and provide clear, detailed information regarding acute pain treatment options. Similar to the ASA guidelines, they stress the importance of patient education and the use of a multimodal approach for management of acute pain.

AUTHORS' RECOMMENDATIONS

Current evidence demonstrates convincingly that epidurals, patient-controlled analgesia (PCA), and adjunctive nonsteroidal antiinflammatory drugs (NSAIDs) improve postoperative analgesia. The evidence for use of continuous peripheral nerve blocks (CPNB) is less concrete, and further investigation is needed. Epidural analgesia, but not PCA, has the additional benefit of sometimes promoting rapid recovery after surgery, although an effect on major morbidity or mortality has not been demonstrated. In the case of PCA, improvements in pain relief are slight, but patients clearly prefer PCA. The material costs of epidural analgesia, CPNB, and PCA are substantial, and the labor costs of epidural management are even greater. Epidurals and PCA are recommended for their demonstrated ability to provide good analgesia, improve patient satisfaction, and, in the case of epidurals, hasten recovery. Many aspects of CPNB have yet to be fully understood, including technical skills of catheter insertion, effects of varying the location of catheter placement, different types of infusate used, and overall morbidity and mortality related to placement.

The use of NSAIDs to supplement systemic and neuraxial opioid therapy has also demonstrated benefit in terms of improved analgesia, opioid sparing, and a moderate reduction in some opioid-induced adverse effects. However, NSAID opioid sparing has not been demonstrated to improve overall surgical outcomes, and care must be taken to balance the benefits of NSAID administration with the risk of harm. Nonetheless, it appears that many patients can benefit from perioperative NSAID administration.

Individual institutions must be prepared to devote the necessary resources before offering advanced analgesic

Continued on following page

AUTHORS' RECOMMENDATIONS
(Continued)

technologies. Because it has not yet been possible to demonstrate decreases in major morbidity and mortality rates in association with epidurals (or PCA), the question of whether to offer these advanced pain treatments often turns to cost and feasibility. Institutional differences in drug and equipment costs, staffing levels (particularly anesthesia staffing levels), and patients (and their expectations) may determine whether an institution chooses to offer epidural analgesia or PCA.

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CHAPTER 72

Is Pre-Emptive Analgesia Clinically Effective?

Allan Gottschalk, MD, PhD • E. Andrew Ochroch, MD, MSCE

INTRODUCTION

The concept of pre-emptive analgesia originated at a time of growing appreciation for the dynamic characteristics of the pain pathway. Experimental studies made it clear that noxious stimuli could sensitize both the peripheral and central components of the nociceptive pathway. This insight guided the interpretation of several clinical studies[1-3] that appeared to demonstrate that subjects who underwent surgery having first received opioids or regional blockade experienced less postoperative pain and raised "the possibility that preemptive preoperative analgesia has prolonged effects which outlast the presence of drugs."[4] Since then, a considerable number of laboratory and clinical studies of pre-emptive analgesia have been performed.

Interpretation of this growing body of data is encumbered by evolving concepts as to what constitutes pre-emptive analgesia.[5] Pre-emptive analgesia in the widest sense recognizes that noxious stimuli at any point throughout the entire perioperative period can sensitize the nervous system. More recently, the term *preventive* analgesia has been applied to clinical and laboratory studies that seek to demonstrate a beneficial effect of an analgesic intervention that outlasts the pharmacologic presence of the intervention. Such studies typically determine whether some benefit is observed in those who received the analgesic intervention compared with those who did not. In contrast, pre-emptive analgesia in the narrow sense addresses only a small portion of the perioperative period, such as the time of incision or the time of surgery.[6] Clinical and laboratory studies of pre-emptive analgesia defined in this manner typically administer identical analgesic interventions at different times to test and control groups, where typical times would be preincision and postincision or preoperatively and postoperatively. Subjects in such trials could receive considerable benefit from the intervention provided to the control group.[7] Of late, trials like this are considered tests of pre-emptive analgesia as opposed to preventive analgesia.[8] Meta-analyses of clinical trials with a *pre-emptive* structure[9,10] have been conflicting, and the most recent is supportive of pre-emptive epidural analgesia, local anesthetic infiltration, and nonsteroidal antiinflammatory drug (NSAID) administration (Figure 72-1). Another meta-analysis demonstrated that studies with a preventive design as opposed to a pre-emptive design were more likely to lead to measurable benefits, particularly for use of *N*-methyl-D-aspartate (NMDA) antagonists.[11] A summary of gabapentinoid trials indicates the potential of this drug class, apart from its immediate benefits, to reduce chronic postsurgical pain.[12] In interpreting data from any one of these studies, the timing and duration of the analgesic intervention may mean little if the intervention is not capable of preventing sensitization of the nociceptive pathways.[6]

MOTIVATION FOR PRE-EMPTIVE APPROACHES

The motivation for pre-emptive analgesic strategies is twofold. First, one seeks to minimize perioperative pain as well as pain during the typical recovery period for a given surgical procedure. Apart from the relief offered to patients, there is the expectation of reaping any functional benefits that may be associated with effective analgesic therapy. Second, pre-emptive analgesic approaches recognize that acute painful events can lead to long-term painful consequences, where pain persists even when tissue healing appears complete. Although the best known long-term painful syndromes are associated with limb amputation, in which about 70% of patients report pain 1 year after surgery,[13] long-term painful sequelae are reported for many other types of surgery.[14] In general, prior painful experience is predictive of increased pain and analgesic use after subsequent surgery.[15,16] Even relatively limited surgery can lead to long-term alterations in the response to noxious stimuli. For example, pain-related behavior is increased during vaccination for boys who previously underwent circumcision compared with those who did not.[17] Pain is reported 1 year after surgery in at least half of patients undergoing major thoracotomy[18-20] or breast surgery.[21] About half of patients undergoing lower abdominal surgery will still report some degree of residual pain several months after the surgical procedure.[22,23] Inguinal herniorrhaphy is associated with residual pain in 25% of patients 1 year after surgery.[24] Even low levels of residual pain are associated with decreases in activity and perception of health.[23,25] Thus long-term alterations in pain perception occur frequently after a broad range of surgical procedures, and these alteration may negatively affect quality of life. These long-term changes in pain perception motivate the use of pre-emptive analgesia. The underlying hypothesis is that such changes can be prevented by initiating an

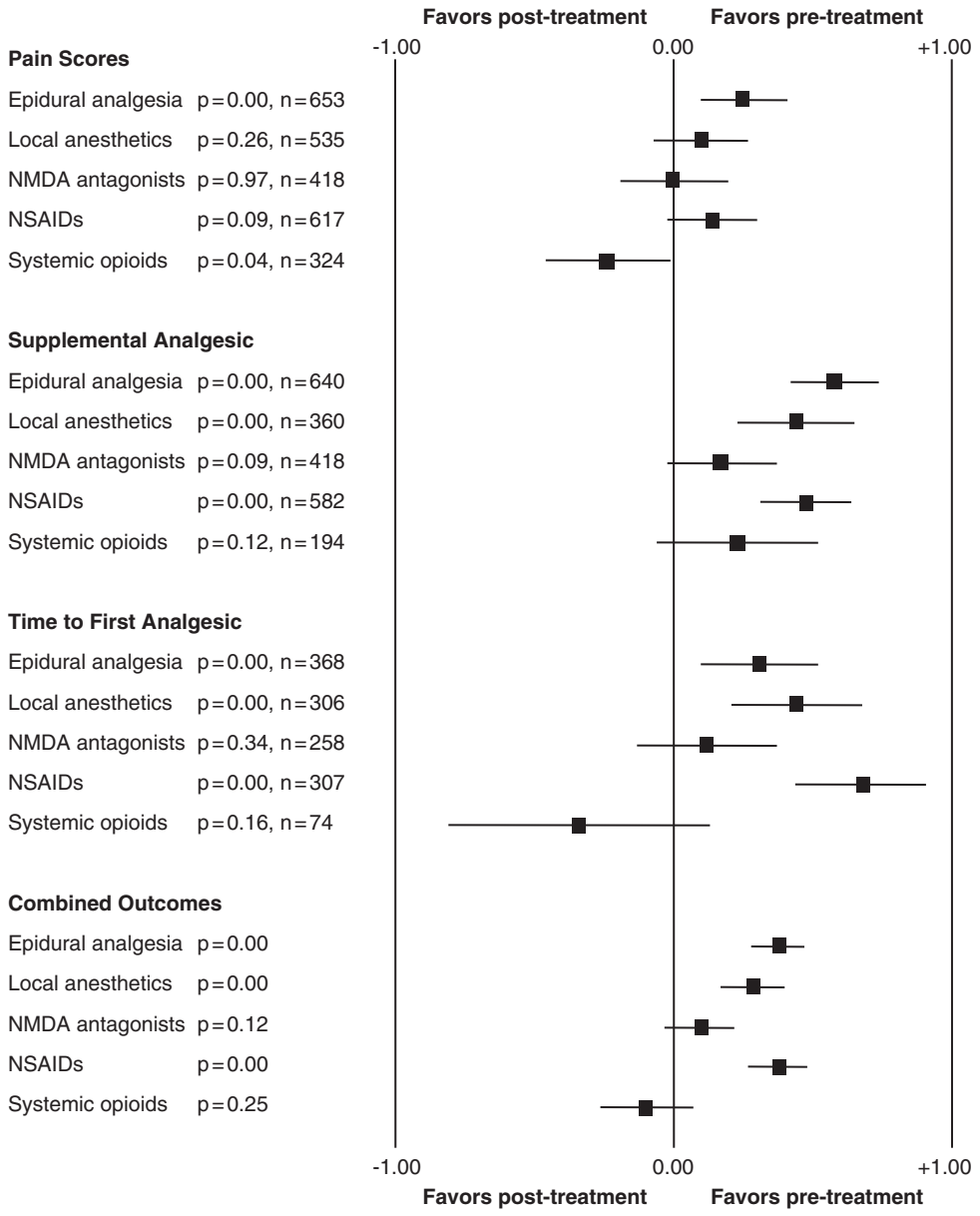

FIGURE 72-1 ■ Summary of Results from Recent Meta-Analysis of Preemptive Analgesia. The plot indicates the effect size (standardized mean difference) for pre-emptive treatment compared with control and the 95% confidence interval. For each intervention and outcome measure, the total number of subjects included in the meta-analysis and the significance of the result are indicated. Results when all three outcomes are combined are given at the bottom. *NMDA, N*-methyl-D-aspartate; *NSAIDs,* nonsteroidal antiinflammatory drugs. (Adapted from Figures 1 to 4 of Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg 2005; 100(3):757–73.)

effective analgesic regimen before the onset of the procedure and maintaining it for a sufficient duration.

OPTIONS

Therapeutic options for pre-emptive analgesia include virtually all analgesic modalities and pharmacologic classes, individually and in combination. Analgesics can be administered systemically, at the site of surgery, along a peripheral nerve, or neuraxially. Analgesics include opioids, alpha-2 agonists, NMDA antagonists, muscarinic stimulation by administration of an anticholinesterase, NSAIDs, anticonvulsants, and local anesthetics.

Timing of the initiation of the analgesic regimen is central to the use of pre-emptive analgesia. Because most practitioners recognize the need for postoperative analgesia, most studies of pre-emptive analgesia have emphasized interventions initiated before the start of surgery and lasting for some portion of the surgical procedure. However, the quality of postoperative analgesia may be an important factor. Periods of intense pain on emergence or during recovery may lead to sensitization of the nociceptive pathway, overwhelming the benefits of preventing intraoperative sensitization.[26] Conversely, highly effective postoperative analgesic regimens could mask the benefits of intraoperative efforts to prevent sensitization and even limit sensitization in control groups. For procedures characterized by a long and painful postoperative course, preventing sensitization in the postoperative period may be just as important as doing so intraoperatively. For analgesics that can take some time to exert their full effect (e.g., NSAIDs, see further on), initiation of the analgesic regimen well in advance of the start of surgery is required for pre-emption to occur. Along with the decision of when in the perioperative

period to initiate analgesic therapy, the necessary dose and duration of analgesic therapy to prevent sensitization during each phase of the perioperative period require elucidation and may vary with the type of surgery.

LABORATORY EVIDENCE OF PRE-EMPTIVE ANALGESIA

Laboratory studies have suggested the clinical applicability of pre-emptive analgesia by identifying the underlying mechanisms and the factors that may play important clinical roles. Painful stimuli can sensitize both the peripheral and central components of the nervous system.[27] In the periphery, repeated applications of noxious stimuli increase the magnitude of the response to subsequent applications of the same stimulus.[28] There is a complex interaction between peripheral nociceptors and inflammatory mediators released in response to tissue injury that can enhance the response of peripheral nociceptors.[29] This enhanced response can be attenuated with local anesthetics, opioids, and NSAIDs as described later on.

Neurons in the dorsal horn of the spinal cord exhibit a biphasic response to formalin injection of the skin.[30] Intrathecal opioids are effective at preventing both phases of this response.[31] However, the second phase is still prevented even after administration of an opioid *antagonist* after the initial response, which indicates that alteration of neural behavior by a noxious stimulus can be prevented. Substance P and excitatory amino acid transmitters acting at NMDA receptors play a crucial role in sensitizing neurons in the dorsal horn.[32-35] Local anesthetic infiltration before formalin injection can limit longer term pain-related behavior,[36] but when noxious inflammatory stimuli of longer duration are used, longer term reductions in pain-related behavior are seen only with local anesthetics whose duration of action matches that of the noxious stimulus.[37,38] Administration of local anesthetic before nerve section can decrease pain-related behavior for a considerable period of time.[39] However, in a laboratory model of incisional pain, rats receiving intrathecal opioids or local anesthetic before an incision in their hindpaw exhibited decreased wound hyperalgesia on the day of surgery, but not longer, when compared with those who received the same analgesics immediately after incision.[40]

Many explicit laboratory tests of pre-emptive analgesia have been negative.[41-43] However, the quality and duration of the pre-emptively administered analgesic relative to the intensity of the experimental stimulus may play an important role in whether pre-emptive analgesic administration is beneficial.[44] Moreover, the extent that laboratory models of surgical pain replicate the nociceptive processing that takes place during major surgical procedures has not been fully determined. For example, a new rat model of thoracotomy has been successful in demonstrating the capacity of systemic and intrathecal analgesics to decrease long-term pain.[45]

Laboratory studies also delineate the contribution of the general anesthetics to pre-emptive analgesic effects. Clinically effective concentrations of volatile anesthetics do not prevent central sensitization,[46] but they can potentiate the effects of neuraxial opioids.[47] Nitrous oxide has been shown to have a pre-emptive analgesic effect that is not realized when a volatile anesthetic is also administered.[48]

CLINICAL EVIDENCE OF PRE-EMPTIVE ANALGESIA

There are hundreds of studies evaluating the clinical use of pre-emptive analgesia. These vary considerably with respect to timing, intensity, and duration of the intervention, the analgesic used in the control group, and the type of surgery. We will evaluate systemic interventions with opioids, NMDA antagonists, gabapentinoids and NSAIDs, and regional administration of local anesthetics and opioids.

Systemic fentanyl administered as a bolus before incision and maintained with an infusion reduced wound hyperalgesia 24 and 48 hours after surgery when compared with control subjects, all of whom received identical postoperative opioid analgesia.[49] Consequently, it is surprising that multiple studies of pre-emptive opioid administration for hysterectomy have, collectively, been somewhat disappointing; multiple meta-analyses have revealed no benefit of preincisional opioid administration (see Figure 72-1) and even a paradoxic effect in favor of analgesics administered postoperatively.[9,10] However, in all of these studies, the same bolus dose of opioid was administered either before incision or at the conclusion of surgery. Consequently, especially because many of the studies used relatively short-acting opioids, it is conceivable that intraoperative opioid levels were inadequate for preventing sensitization in the intervention group. Furthermore, the group receiving an opioid bolus at the conclusion of surgery would have been relatively comfortable during the often painful period immediately after surgery when sensitization is still ongoing. When intraoperative opioid levels were maintained with an infusion, reduced pain and analgesic consumption were seen for the 48 hours after surgery.[50] An additional potentially confounding factor is that acute opioid tolerance could have developed in the group receiving opioids before incision, rendering analgesics administered in the immediate postoperative period less effective.[51-53]

NMDA antagonists have the potential to limit central sensitization[32,35] and, through an additional consequence of their action at the NMDA receptor, decrease the acute tolerance that develops with opioid administration.[54,55] Systemic ketamine administered before surgery can decrease wound hyperalgesia measured 48 hours after surgery, although this was not always associated with decreases in pain.[49] Other studies with lower doses of ketamine conflict as to whether pre-emptive ketamine administration by itself can lead to reductions in postoperative pain.[56-59] Systemic ketamine used in combination with epidural analgesics led to persistent reductions in postoperative pain.[60,61] Preoperative systemic dextromethorphan decreased pain and analgesic consumption in a dose-dependent manner[62-65] and augmented the efficacy of performing surgery under epidural blockade

with a combination of lidocaine and morphine.[66] A meta-analysis of eight trials comparing preincisional administration of ketamine or dextromethorphan with postincisional administration found no consistent benefit of preincisional ketamine administration but did observe a benefit for the two trials of dextromethorphan that were included in the meta-analysis.[9] This negative result for NMDA antagonists was echoed (see Figure 72-1) by a more recent meta-analysis.[10] However, studies of NMDA antagonists that were more *preventive* in their design were associated with beneficial effects.[11] Importantly, systemic NMDA antagonists can also enhance the benefits of epidural analgesia.[67-69]

Peripheral inflammation in response to tissue injury is painful and can enhance the sensitivity of the peripheral nociceptors, which are themselves a source of proinflammatory mediators.[29,70] The analgesic effects of NSAIDs are due to both their ability to reduce peripheral nociceptor output by modulating the peripheral inflammatory response and their more central effects.[71] A considerable number of studies demonstrate the ability of NSAIDs to reduce perioperative pain and limit the need for other analgesics.[72] Although the mechanism of action of NSAIDs suggests that administering them before the onset of surgery should be beneficial, the available studies indicate that expectations and strategies for the use of these drugs in a pre-emptive manner need revision.

In an initial meta-analysis of 19 trials of preincisional versus postincisional administration of NSAIDs, only four studies demonstrated any reduction in pain, decreased analgesic consumption, or delay until first analgesic request with preincisional NSAIDs.[9] However, a more recent meta-analysis of 17 studies (see Figure 72-1) was more supportive of a pre-emptive analgesic effect.[10] One favorable study not included in the first meta-analysis compared the effects of intravenous NSAID administration 30 minutes before induction to its administration at the conclusion of surgery. Pre-emptive administration resulted in improvement in pain scores, increased time until first analgesic request, and decreased analgesic consumption for the 4-hour period of study.[73] A follow-up study demonstrated similar results when the same NSAID was administered either 30 minutes before induction in the intervention group or at the time of induction, as opposed to the conclusion of surgery, in the control group,[74] which emphasizes the importance of timing in observing a pre-emptive effect.[26]

The gabapentinoids gabapentin and pregabalin appear to contribute to perioperative pain relief in studies in which they were used in a *preventive* fashion. Decreased pain and opiate sparing have been demonstrated for lumbar spine surgery,[75] breast surgery,[76] and laparoscopic surgery.[77] Preventive use of gabapentin in combination with local anesthetics has demonstrated a reduction in acute pain as well as chronic pain 6 months after breast surgery.[78] A recent meta-analysis supports the hypothesis that gabapentinoids can reduce the incidence of chronic postsurgical pain.[12]

Local anesthetic infiltration is a relatively safe and simple analgesic modality that can decrease peripheral sensitization and reduce or prevent the nociceptor barrage at the spinal cord. A local anesthetic administered before a surgical procedure can have benefits that outlast the duration of action of the local anesthetic. Pain-related behavior by boys during vaccination is reduced in those who previously underwent circumcision after application of a local anesthetic cream compared with those who did not receive a local anesthetic for the procedure.[79] Local anesthetic infiltration with bupivacaine before surgery for inguinal herniorrhaphy reduced wound hyperalgesia compared with general anesthesia alone. This difference was seen 10 days after surgery and was superior to spinal anesthesia.[80] Patients undergoing inguinal herniorrhaphy under general anesthesia who received preincisional infiltration of the incision site with lidocaine waited longer until their first analgesic request and were less likely to request analgesics than those who received lidocaine infiltration at the time of closure.[81] When inguinal herniorrhaphy is performed under spinal anesthesia, subjects who had an ilioinguinal–iliohypogastric nerve block experienced less pain and had decreased analgesic consumption during the first 2 postoperative days.[82] Pre-emptive incisional[83] or peritoneal[84] use of local anesthetic for laparoscopic surgery may also have benefits that can be long-term.[85]

A systematic review of studies using local infiltration that contrasted interventions performed before incision with those performed before the conclusion of the procedure was generally not supportive of preincisional interventions with local anesthetics, except during herniorrhaphy.[86] A subsequent meta-analysis was generally not supportive of preincisional local anesthetic infiltration compared with postincisional infiltration.[9] Another review stressed the importance of using a local anesthetic block of adequate strength and duration.[44] A more recent meta-analysis (see Figure 72-1) was more supportive of pre-emptive local anesthetic infiltration of the wound.[10]

Neuraxial blockade with a single dose of local anesthetic placed in the subarachnoid space produces profound but not complete[87] blockade for the duration of surgery and the immediate postoperative period. The use of spinal anesthesia may confer some longer term benefits,[2,80,88] but when administration of a spinal anesthetic either before the start of surgery or after its conclusion was compared, only small differences in analgesic use were sometimes seen.[89,90]

The use of epidural catheters for the neuraxial administration of local anesthetics, opioids, and other drugs continues to be an important technique for perioperative pain control for major surgery. Because epidural catheters are often placed to provide postoperative pain relief and have been shown to do this effectively,[91] studies involving pre-emptive epidural analgesia often focus on the somewhat narrower question of whether there is a benefit to intraoperative use of the epidural catheter. Epidural anesthesia by itself may confer an analgesic benefit that outlasts the duration of the blockade.[1,3,92] Neuraxial fentanyl administered immediately before incision reduced pain in the immediate postoperative period compared with the same intervention given shortly after incision.[93] A single preoperative dose of epidural morphine appears to have analgesic benefits that outlast its duration of action for certain types of procedures.[94,95] When local anesthetic alone or in combination with opioids is

administered through epidural catheters during surgery, the impact on postoperative analgesia is often, but not always, limited,[22,96-108] as reflected by meta-analyses (see Figure 72-1) with different conclusions regarding the benefits of pre-emptive epidural analgesia.[9,10] However, with the exception of studies addressing long-term pain after amputation or major thoracotomy (see further on), studies addressing pain or functionality after discharge are rare but often favorable.[22,109]

Given the aforementioned ability of pre-emptively administered local anesthetic to limit long-term pain-related behavior after nerve section in the laboratory,[39] it might be anticipated that a pre-emptive analgesic approach might be particularly effective in preventing the long-term pain syndromes that are associated with thoracotomy and limb amputation. Initiation of epidural blockade before the onset of surgery as compared with after surgery and then maintained for 48 hours in both groups has had a positive long-term impact on the rate of post-thoracotomy pain.[102,107] In contrast, a study that initiated epidural analgesia before incision or at the start of closure and then maintained the block until thoracostomy tube removal demonstrated only short-term analgesic sparing effects when the two groups were compared.[110] However, this study reported substantially lower rates of post-thoracotomy pain than the prior studies. Several early studies of long-term pain after amputation[1,92] demonstrated a benefit of pre-emptive approaches that was not observed in a larger study with a somewhat weaker intervention.[111] The editorial that accompanied this last study reviews the related literature in detail and concludes that the likelihood of benefits when epidural analgesia is used to prevent long-term pain after limb amputation varies with the quality and duration of the blockade.[112]

AREAS OF CONTROVERSY AND UNCERTAINTY

As already emphasized, pre-emptive analgesia continues to be a controversial area with a large and growing clinical and experimental literature that can be selectively mobilized to support multiple points of view. Whether pre-emptive anesthesia is defined in the wide (preventive analgesia) or narrow sense, there is a relative lack of studies that address long-term outcomes, particularly other than pain and analgesic use. However, even for rather narrow definitions of pre-emptive analgesia, long-term benefits have been demonstrated for major abdominal[22,109] and thoracic surgery.[102,107] Apart from the timing of the intervention, there is considerable debate about the magnitude of the intervention. This applies to both the initial drug doses and to whether this level of intervention is maintained throughout surgery and into the postoperative period. Interventions must be capable of preventing sensitization of the pain pathways.[6] Studies defining and testing pre-emptive analgesia in the narrow sense generally use interventions and study designs that permit patients in both the control and intervention groups a comfortable transition to the postoperative period. Consequently, even the control groups often receive an analgesic regimen that might be expected to limit peripheral or central sensitization or both.[6,7] When consideration is given to outcomes other than pain, it remains uncertain how much any benefit of the intervention is due to reductions in pain and how much is a consequence of other effects of the intervention. For example, intra-articular local anesthetic infiltration reduces postoperative pain, and this pain reduction is associated with improved tissue oxygenation[113]; on the other hand epidural analgesia modulates a number of physiologic variables[114] that may contribute to favorable outcomes.[115-119] Lastly, few economic data are available to guide the choice of interventions and to assess the cost of inadequately treated pain.[120]

GUIDELINES

The studies that present a less than overwhelming case for pre-emptive analgesia generally define pre-emptive analgesia narrowly, using relatively limited interventions for a brief portion of the perioperative period. These studies should not obscure the importance of providing continuous outstanding pain relief throughout the entire perioperative period. There are enough studies demonstrating residual pain once tissue healing appears complete and analgesic benefits that outlast the duration of action of the intervention to motivate aggressive perioperative pain control. At the very least, this involves the use of sufficient systemic analgesics, local anesthetic infiltration, nerve blocks, and neuraxial analgesic administration to permit patients to emerge comfortably from surgery and remain comfortable throughout the postoperative period while achieving milestones for rehabilitation. One thing remains clear: modest interventions by themselves are unlikely to be beneficial, regardless of the timing of their administration.

AUTHORS' RECOMMENDATIONS

- An analgesic plan should blunt noxious input seamlessly throughout the entire perioperative period.
- Regional adjuncts alone or in combination with systemic adjuncts should be used.
- Multimodal approaches should combine multiple systemic analgesics, multiple neuraxially administered analgesics, or both.
- Patients with chronic painful conditions and those who are opioid-dependent require robust analgesic regimens that account for their special requirements.
- Postoperative regimens should be implemented before emergence from anesthesia.
- Where possible, nerve blocks, epidural blockade, and local anesthetic infiltration should be maintained throughout surgery and readministered at its conclusion.
- Ineffective nerve blocks should be identified and redone before emergence from general anesthesia, or an alternative should be implemented.
- Concern about loss of sympathetic tone with neuraxial blockade[121] may be misplaced because it may actually be protective.[122,123]
- Research emphasizing long-term outcomes, economics, and functionality is still necessary.

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