STOELTING'S

ANESTHESIA AND CO-EXISTING DISEASE

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EIGHTH EDITION

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ELSEVIER

Elsevier
1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

STOELTING'S ANESTHESIA AND CO-EXISTING DISEASE, EIGHTH EDITION
ISBN: 978-0-323-71860-8

Library of Congress Control Number: 2021940083

Publisher: Sarah Barth
Senior Content Development Manager: Kathryn DeFrancesco
Senior Content Development Specialist: Joanie Milnes
Publishing Services Manager: Shereen Jameel
Senior Project Manager: Manikandan Chandrasekaran
Design Direction: Renee Duenow

Printed in Canada

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Preface

In 1983, the first edition of *Anesthesia and Coexisting Disease* by Drs. Robert K. Stoelting and Stephen F. Dierdorf was published with the stated goal "to provide a concise description of the pathophysiology of disease states and their medical management that is relevant to the care of the patient in the perioperative period." Beginning with the fifth edition Drs. Roberta Hines and Kathrine Marschall assumed the editorship, continuing for the sixth and seventh editions. Succeeding Dr. Marschall for the eighth edition is a new editor, Dr. Stephanie B. Jones.

This latest edition of *Anesthesia and Coexisting Disease* continues the tradition of presenting new, updated, and relevant medical information to the anesthesiology community. A chapter on chronic pain has been added, and new authors have made major updates to several other chapters, including valvular heart disease, pericardial disease and cardiac trauma, endocrine disease, and pediatric and pregnancy-associated diseases. All chapters contain contemporary clinical information, reference to major medical society guidelines, and recommendations that impact the practice of perioperative medicine. In addition, numerous tables, figures, and illustrations have been refreshed and expanded to aid in the understanding of key clinical concepts. We trust that our readers continue to find this text a valuable reference for optimizing patient care.

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CONTENTS

1

Sleep-Related Breathing Disorder

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OUTLINE

Sleep-related breathing disorder (SRBD) is the second most common category as classified by the International Classification of Sleep Disorders (ICSD-3), after insomnia, and the most common disorder encountered in sleep medicine labs.

SRBD can refer to an exclusively sleep-related disorder or as sleep-induced exacerbation of a baseline persistent disorder. SRBDs are divided into four main categories: obstructive sleep apnea (OSA) disorders, central sleep apnea (CSA) syndromes, sleep-related hypoventilation (SRHV) disorders, and sleep-related hypoxemia (SRHO) disorders. OSA accounts for about 90% of SRBDs, CSA syndromes 9%, and sleep-related hypoventilation/hypoxemia disorders 1% (Box 1.1).

BOX 1.1 Sleep-Related Breathing Disorders According to ICSD-3

Obstructive sleep apnea (OSA) disorders
1. OSA, adult
2. OSA, pediatric

Central sleep apnea (CSA) syndromes
1. CSA with Cheyne-Stokes breathing (CSB)
2. CSA due to a medical disorder without Cheyne-Stokes breathing
3. CSA due to high-altitude periodic breathing (HAPB)
4. CSA due to a medication or substance
5. Primary CSA
6. Primary CSA
7. Primary CSA of prematurity
8. Treatment-emergent CSA

Sleep-related hypoventilation (SRHV) disorders
1. Obesity hypoventilation syndrome (OHS)
2. Congenital central alveolar hypoventilation syndrome (CCAHS)
3. Late-onset central hypoventilation with hypothalamic dysfunction
4. Idiopathic central alveolar hypoventilation (ICAH)
5. SRHV due to a medication or substance
6. SRHV due to a medical disorder

Sleep-related hypoxemia (SRHO) disorder

Isolated symptoms and normal variants
1. Snoring
2. Catathrenia

ICSD, International Classification of Sleep Disorders

Standardized classifications of sleep disorders serve as a tool for disease definition, establishing criteria for diagnosis and treatment, compiling epidemiologic data, and managing coding and billing.

OBSTRUCTIVE SLEEP APNEA (OSA)

Adult OSA

OSA refers to decreased or absent airflow in the presence of muscular inspiratory effort. On the polysomnography (PSG) recording, obstructive apnea events can take one of three forms: apnea, hypopnea, or respiratory effort–related arousals (RERAs) (Figs. 1.1 and 1.2). Defining these events depends on recordings of airflow, thoracic and abdominal respiratory muscle movement (Mvmt), oxygen saturation (Spo_2), and electroencephalography (EEG). A duration of 10 seconds or more is required to score any of these respiratory events.

Apnea

Apnea is diagnosed based on the findings from a single PSG channel using a specific sensor. It is defined as a 90% or more reduction in the amplitude of airflow signal as measured by an oral/nasal thermal sensor, whose signal is not linear. Defining the type of apnea event requires examining two PSG channels: respiratory effort and airflow. Based on the respiratory effort recording that is coinciding with the airflow signal, the apnea event is classified into one of three types:

- Obstructive apnea event: There is breathing effort during the apnea.
- Central apnea event: There is no breathing effort during the apnea.
- Mixed apnea event: The apnea event starts as a central apnea and ends as an obstructive apnea.

Hypopnea

Hypopnea is defined based on the findings of two or three PSG channels, using a nasal pressure sensor. The nasal pressure sensor is used for scoring hypopnea because its signal is linear, but it is not used for apnea scoring because it may be misleading in a mouth breather. The sensor for oxygen saturation is a pulse oximeter with signal averaging of 3 seconds (3 Hz) or less. The duration requirement for hypopnea is 10 seconds or more. Hypopnea events have two definitions, recommended and alternative.

The recommended definition of hypopnea is a drop of 30% or more in the amplitude of the nasal pressure sensor that lasts for 90% or more of the event and is associated with a 4% or more drop in Spo_2. This definition of hypopnea is simplified as the 30-4 rule. It is the recommended definition by the American Academy of Sleep Medicine (AASM) and the definition accepted by Medicare; therefore it is also known as the Medicare hypopnea rule. This definition requires examining two PSG channels: the airflow as measured by the nasal pressure sensor and Spo_2 (Fig. 1.3).

An alternative definition of hypopnea is a drop of 50% or more in the amplitude of airflow as measured by nasal pressure sensor that lasts 90% or more of the event and is associated with either a 3% or more drop in Spo_2 or EEG arousal. EEG arousal refers to an abrupt shift in EEG frequency lasting more

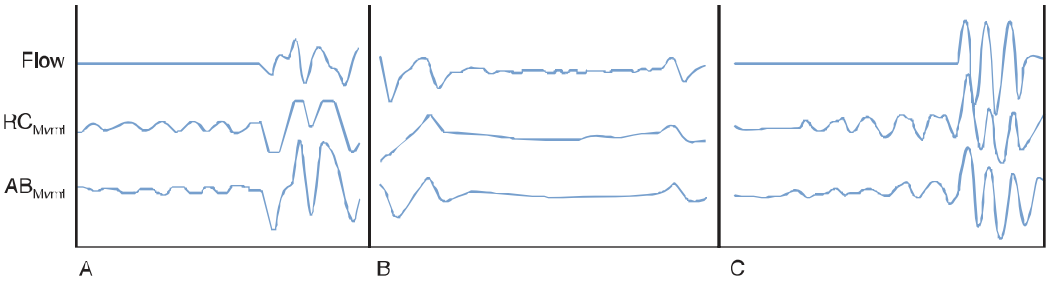

Fig. 1.1 Polysomnography (PSG) features of the three types of apnea events. (A) Obstructive apnea event. The top Flow channel demonstrates no airflow while the bottom two channels demonstrate respiratory efforts in the chest (RC_{Mvmt}) and abdomen (AB_{Mvmt}). (B) Central apnea event. The top Flow channel demonstrates no airflow while the bottom two channels demonstrate no respiratory efforts in the chest (RC_{Mvmt}) and abdomen (AB_{Mvmt}). (C) Mixed apnea event. The apnea event starts a central apnea event (no Flow and no effort) and ends as an obstructive apnea event (no Flow with respiratory muscle effort).

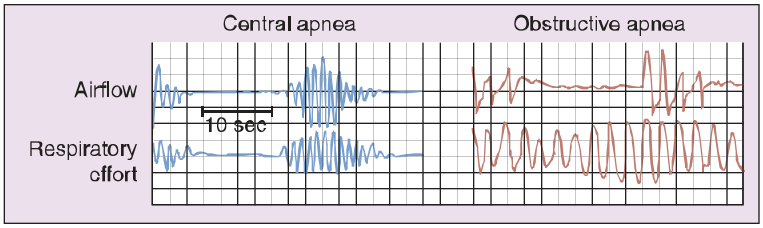

Fig. 1.2 The relation between airflow and respiratory effort in apnea events. In the central apnea event, the airflow channel shows a cessation of airflow for more than 10 seconds, and the respiratory effort channel shows no respiratory effort during the entire apnea period. In the obstructive apnea event, the airflow channel shows cessation of airflow, and the respiratory effort channel shows persistent and progressively increasing effort during the entire apnea period.

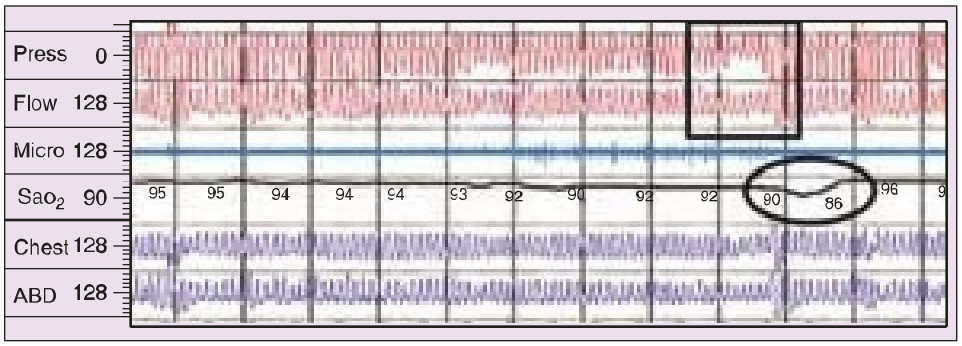

Fig. 1.3 Polysomnography (PSG) features of obstructive hypopnea event. The top channel *(Press)* displays airflow as measured by a nasal pressure transducer. It demonstrates 30% or more reduction from baseline in the amplitude of the signal that lasts for 90% or more of the event, which lasts 10 or more seconds. The channel Flow displays airflow as measured by a thermal sensor. It demonstrates less reduction from baseline in the amplitude of the signal. The channel Sao_2 demonstrates a drop in oxygen saturation by 4%, from 90% to 86%. Thus the findings on the two channels of airflow pressure and oxygen saturation meet the definition of the 30-4 rule for hypopnea. The bottom channels (*Chest* and *ABD*) display chest and abdomen movement as measured by inductance plethysmography. They demonstrate continuous respiratory effort during the hypopnea event, which defines it as an obstructive hypopnea.

than 3 seconds and preceded by more than 10 seconds of stable EEG and has different rules for scoring based on sleep stage (rapid eye movement [REM] or non-REM [NREM] sleep). In PSG sleep studies, arousal refers to EEG arousal, whereas awakening refers to clinical awakening. This alternative definition of hypopnea is simplified as the 50-3a rule, with the *a* standing for *arousal*. This is considered an alternative definition by AASM and is not accepted by Medicare for the purposes of scoring respiratory events, diagnosing OSA, or coding and billing.

The total number of apnea and hypopnea events during a PSG study is used to calculate an apnea-hypopnea index (AHI), defined as the number of apnea and hypopnea events per hour of sleep. The PSG-derived AHI is used in the diagnosis of sleep apnea disorders, assessing severity, titrating positive airway pressure (PAP) therapy, evaluating the therapeutic efficacy of various interventions, assessing the diagnostic utility of other tools and surveys, and establishing a severity-outcome relationship when studying the association between sleep apnea, or its treatment, and a given outcome.

Respiratory Effort–Related Arousals

RERA is determined based on the findings of three PSG channels: airflow, respiratory effort, and EEG. RERA is defined as a limitation in the airflow followed by an arousal on the EEG channel, with the limitation in airflow being defined either by flattening of the airflow in a way that does not meet the criteria for apnea or hypopnea or by increased respiratory effort. Unlike apnea and hypopnea, the definition of RERA lacks numeric criteria, other than a duration of 10 seconds or more. Using RERA events as part of scoring respiratory events on the PSG is an option, not a recommendation. When RERA events are added to the apnea and hypopnea events, a respiratory disturbance index (RDI) is calculated. The ICSD-3 allows the use of RDI as a substitute for AHI in the diagnosis of OSA. Medicare allows only the use of AHI and allows only one rule for the definition of hypopnea.

Diagnosing OSA in Adults

The diagnosis of OSA in adults can be based either on the presence of an AHI of 15 or above alone or on the combination of an AHI of 5 or above plus clinical signs and symptoms (associated sleepiness, fatigue, insomnia, snoring, subjective nocturnal respiratory disturbance, or observed apnea) or associated medical and psychiatric disorders (hypertension [HTN], coronary artery disease, atrial fibrillation [AF], congestive heart failure [CHF], stroke, diabetes mellitus, cognitive dysfunction, or mood disorder). The term *obstructive sleep apnea syndrome* (OSAS) refers to the combination of AHI of 5 or above and daytime somnolence that is present for 2 or more days/week. Based on this definition, the prevalence of OSAS is about 2% for women and 4% for men, while the prevalence of AHI of 5 or above alone is about 9% in women and 24% in men. In using AHI to assess the severity of OSA, three grades are defined: mild (AHI 5–15), moderate (AHI 15–30), and severe (AHI ¯30).

Levels of Sleep Apnea Testing

There are four levels of sleep apnea testing. Level I is attended comprehensive (7–12 channels) PSG, the gold standard. Level II is unattended comprehensive PSG, which is rarely done. Level III is unattended four-channel portable monitoring, including airflow, respiratory effort, and Sao_2, with additional electrocardiography (ECG) and/or actigraphy. Level III is commonly used to diagnose OSA in someone with high pretest probability and no comorbidity. It cannot rule out OSA, lacks information about sleep stage and body position, and tends to underestimate AHI because it uses recording time as the denominator, which is usually longer than sleep time. Level IV is home monitoring of Sao_2 with or without airflow. Level IV cannot diagnose OSA because it lacks a respiratory effort channel, but it can provide an oxygen desaturation index (ODI), the hourly rate of decreased Sao_2 of 3% or more, and T-90, the total time spent with Sao_2 of 90% or less. Level IV oximetry can be enhanced by adding both actigraphy, which measures wrist

activity as an indication of sleep state, and peripheral arterial tonometry (PAT). PAT measures finger plethysmography as an indication of sympathetic α-adrenergic activity, which in turn is used as a marker of apnea, hypopnea, and hypoxia events.

Pathogenesis of OSA

Direct physiologic mechanisms involved in the pathogenesis of OSA include anatomic and functional upper airway obstruction (UAO), decreased respiratory-related EEG arousal response, and instability of the ventilatory response to chemical stimuli. The apnea episodes are resolved as a result of three events: (1) increased muscular activity at the upper airway muscles that restores airway patency; (2) increased muscular activity at the thoracoabdominal respiratory muscles that generates increased negative intrathoracic pressure; and (3) EEG arousal, which stimulates central respiratory centers. PSG recording can help elucidate the sequence of, and relationships between, events both during apnea episodes and their resolution (Fig. 1.4).

Cardiovascular Consequences

Cardiovascular pathophysiologic consequences of OSA are the result of hypoxia/hypercarbia, EEG arousal, and increased inspiratory efforts. These physiologic disturbances affect cellular and tissue function of the cardiovascular system leading to a wide range of clinical morbidity and mortality (Fig. 1.5).

Pathophysiologic consequences of OSA contribute to the difference in timing of cardiac death between patients with OSA and the general population, in whom peak incidence of death due to cardiac arrhythmias and ischemia occurs during the daytime (06:00–12:00). In the patient with OSA the peak incidence of death due to cardiac arrhythmias and ischemia occurs at night (00:00–06:00).

The causal relationship between OSA and cardiovascular morbidity and mortality is supported by observational studies demonstrating (1) a dose-response relationship between severity of OSA and observed morbidity and mortality, (2) positive effect of OSA treatment, and (3) dose-response relationship between efficacy of treatment and observed morbidity and

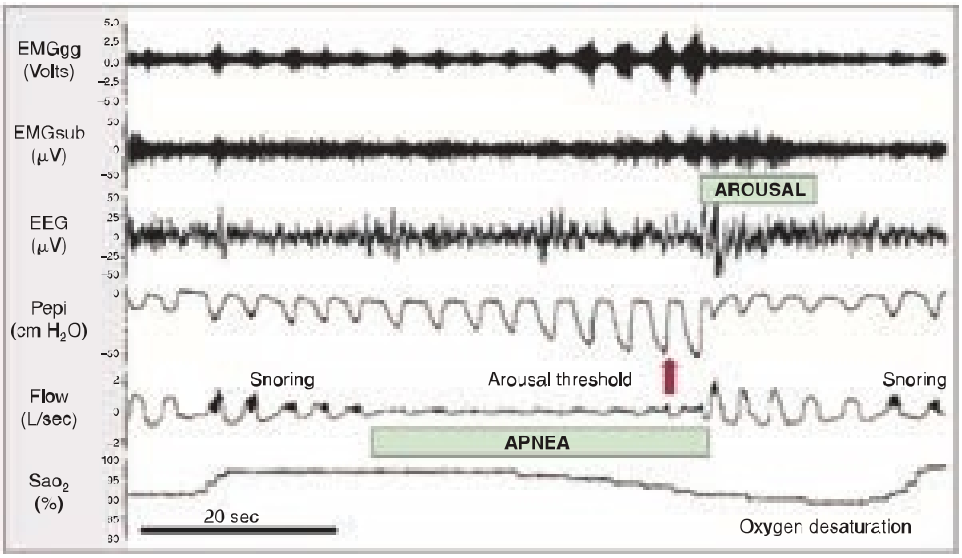

Fig. 1.4 Experimental polysomnography (PSG) in obstructive sleep apnea showing sequence and resolution of apnea events. This experimental PSG in a patient with obstructive sleep apnea (OSA) includes recordings of electromyography (EMG) of upper airway muscles (genioglossus *[EMGgg]* and submental muscles *[EMGsub]*), electroencephalography *(EEG)*, intrathoracic pressure approximated by epiglottic catheter *(Pepi)*, nasal airflow *(Flow)* by thermal sensor, and oxygen saturation *(Sao_2)* by pulse oximetry with a minimal sampling rate of 10 Hz. The top channel *(EMGgg)* demonstrates progressively increased EMGgg activity (amplitude) until this increased activity reaches a sufficient level to open the upper airway and allow breathing (Flow) to resume. The middle channel *(Pepi)* demonstrates a progressive increase in respiratory muscle effort until breathing (Flow) resumes. The increase in respiratory muscle effort is considered the primary stimulus for EEG arousal, through stimulation of the mechanoreceptors in the chest muscles, which provide input both to the medullary respiratory centers and the wake/sleep neurochemical pathways. The EEG channel shows that the occurrence of the EEG arousal occurs immediately following the peaks in EMGgg and Pepi and coincides with the resumption of breathing as demonstrated by nasal airflow (Flow). The airflow *(Flow)* thermal sensor channel shows the resumption of breathing at the time of EEG arousal, immediately after the peaks of upper airway (EMGgg) and respiratory (Pepi) muscle activity. The oxygen saturation channel *(Sao_2)* demonstrates the lag time between ventilation and oxygenation, which leads to paradoxic restoration of oxygen saturation during the apnea episode, and the occurrence of oxygen desaturation during the resumption of breathing period. The increased activity of EMG, Pepi, and EEG at the end of the apnea period results in a subsequent period of hyperpnea. The cyclic alteration of periods of apnea and hyperpnea disrupts the chemoreceptor stability of the respiratory control system and leads to a periodic breathing pattern similar to that encountered in several forms of central sleep apnea.

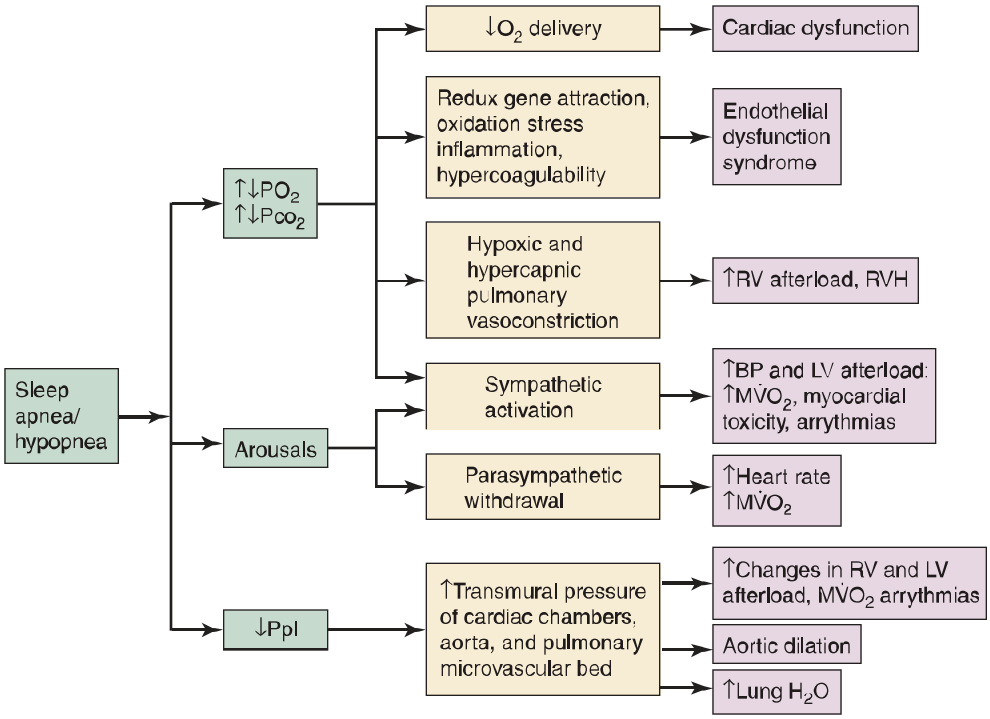

Fig. 1.5 Schematic representation of cardiovascular pathophysiologic consequences of obstructive sleep apnea.

mortality. Outcomes for which such relationships have been found include all-cause mortality; a composite outcome of stroke, transient ischemic attack (TIA), and all-cause mortality; stroke; coronary artery disease; HTN; and need for repeat revascularization after percutaneous coronary intervention. The causal relationship between stroke and OSA may be bidirectional, as stroke is considered both a risk factor for and an outcome of OSA. The causal relationship between OSA and cardiovascular and metabolic disorders may also be bidirectional, or noncausal due to shared risk factors (Fig. 1.6).

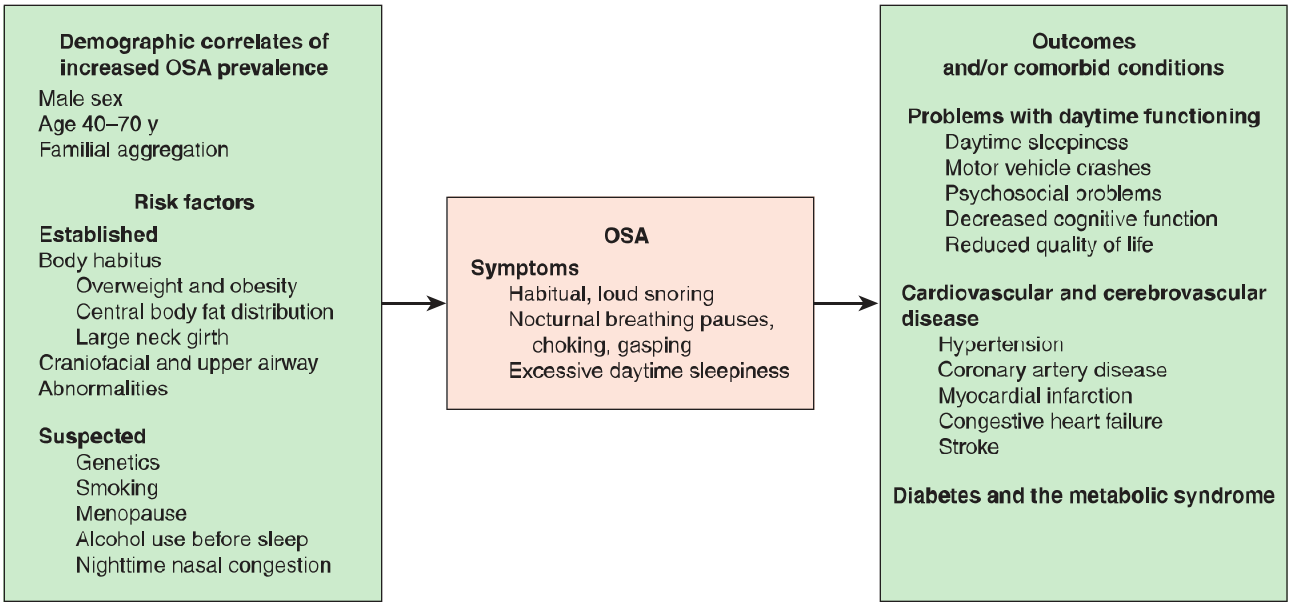

Fig. 1.6 Schematic representation of overlap between risk factors, symptoms, and outcomes of obstructive sleep apnea (OSA). There is significant overlap between what are considered risk factors, symptoms, and outcomes in OSA. Overlap can be seen between symptoms (e.g., excessive daytime sleepiness [EDS]) and outcomes. This overlap may be a causal association or due to shared risk factors of chronic sleep deprivation and disrupted sleep architecture. Overlap can be observed between risk factors and outcomes in the form of metabolic and cardiovascular disorders. This overlap may represent reciprocal causal association or noncausal association due to shared risk factors.

Neurocognitive Consequences

Repeated EEG arousal, clinical awakening, and disrupted sleep architecture (decreased deep sleep and increased lighter sleep) induce a state of overall slowing of the EEG, chronic sleep deprivation, excessive daytime sleepiness (EDS), increased number of lapses on psychomotor vigilance task testing, decrease in cognition and performance (attention, memory, executive functioning), decreased quality of life, mood disorders, and increased rates of motor vehicle collisions.

Metabolic Consequences

Pathophysiologic mechanisms for metabolic derangements in OSA include hypoxic injury, systemic inflammation, increased sympathetic activity, alterations in hypothalamic-pituitary-adrenal function, and hormonal changes. Metabolic derangements of OSA lead to worsening of OSA and produce a vicious perpetuating cycle. Metabolic derangements and disorders linked to OSA include insulin resistance, glucose intolerance, dyslipidemia, type 2 diabetes mellitus (T2DM), central obesity, and metabolic syndrome. OSA is common in patients with nonalcoholic steatohepatitis (50%) and polycystic ovarian syndrome (PCOS [30–50%]). Sleep deprivation has been implicated as a risk factor for common cancers, including cancers of the breast, colon and prostate.

Mortality and Economic Consequences

The mortality impact of OSA is evident in moderate to severe OSA. The economic impact is due to increased healthcare utilization, decreased productivity, and years of potential life lost. It is estimated that the yearly incidence of OSA-related motor vehicle accidents alone costs approximately $16 billion and 1400 lost lives. It is also estimated that treating all drivers with OSA with positive airway therapy (at a cost of ~$3 billion/year) would save about $11 billion and 1000 lives. OSA has a significant public health impact due to its high prevalence (estimated 25 million in United States), high proportion of undiagnosed cases (80% for men and 90% for women), and association with significant morbidity, mortality, and decreased quality of life.

Treatment of Adult OSA

Treatment of OSA includes the use of devices, surgery, and medications. All modes of treatment should include patient education and long-term follow-up. General measures that should be applied with all modes of therapy include reducing modifiable risk factors and treating comorbid conditions. Potentially modifiable risk factors include alcohol consumption, use of sedative medication, cigarette smoking, obesity, nasal obstruction, and tonsils grade (≥3). Common comorbidities include difficult to control HTN, AF, coronary artery disease, myocardial infarction, CHF, stroke, T2DM, hypothyroidism, Graves disease, acromegaly, nonalcoholic steatohepatitis (NASH), and PCOS. Women with OSA are more likely than men to present with insomnia, thyroid disease, depression, and antidepressant use. General measures in the treatment of OSA include weight reduction, avoiding alcohol and central nervous system (CNS) depressant drugs, improving sleep hygiene, and refraining from driving when sleepy. In extreme cases of sleepiness (e.g., patients reporting the maximum score of 24 on the Epworth sleepiness scale [ESS]), patients should be forbidden from driving unless they are treated and their OSA and ESS improved.

PAP Therapy for OSA

Positive airway pressure therapy is the most commonly studied and prescribed therapy for OSA as well as for some forms of central and mixed sleep apnea. PAP therapy is considered tier 1 therapy for OSA. The most common form of PAP is continuous PAP (CPAP). Other forms of PAP therapy consist of various electronic modifications of PAP delivery patterns such as bilevel PAP (BPAP), autotitrated PAP (APAP), and adaptive servo ventilation (ASV). The three elements of a PAP device are the flow generator, a connecting hose, and a patient interface, which has three forms: nasal mask, nasal pillows, and full-face mask. Technologic advancements have allowed reduction in the size and the noise level of flow generators as well as the options of PAP delivery patterns. The aim of these modifications is to enhance individual customization of PAP therapy, and therefore improve adherence to and effectiveness of the therapy. Critical steps in application of PAP therapy are patient education, mask fitting, and titration of therapy. Effective PAP titration can result in elimination of apnea events and normalization of oxygen saturation. Long-term effects of effective PAP therapy include improved sleep efficacy and architecture, improved neurocognitive function, and reversal of many of the metabolic and cardiovascular effects of OSA.

Adherence to PAP therapy is the major limitation of its effectiveness. Initial acceptance rates of PAP therapy of 70% might decrease to 50% or less over time. Complications of PAP therapy are uncommon and can be managed with therapy modification. The most common complications are mechanical and include nasal obstruction or stuffiness, facial pressure ulcers, and skin rash. Other complications are social or psychological in nature and are related to self-image and intimacy.

The goal of PAP titration is to select the lowest airway pressure that eliminates all respiratory events, including apneas, hypopneas, arousals, and snoring, so that the RDI decreases to less than 5/hour, with acceptable oxygenation (Spo_2 ⁻90%), and an acceptable mask leak level (Fig. 1.7).

Suggested mechanisms of action of PAP therapy include (1) increasing the pharyngeal transmural pressure (pneumatic splint effect), (2) reducing pharyngeal wall thickness and airway edema, (3) increasing airway tone by mechanoreceptor stimulation, and (4) increasing end-expiratory lung volume and producing a tracheal tug effect. Manual in-laboratory, PSG-guided, full night titration of fixed PAP is considered the standard. APAP is an acceptable alternative for the treatment of uncomplicated moderate to severe OSA that is associated with snoring. APAP consists of a single variable PAP that is maintained during both inhalation and exhalation, with variation from breath to breath according to the presence or absence of apnea, hypopnea, or snoring. APAP mode may improve patient adherence and may minimize the average airway pressure by allowing higher PAP during periods of greater obstruction, such as in the

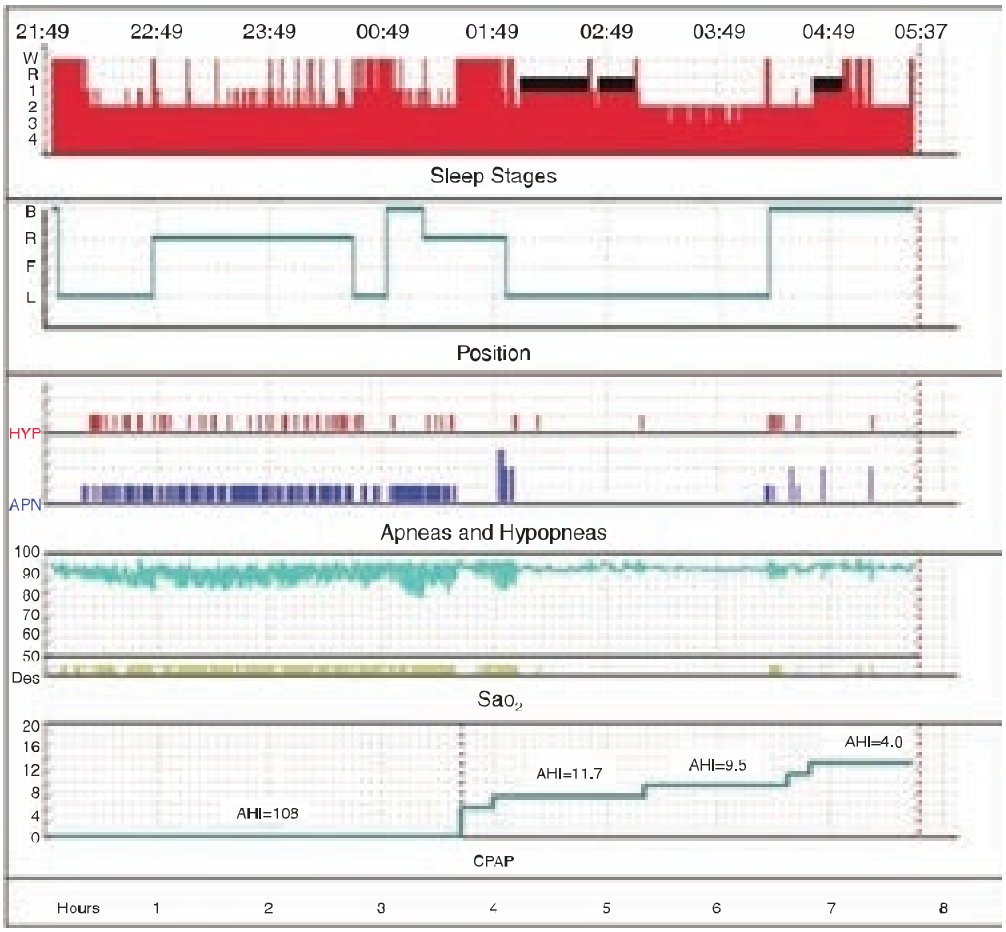

Fig. 1.7 All-night hypnogram demonstrating optimal continuous positive airway pressure (CPAP) titration. This is an all-night hypnogram of about 8-hour duration that represents a split-night PSG study, in which the first half of the study is used for diagnosis and the second half for therapeutic titration of CPAP. The time in hours is listed at the bottom of the graph. The first panel from the bottom shows the CPAP level. During the first half of the study, the diagnostic PSG study yields an AHI of 108/h. Toward the middle of the study, CPAP titration started at 6 cm H_2O then increased to 8 cm H_2O, which resulted in reducing the AHI to 11.7/h; progressive increases in CPAP and decreases in AHI follow. The second panel from the bottom shows the oxygen saturation (*Sao_2*) during the night and demonstrates the frequent desaturation episodes during the first half of the night to Sao_2 levels of 75%, and resolution during CPAP titration. The third panel from the bottom shows the apnea and hypopnea events, with frequent occurrence of these events during the first half of the night (AHI 108/h) and the significant resolution of these events by CPAP (AHI 4/h). The fourth panel from the bottom shows the patient position, which demonstrates that the patient avoided the supine position (*labeled B for back*) during the first half of the night and only maintained the supine position during the last period of sleep during the CPAP titration. The top panel shows the sleep stage with the REM sleep period indicated in black. It shows that CPAP titration achieved adequate resolution of the respiratory events even during REM sleep period. The patient was not able to achieve any deep sleep (N3) during the first half of the night, while compensatory N3 stage of sleep was reached during CPAP titration. N3 normally occurs during the first third of the night. This CPAP titration is considered optimal because it was the lowest level of CPAP that reduced AHI to 5/h or less and achieved that reduction during all sleep positions, including supine, and during all stages of sleep, including REM.

supine position and during REM sleep, and lower PAP during periods of lesser obstruction.

Depending on the examined outcome, four levels of evidence are found in the literature regarding the efficacy of PAP therapy in OSA. There is clear evidence for reducing AHI; strong evidence for increasing deep sleep and decreasing EEG arousals; less clear evidence for improved sleep architecture; and equivocal evidence for improved daytime sleepiness, neurobehavioral performance, psychological functioning, quality of life, and cardiovascular outcomes, especially HTN. One example of establishing the efficacy of CPAP therapy in increasing deep sleep is through the demonstration of CPAP-induced restoration of nocturnal surge in the release of growth hormone during deep sleep, also known as slow-wave sleep (SWS) or non-REM sleep stage 3 (N3).

Oral Appliance Therapy for OSA

Oral appliance (OA) therapy is considered second tier treatment in the management of OSA. The most common forms of OA are mandibular advancement devices (MADs) and tongue retaining

devices (TRDs). MADs are usually custom-made devices that are fitted to the teeth like a mouth guard and act to advance and stabilize the mandible to increase upper airway capacity. TRDs advance and retain the tongue in an anterior position by holding it by a suction cup placed over the front teeth. OA therapy is indicated for the treatment of snoring, mild-moderate OSA, and select cases of moderate-severe OSA, such as predominantly supine OSA or OSA due to a proportionally large tongue relative to oral cavity capacity. OA therapy is less effective than PAP therapy in reducing AHI, but may be better tolerated and preferred by patients, and has been shown to be effective in reducing sleep interruption, EDS, neurocognitive impairment and cardiovascular complications. Side effects include excessive salivation, temporomandibular joint discomfort, and long-term occlusion changes. OA therapy should be provided jointly by a qualified dentist and sleep medicine physician with appropriate follow-up testing to document maintained efficacy.

Other Device Therapy for OSA

Many forms of device therapy continue to be introduced for the treatment of OSA. These devices have a wide range of complexity, invasiveness, price, and need for medical prescription and application. Nasal expiratory PAP (EPAP) is a diaphragm-like membrane applied to both nares to provide resistance to exhalation and stent the upper airway. Oral pressure therapy is a mouthpiece attached to a vacuum source, which pulls the soft palate forward and increases the size of pharyngeal cavity.

Airway Surgical Therapy for OSA

Currently, airway surgical therapy for OSA in adults is considered third tier. Airway surgical therapy includes tracheostomy, maxillomandibular advancement (MMA), laser-assisted uvulopalatoplasty (LAUP), uvulopalatopharyngoplasty (UPPP), radiofrequency ablation (RFA), and palatal implants. Most of these procedures are considered options for the treatment of OSA when other treatment options are lacking, failed, or refused with the exception of LAUP, which is graded as not routinely recommended. MMA may be associated with better safety and efficacy than UPPP.

Implantable hypoglossal nerve stimulation consists of implanting a hypoglossal nerve stimulator in the chest with sensing leads between the internal and external intercostal muscles to detect breathing and signal the device to stimulate the hypoglossal nerve during inhalation, which results in enlargement of upper airway capacity. The system is turned on by the patient before going to sleep and turned off upon awakening.

Bariatric Surgery for OSA

Bariatric surgery aims to restrict caloric intake, absorption, or both. Bariatric surgery can be a sole therapy or adjunct to PAP therapy in patients with severe obesity associated with OSA or OHS. Screening for OSA should be performed in all patients undergoing bariatric surgery.

Adjunct Medical Therapy for OSA

Adjunct medical therapy for OSA can be considered with any of the three tiers of OSA treatment: PAP therapy, oral appliance, or surgery. Adjunct therapy includes diet, exercise, positional therapy, avoidance of alcohol and sedatives before sleep, supplemental oxygen, and pharmacologic therapy. Positional therapy consists of devices that discourage or prevent the patient from sleeping in the supine position. Coexisting medical conditions should be treated, including hypothyroidism and acromegaly. In hypothyroidism, hormonal therapy can attenuate EDS, OSA, respiratory insufficiency, and bradycardia. CNS stimulants such as modafinil can be used to treat residual EDS only in conjunction with effective PAP therapy and in the absence of an identifiable cause of residual EDS. Patients may often self-medicate with caffeine to treat EDS. Supplemental oxygen should be used to treat residual hypoxia (188%) that persists despite adequate treatment of OSA.

Pediatric OSA

An age cutoff for applying pediatric or adult rules for OSA is not clearly established. In general, pediatric rules are used for children below the age of 12 years, and adult rules are used above the age of 18 years; either adult or pediatric rules apply for those 13 to 18 years of age.

In children, OSA diagnosis can be based either on clinical findings alone or a combination of clinical and PSG findings. PSG findings are used to support the clinical diagnosis, assess the severity of OSA, and provide a basis for treatment recommendations. When clinical criteria alone are used to diagnose OSA they must include one of these three findings: (1) snoring, (2) labored or obstructed breathing, or (3) daytime consequences such as sleepiness, hyperactivity, or impaired performance.

When PSG is performed for OSA assessment, there are differences between children and adults in terms of recommended modes of monitoring for the respiratory events, scoring respiratory events, and using PSG data to establish the OSA diagnosis, grade its severity, and provide recommendations for treatment.

When monitoring for respiratory events, it is recommended that PSG in children include either end-tidal Pco_2 ($PETco_2$) or transcutaneous Pco_2 ($PTCco_2$) using properly calibrated and validated equipment. In children, a duration of two missed breaths is used to define a respiratory cycle, instead of the 10-second duration that is used in adults. Therefore an obstructive apnea event is defined as a 90% or greater reduction in the amplitude of airflow (Flow) as measured by oral/nasal thermal sensor, that lasts 90% of a respiratory cycle of two missed breaths, with continued respiratory effort throughout the period of decreased airflow. In defining hypopnea events in children, the 50-3a rule is used exclusively and is modified to include awakening in addition to EEG arousal. Awakening may occur in children before EEG arousal owing to the increased threshold for EEG arousal in children. Thus the 50-3a rule in children could be called the 50-3aa rule, with one *a* standing for *arousal* and another *a* for *awakening*. Using the two missed breaths duration and the 50-3aa rule, an obstructive hypopnea event is defined as a drop of 50% or more in the amplitude of airflow as measured by nasal pressure sensor that lasts for 90% or more of the hypopnea event and is associated with either a 3% or greater drop in Spo_2 or EEG arousal (or awakening).

PSG criteria for OSA diagnosis in children consist of either of two findings:

1. One or more obstructive events per hour of sleep (i.e., an AHI ≥ 1); with obstructive event being defined as obstructive or mixed apnea or obstructive hypopnea
2. Obstructive hypoventilation, manifested by $Paco_2$ greater than 50 mm Hg for more than 25% of sleep time, coupled with snoring, paradoxic thoracoabdominal movement, or flattening of the nasal airway pressure waveform. Proxies for $Paco_2$ include properly calibrated and validated $PETco_2$ or $PTCco_2$ monitors.

Severity assessment of OSA in children is based on a combination of AHI, Spo_2, and clinical findings; and severity of OSA is used as a basis for necessity of treatment.

1. Mild OSA: AHI greater than 4 and no drop in Spo_2. Treatment is indicated if there are daytime consequences, such as sleepiness, hyperactivity, or decreased performance.
2. Moderate OSA: AHI 5 to 10 and/or Spo_2 less than 85%. Most children should be treated.
3. Severe OSA: AHI greater than 10, with Spo_2 less than 85%, and clinical consequences. Treatment is strongly recommended.

Overall frequency of OSA in children is similar to that in adults, with peak prevalence of about 2% to 3% in the age group 2 to 6 years, which coincides with the period of lymphoid hyperplasia, which increases the likelihood of adenotonsillar hypertrophy. Common causes of OSA in children include enlarged tonsils and adenoids, obesity, and congenital abnormalities that affect the head and neck. These include laryngomalacia, Pierre-Robin syndrome, Down syndrome, achondroplasia, spinal muscle atrophy, Prader-Willi syndrome, Klippell-Feil syndrome, and Arnold-Chiari malformation type II. Pathophysiologic and clinical consequences of OSA in children include increased risk for poor growth, failure to thrive, developmental delays, decreased cognitive function, behavioral problems, hyperactivity, obesity, and pulmonary and systemic HTN.

Treatment of OSA in children includes surgery, PAP therapy, and adjunct measures. In children, the variety of congenital syndromes and their comorbidities may require concurrent use of different modes of therapy and may present unique challenges.

Surgical Therapy for OSA in Children

In children, surgical therapy in the form of tonsillectomy and adenoidectomy (T&A) is a first-line therapy because enlarged tonsils and adenoids is the most common cause of OSA. Additional orthopedic or plastic surgery may be required to correct anatomic abnormalities in certain congenital syndromes such as correction of small mandible in Pierre-Robin syndrome or correction of anatomic abnormalities in Klippel-Feil syndrome, which include fusion of cervical vertebrae, cleft palate, and kyphoscoliosis.

PAP Therapy for OSA in Children

Desensitization to PAP therapy in children is important in improving compliance and may have to be initiated prior to pressure titration. Proper functioning of the PAP therapy can be challenged by anatomic difficulties such as short neck in Klippel-Feil syndrome, which can interfere with proper fitting of the PAP device–patient interface.

Adjunct Medical Therapy for OSA in Children

Adjunct therapy includes diet, exercise, avoidance of sedatives, supplemental oxygen, and pharmacologic therapy. In Prader-Willi syndrome, the use of growth hormone (GH) therapy for the treatment of small stature may worsen OSA and necessitate additional titration of the PAP therapy.

CENTRAL SLEEP APNEA SYNDROMES

CSA refers to cessation or decrease in airflow in conjunction with absence or decrease in respiratory effort. This definition of CSA does not differentiate between lack of respiratory muscle activity due to neuronal dysfunction, neuromuscular disease, or musculoskeletal deformities. Because of this lack of differentiation, CSA describes a variety of sleep apneas that are unrelated in their etiology and pathophysiology and can coexist with each other or with other forms of SRBD. In some forms of CSA, there is heightened chemoreceptor sensitivity that produces periodic oscillation between periods of apnea and hyperpnea; these types of CSA tend to attenuate or resolve during REM sleep when chemoreceptor sensitivity is blunted. Treatment of CSA can be quite varied due to the large variety of disorders that can cause CSA. Adjunct medical therapy for treatment of the underlying disorder is the first line of therapy in many medical conditions, including CHF, AF, and chronic renal failure (CRF). Different modes of noninvasive positive pressure ventilation (NIPPV), and even invasive positive pressure ventilation, may be required for the treatment of CSA due to neurologic, neuromuscular, or musculoskeletal disorders. ASV mode is usually effective in patients with respiratory control system instability due to increased respiratory drive or in complex (treatment emergent) CSA. Surgical therapy or other device therapy can be required to treat other underlying disorders of CSA.

CSA With Cheyne-Stokes Breathing

Cheyne-Stokes breathing refers to a periodic breathing pattern in which periods of apnea are followed by periods of hyperpnea, during which tidal volume waxes and wanes in a crescendo–decrescendo pattern. It occurs both during wakefulness and sleep. CSA with Cheyne-Stokes breathing is a CSA that has Cheyne-Stokes breathing pattern, particularly as it appears on PSG.

The central nature of the apnea event is determined based on concurrent reduction or absence both in airflow (Flow), as detected by oral or nasal thermal sensor, and in respiratory effort, as detected on thoracic and abdominal movement (Mvmt) channels. Detecting Cheyne-Stokes breathing pattern depends on detecting a crescendo–decrescendo pattern both in the airflow and respiratory effort channels, which reflect tidal volume, as well as on calculating the frequency of apnea events and the duration of pattern. The criteria for Cheyne-Stokes breathing are as follows:

1. Three or more consecutive cycles of crescendo–decrescendo pattern on the Flow and Mvmt channels; plus either one of the following:

2. A frequency of five or more central apnea or hypopnea events per hour of sleep (i.e., an AHI ≥5)
3. A duration of 10 minutes or more of crescendo–decrescendo pattern on the Flow and Mvmt channels (Fig. 1.8)

Common causes of CSA with Cheyne-Stokes breathing include CHF, AF, and stroke. Other causes of CSA with Cheyne-Stokes breathing include brain injury, CRF, and high-altitude periodic breathing (HAPB). In chronic renal failure, CSA with Cheyne-Stokes breathing is caused mainly by acid-base disturbances and compensatory hyperventilation.

CSA with Cheyne-Stokes breathing in CHF has distinctive diagnostic and prognostic features. While CSA with Cheyne-Stokes breathing is common in CHF, it is not the only SRBD that is encountered. In general, the rule of thirds applies to SRBD in CHF, stating that one-third of CHF patients have CSA with Cheyne-Stokes breathing, one-third have OSA apnea, and one-third have neither. Risk factors for CSA in CHF include male gender, age over 60 years, and baseline hypocapnea. In CHF, the pathophysiologic basis for CSA with Cheyne-Stokes breathing consists of long circulation time due to decreased left ventricular function, decreased oxygen stores due to pulmonary edema, and respiratory center instability due to heightened chemoreceptor responsiveness to CO_2 and O_2. These pathophysiologic features lead to periodic alteration between the periods of hyperventilation and hypocapnia and the periods of apnea and hypoxemia.

These periodic physiologic oscillations are reflected on the PSG by: (1) prominent crescendo–decrescendo pattern of the hyperpnea period, (2) hyperpnea periods that are two to three times as long as apnea periods, (3) duration of the breathing cycle of apnea plus hyperpnea that is 60 seconds or

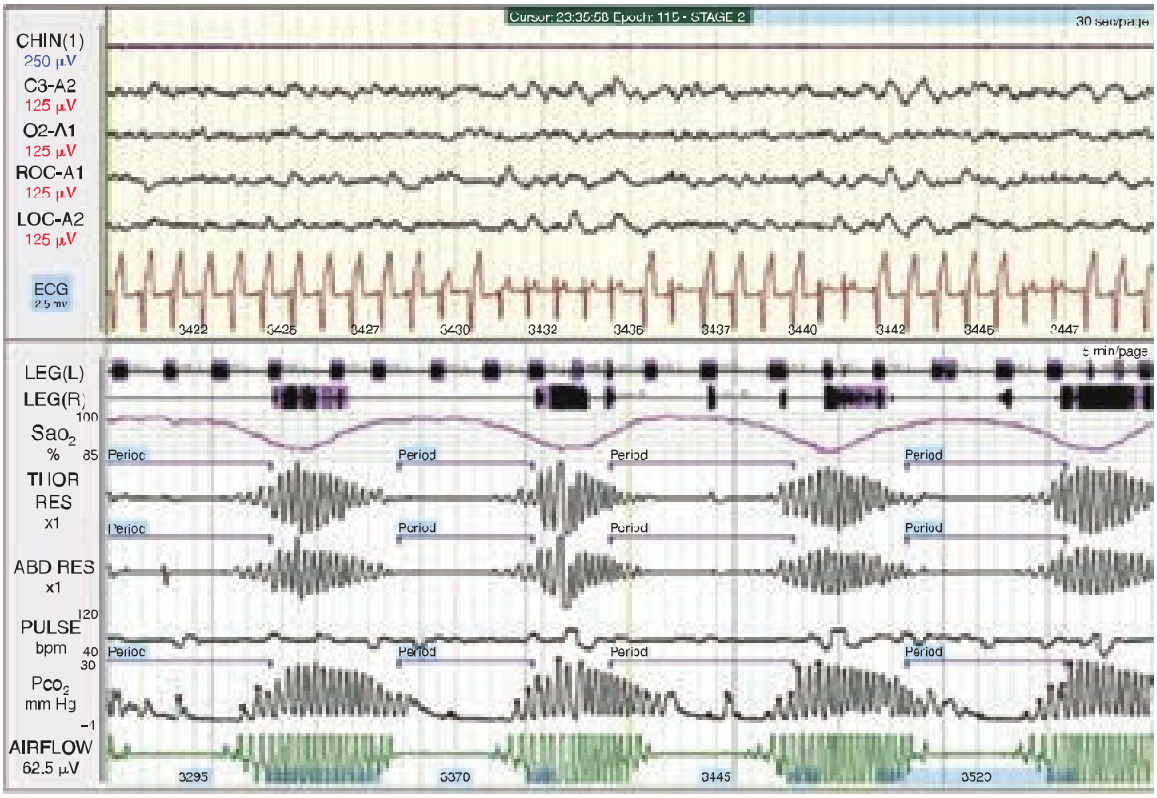

Fig. 1.8 Polysomnography (PSG) features of central sleep apnea with Cheyne-Stokes breathing in a patient with congestive heart failure (CHF). This PSG display is split into upper and lower windows of different durations. The upper window is a 30-second epoch that displays the channels that are used for the recording and staging of sleep: electromyography (EMG), electroencephalography (EEG), electrooculography (EOG), and electrocardiography (ECG). The lower window is a 5-minute epoch that displays the channels that are used to document movement disorders and breathing disorders. Starting from the bottom of the lower window, the airflow channel shows a flow pattern of periodic oscillation between periods of apnea that last more than 10 seconds, and periods of hyperpnea that have crescendo–decrescendo pattern. The Pco_2 channel shows that Pco_2 recordings very slightly lag behind airflow recordings and display an identical periodic oscillation between periods of apnea and hyperpnea. The pulse channel shows heart rate changes that are most prominent at the peak of hyperpnea periods, which usually corresponds with nadir Spo_2 and EEG arousal. The abdominal and thoracic resistance channels show that the apnea events are central apneas since there is no respiratory effort during the apnea periods. These respiratory effort channels demonstrate the same crescendo–decrescendo pattern during the hyperpnea periods, which reflect tidal volume. The Spo_2 channel shows that the nadir Spo_2 level corresponds with the peak of the hyperpnea period and the recovery of Spo_2 occurs during the apnea period. The LEG channels record the occurrence of periodic leg movements (PLMs), which are common in CHF. In the upper window, the ECG channel shows wide complex paced beats and narrow complex irregular beats that represent an underlying atrial fibrillation.

more, and (4) number of breaths per breathing cycle that is 25 or more per cycle.

Correlations exist between physiologic and PSG features. Severity of left ventricular dysfunction (slow circulation time) correlates with prominence of crescendo–decrescendo pattern of the hyperpnea period, duration of hyperpnea period, length of apnea plus hyperpnea cycle, and the delay of nadir Sao_2 to the peak of the hyperpnea period, which also coincides with peak work of breathing (WOB) and EEG arousals. Severity of pulmonary edema (depletion of oxygen stores) correlates with tachypnea (number of breaths per cycle of apnea plus hyperpnea) and severity of heightened chemosensitivity to CO_2 and O_2 with the likelihood of REM sleep-induced resolution of CSA with Cheyne-Stokes breathing. There is also an increased risk of death from CHF if Cheyne-Stokes breathing is present.

Pathophysiologic consequences of CSA with Cheyne-Stokes breathing are the result of prolonged periods of severe hypoxia and severe sleep disruption due to EEG arousal events and periodic leg movement (PLM). CHF and chronic renal failure are associated with high rates of periodic leg movements; and the CRF-associated restless leg syndrome (RLS) is usually difficult to treat. The resulting hypoxia and sleep disruption may increase left ventricular dysfunction, which may further worsen CSA and sleep disruption and result in a vicious perpetuating cycle. Treatment of CSA with Cheyne-Stokes breathing consists of adjunct medical therapy for the treatment of the underlying condition, PAP therapy, and supplemental oxygen. In CSA with Cheyne-Stokes breathing due to CHF, first-tier therapy consists of CPAP therapy and nocturnal oxygen supplementation. This can be augmented with BPAP or drug therapy with acetazolamide and theophylline after medical optimization of CHF. In CSA with Cheyne-Stokes breathing due to CRF, treatment includes CPAP, supplemental oxygen, use of bicarbonate during dialysis, and nocturnal dialysis. Iron supplementation in patients with iron deficiency is an effective adjunct medical therapy in the treatment of RLS.

CSA Due to a Medical Disorder Without Cheyne-Stokes Breathing

Medical conditions associated with this type of CSA include Shy-Drager syndrome, familial dysautonomia, diabetes mellitus, postpolio syndrome, muscular dystrophy, myasthenia gravis, cerebral palsy, spinal muscle atrophy, and kyphoscoliosis. Multiple causes of CSA can coexist as well as multiple types of SRBD.

CSA Due to High-Altitude Periodic Breathing

CSA due to HAPB is usually encountered at altitudes of 7600 m (25,000 ft) or more (but occasionally less). It usually has a periodic pattern of alternating periods of apnea and hyperpnea of 35-second cycle length or less (apnea plus hyperpnea). If the periodic breathing pattern of HAPB meets the criteria of Cheyne-Stokes breathing, then it is called CSA with Cheyne-Stokes breathing due to HAPB.

CSA Due to a Medication or Substance

CSA due to a medication or substance is caused by a medication or substance that suppresses the chemical or neural control of breathing. Long-term opioid use (2-month use of long-acting opioid [e.g., methadone]) is the most common cause of this CSA. Opioids suppress both the chemical and neural control of breathing through -opioid receptors in the medullary pre-Botzinger complex (pre-BOTC), which is the main autonomic respiratory pacemaker. Opioid-induced CSA is more prominent during NREM sleep and may resolve during REM sleep. The severity of opioid-induced CSA correlates with a daily morphine dose equivalent (MDE) of 200 mg or more and with low to normal body mass index (BMI). The two main types of breathing patterns associated with opioid-induced CSA are periodic Biot breathing and irregular ataxic breathing. Biot breathing consists of abruptly alternating periods of apnea and hypopnea (low tidal volume), with background bradypnea (respiratory rate [RR] 10) and periodic hypoxia. It is also encountered in pontine injury and brainstem herniation. Ataxic breathing consists of irregular variations both in tidal volume and respiratory rate, with prolonged apneas and profound hypoxia. Treatment of opioid-induced CSA consists of reducing long-term opioid use and may require providing PAP therapy with ASV mode (Fig. 1.9).

Primary CSA

Primary (idiopathic) CSA is of unknown cause, but it is more common in middle-aged men and possibly associated with nasal obstruction, anxiety, reduced arousal threshold, and insomnia. The pathogenesis includes heightened chemoreceptor response to CO_2 and O_2, which leads to hyperventilation during wakefulness and to ventilatory control system instability during sleep manifesting as periodic alteration between periods of apnea and hyperpnea. Therefore REM sleep, by decreasing chemoreceptor sensitivity to CO_2, may attenuate primary CSA. PSG features that distinguish primary CSA from CSA with Cheyne-Stokes breathing due to CHF include (1) EEG arousal occurs at the end of the apnea period instead of the peak of hyperpnea period, (2) hyperpnea periods have a more abrupt onset and offset pattern instead of the crescendo–decrescendo pattern, (3) duration of a breathing cycle of apnea plus hyperpnea of 30 to 40 seconds instead of 60 to 90 seconds, and (4) number of breaths per cycle usually in the teens instead of the 20s or 30s. Because of heightened chemoreceptor response to CO_2 and O_2 in primary CSA, treatment consists of supplemental oxygen, acetazolamide, and PAP therapy with ASV mode, which can compensate for the respiratory control system instability due to increased respiratory drive.

Primary CSA of Infancy

Primary CSA of infancy refers to apnea episodes that either last 20 seconds or longer or are associated with bradycardia or hypoxia in a newborn infant who is older than 37 weeks gestational age. Under 37 weeks gestational age, this disorder is called primary CSA of prematurity. Differential diagnosis includes normal breathing pauses of newborn, periodic breathing of infancy, congenital central alveolar hypoventilation syndrome (CCAHS), and apparent life-threatening event (ALTE).

Normal breathing pauses of newborn are short central apnea events that are not associated with bradycardia or hypoxia and are common in healthy newborns, especially during active sleep. Periodic breathing of infancy has a Cheyne-Stokes breathing

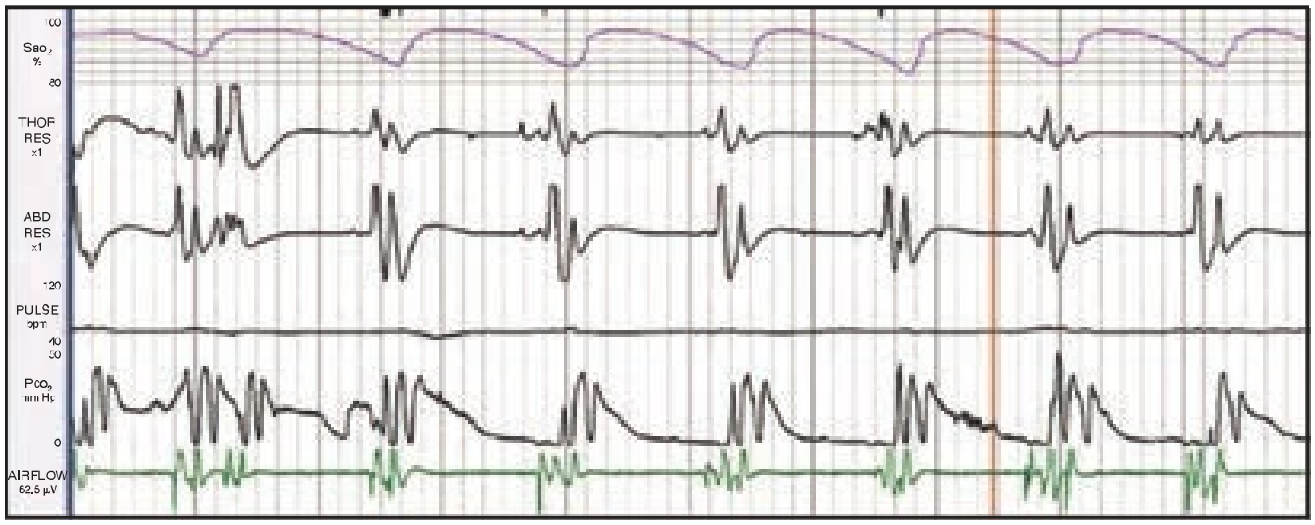

Fig. 1.9 Polysomnography (PSG) features of opioid-induced central sleep apnea (CSA). This is a 5-minute epoch of PSG displaying CSA in a patient with long-term opioid use. The central nature of the apnea events is evident from the coupling of the airflow and respiratory effort. Features of opioid-induced CSA include significant bradypnea (four to five breaths per minute), prolonged apnea periods (≥30 seconds), followed by few breaths (two to three) per cycle length (apnea plus subsequent hypopnea). The nadir oxygen saturation coincides with the breathing periods, and the recovery of oxygen saturation occurs during the apnea period.

pattern, with apnea periods of 3 to 10 seconds and cycle length (apnea plus hyperpnea) of 10 to 18 seconds. It is considered a normal variant if not associated with bradycardia or hypoxia. Congenital central alveolar hypoventilation syndrome is one of the types of sleep-related hypoventilation disorders that is associated with apnea and erratic breathing, which lead to hypoxemia and hypercarbia. ALTE refers to the occurrence of one or more of the quartet of apnea, pallor, hypotonia, or choking, during the first 6 months of infancy. Common etiologies of ALTE include gastroesophageal reflux disorder (GERD), respiratory infections, seizures, other infections, or unknown (20–30%). Hospital admission is recommended after an ALTE to rule out serious conditions. Home apnea monitoring is not recommended as it has not been shown to decrease the risk of sudden infant death syndrome (SIDS). Treatment depends on clinical and PSG findings, and may include theophylline and supplemental oxygen.

Treatment-Emergent CSA

Treatment-emergent, also known as complex, CSA refers to a predominantly CSA pattern that cannot be attributed to morbidity or substance, which emerges during titrating PAP therapy for predominantly OSA with resulting adequate resolution of the OSA. Treatment-emergent CSA may resolve over time once PAP therapy is well established. Persistent treatment-emergent CSA that is due to respiratory control system instability may respond to treatment with PAP therapy with ASV.

SLEEP-RELATED HYPOVENTILATION DISORDERS

Hypoventilation during sleep is defined as sustained (≥10 minutes) Pco_2 elevation (either to >55 mm Hg or to >10 mm Hg above wake supine baseline) as measured by arterial blood gas (ABG), end-tidal CO_2 ($ETCO_2$), or transcutaneous CO_2 ($TCCO_2$). SRHV is commonly a nocturnal exacerbation of diurnal hypoventilation ($Paco_2$ >45 mm Hg). SRHV may be primary (idiopathic) or secondary to neurologic, neuromuscular, or pulmonary disorder. Sleep-related hypoventilation disorders tend to get worse during REM sleep due to REM sleep-induced decreases in muscle tone and chemoreceptor response to hypercarbia. Depending on the underlying cause and coexisting morbidities, treatment of SRHV can include PAP therapy, surgical therapy, and adjunct medical therapy. Patients with instability of the respiratory control system may benefit from ASV mode. Some severe forms of SRHV may require invasive ventilation via tracheostomy. Other forms of surgical therapy and adjunct medical therapies may be required depending on the underlying and comorbid conditions.

Obesity Hypoventilation Syndrome (OHS)

OHS consists of the combination of obesity (BMI >30 kg/m^2), daytime hypoventilation ($Paco_2$ >45 mm Hg), and a SRBD that meets the definition of either OSA (90% of cases) or SRHV (10% of cases). OHS leads to chronic hypoxia and hypercarbia. Common manifestations of OHS-induced hypoxia and hypercarbia include somnolence, muscle twitching, headache, cyanosis, secondary polycythemia, pulmonary HTN, right ventricular hypertrophy, and right ventricular failure (cor pulmonale). It also increases the risk of sudden unexplained nocturnal death syndrome (SUNDS). OHS has an estimated prevalence of 0.15% to 0.3% in the general population, with higher rates among women probably due to higher rates of obesity. Pathogenesis of OHS include decreased chemosensitivity to CO_2, leptin resistance, increased upper airway resistance, increased WOB, and decreased maximal inspiratory and expiratory pressures. OHS is exacerbated both during REM sleep, due to decreased muscle tone and ventilatory response to CO_2, and in

supine position, due to increased UAO by increased pharyngeal extraluminal pressure due to the effect of gravity. Common comorbidities include chronic obstructive pulmonary disease (COPD), overlap syndrome (COPD plus OSA), interstitial lung disease (ILD), drug-induced respiratory depression, amyotrophic lateral sclerosis, spinal cord injury, postpolio syndrome, neuromuscular disorders (NMD), and kyphoscoliosis.

Treatment of OHS includes treatment of coexisting disorders, weight reduction, avoidance of alcohol and other CNS or respiratory depressants, supplemental oxygen for hypoxia (Spo_2 88 for 5 min), and various forms of PAP therapy, including CPAP, BPAP, BPAP with backup rate, and ASV. Patients who have residual daytime sleepiness despite adequate PAP therapy may be treated with CNS stimulants such as modafinil or armodafinil.

Congenital Central Alveolar Hypoventilation Syndrome

CCAHS is a congenital failure of automatic central control of breathing. It manifests during infancy with apnea, hypopnea, and erratic breathing that leads to hypercarbia ($Paco_2$ 45 mm Hg) and hypoxemia (Sao_2 88%), which results, within months, in polycythemia and cor pulmonale. CCAHS is one of the causes of ALTE. The pathogenesis of CCAHS includes blunted hypoxic and hypercapnic responses that lead to hypoventilation that it is worse during sleep than wakefulness. More than 90% of patients have *PHOX2B* gene mutation. Common comorbidities include autonomic dysfunction, aganglionic megacolon (Hirschsprung disease, 20%), and neural crest tumors (neuroblastoma, 5%). The combination of CCAHS and Hirschsprung disease is called Haddad syndrome. PSG study shows apnea and hypopnea events, and continuous hypoventilation, hypercarbia, and hypoxemia. Treatment often requires tracheostomy, ventilatory support, and possibly diaphragmatic pacing.

Late-Onset Central Hypoventilation Syndrome With Hypothalamic Dysfunction (LO-CHS/HD)

LO-CHS/HD refers to cases whose manifestations appear during the first decade of life (late onset) and include hypothalamic dysfunction (usually rapid onset obesity due to hyperphagia) and central hypoventilation syndrome (usually persistent central alveolar hypoventilation without sleep apnea), in addition to autonomic dysfunction (affecting the heart, gastrointestinal system, temperature control, and eye movements), neural crest tumors (neuroblastoma), and neuro-cognitive-behavioral problems. Pathogenesis includes genetic mutations or CNS lesions, including tumor, trauma, infection, or vascular events. Treatment of the hypothalamic dysfunction component includes hormonal replacement, including growth hormone. Treatment for central hypoventilation includes various modes of noninvasive ventilatory support but may include tracheostomy. Treatment of autonomic dysfunction is usually symptomatic but might include permanent pacemaker insertion and strabismus repair surgery. Neural crest tumors usually require surgical resection and adjunct therapy.

Idiopathic Central Alveolar Hypoventilation (ICAH)

ICAH refers to persistent diurnal hypoventilation ($Paco_2$ 45 mm Hg) in the absence of pulmonary pathology with nocturnal exacerbation leading to increased hypercarbia and hypoxia. Treatment consists of PAP therapy (NIPPV), ASV, or even invasive positive pressure therapy via tracheostomy.

SRHV Due to a Medication or Substance

This category refers to hypoventilation that is caused or exacerbated by medications or substances that suppress respiratory drive or cause CNS depression. They include alcohol, opioids, and benzodiazepines. Treatment consists of removing the underlying cause, when possible, and providing supplemental oxygen and ventilatory support.

SRHV Due to a Medical Disorder

Medical disorders that can cause sleep-related hypoventilation include ILD, interstitial pneumonitis, sickle-cell anemia, hemoglobinopathies, chronic obstructive lung disease, emphysema, bronchiectasis, α_1-antitrypsin deficiency, neurologic disorders, neuromuscular disease, and kyphoscoliosis. Treatment consists of treating the underlying cause and providing various forms of NIPPV.

SLEEP-RELATED HYPOXEMIA DISORDER

SRHO disorder refers to sleep-related sustained hypoxia, which is defined as Sao_2 of 88% or less for more than 5 minutes. It is commonly present in conjunction with other SRBD, particularly with SRHV, and represents an exacerbation of diurnal hypoxemia due to cardiopulmonary disease. Sleep-related hypoxemia disorder occurs in Rett syndrome as part of diurnal and nocturnal sleep-related breathing disorder that includes diurnal hyperventilation, prolonged apneas, hypoxemia, and nocturnal CSA. The pathogenesis of SRBD in Rett syndrome consists of abnormal cortical input to the brainstem breathing centers (BBC). Other features of Rett syndrome include seizures and progressive cognitive impairment. Treatment for SRHO disorder includes supplemental oxygen in addition to treating the underlying disorder. Coexisting SRHD is treated with appropriate mode of noninvasive ventilatory support.

ISOLATED SYMPTOMS AND NORMAL VARIANTS

Snoring

Snoring refers to breathing noise produced mostly by vibration of soft tissues in the upper airway during inhalation or exhalation. Habitual snoring refers to snoring that occurs three or more times per week. Snoring is one of the clinical findings that support the diagnosis of OSA in children or adults and is consistently included in questionnaires of OSA. It is the most common cause of referral to PSG sleep studies. It is more common than OSA, with a prevalence of about 20% in preschool children, 30% in pregnant women, and 40% in adults. It is usually reported by the patient's bedmate or captured by sound recording during PSG. In addition, the redness in the pharyngeal

mucosa that is produced by snoring-induced trauma can be detected during routine examination of the oral cavity or during direct or video laryngoscopy. Snoring can be nonapneic (isolated, benign, not associated with OSA) or apneic (associated with OSA). Nonapneic snoring is not associated with the same comorbidities as OSA. However, snoring in pregnant women is associated with increased risk of pregnancy-induced hypertension (PIH) and delivery of a newborn with small size and low Apgar score. Surgical UPPP may alleviate snoring without resolution of OSA if the etiology of OSA is not limited to excessive pharyngeal tissue.

Catathrenia

Catathrenia, which is also called sleep-related groaning, refers to loud humming noise during sleep, usually during exhalation. It can be reported by the patient's bedmate or captured by sound recording during PSG. Catathrenia is categorized as a parasomnia sleep disorder but it can still be mistakenly diagnosed and treated as a form of sleep apnea, even when no clear features of sleep apnea are present. It is more common in women than men. Its treatment is unclear but can include PAP or OA therapy.

EFFECT OF SLEEP ON CONTROL OF BREATHING

Sleep decreases both neural and chemical modulation of breathing. It decreases forebrain regulation of brainstem respiratory centers as well as the ventilatory response to hypoxia and hypercarbia. This blunting of responses is more severe during REM sleep than non-REM sleep, and during phasic REM sleep than during tonic REM sleep. Sleep onset can be associated with irregular breathing, periodic breathing, and sleep-onset apnea. These effects are more prominent during REM sleep, and particularly during phasic REM sleep where breathing becomes irregular, fast, and shallow, with the tidal volume decreasing by 40%. Also, REM sleep decreases the role of respiratory mechanisms in regulating blood pressure, which may explain the association between OSA and HTN as well as the improvement in blood pressure control as a result of OSA treatment with PAP therapy.

Sleep-induced changes in respiratory parameters include increases in airway resistance (↑200%) and in $Paco_2$ (2–8 mm Hg), and decreases in tidal volume, minute ventilation (0.5–1 L/min), CO_2 production (10–15%), Pao_2 (3–10 mm Hg), and chemosensitivity (20–50%), with greater decrease in the chemosensitivity to hypercarbia than to hypoxia, and greater decrease during REM sleep than non-REM sleep (N3).

The sleep-induced blunting of the response to hypercarbia and hypoxia results in nocturnal oxygen desaturation that reaches its nadir during the early morning hours. This desaturation is well tolerated in people with adequate cardiopulmonary reserve but is less so in people with decreased reserve, including the elderly, the patient with severe obesity, and those with cardiopulmonary disease or SRHV or SRHO disorders.

Paradoxically, the sleep-induced blunting of the response to hypercarbia, particularly during REM sleep, may attenuate certain forms of CSA whose mechanisms involves heightened response to hypercarbia such as CSA with Cheyne-Stokes breathing and CSA of HAPB.

CONTROL OF UPPER AIRWAY PATENCY

Upper airway patency is controlled by neural and chemical pathways that are similar to those involved in the control of breathing. The pharynx is devoid of bony support, and its patency is maintained by reflex activation of dilatory muscles that function as respiratory muscles by producing pharyngeal dilation and stiffening during inhalation. UAO and increased resistance to airflow activates three reflexes, all of which stimulate breathing and airway patency: (1) reflex activation of pharyngeal dilatory muscles, (2) reflex activation of thoracic respiratory muscles, and (3) reflex electroencephalographic (EEG) arousal. The main dilatory pharyngeal muscles are the genioglossus (tongue), tensor palatini (soft palate), and stylopharyngeus (pharynx). The genioglossus receives its motor innervation from the hypoglossal nerve (XII), whose activity is modulated by inputs from the cerebral cortex, brainstem breathing centers, wake/sleep pathways, central and peripheral chemoreceptors, and pharyngeal mechanoreceptors.

Reflex EEG arousal is stimulated by chemical and mechanical mechanisms, which consist of (1) hypercapnia, which results in reliable EEG arousal when $Paco_2$ increases by 15 mm Hg or more; (2) hypoxia, which may not result in arousal until Sao_2 is 70% or less; (3) mechanical effort of the respiratory muscles, which is the most reliable stimulator of respiratory-related EEG arousal; and 4) UAO and increased resistance to airflow. Airflow dynamics and lung volume have indirect effects on UAO. Excessive negative airway pressure transmitted to the pharynx promotes pharyngeal collapse, whereas lung expansion promotes pharyngeal dilation by providing longitudinal traction on the pharynx (tracheal tug).

Factors that promote upper airway collapse include (1) decreased muscle tone due to physiologic factors (REM sleep), pathologic factors (neural or neuromuscular disorder), or pharmacologic factors (alcohol); (2) increased negative pressure inside the airway; (3) increased positive pressure outside the airway; (4) mechanical compression such as that produced by enlarged tonsils, pharyngeal fat pads, or cervical subcutaneous fat.

EFFECT OF SLEEP ON CONTROL OF UPPER AIRWAY PATENCY

UAO contributes to sleep-induced increase in airway resistance by over 200%. Sleep, and in particular REM sleep, decreases both reflex activation of pharyngeal dilator muscles and respiratory-related EEG arousal. REM sleep, more than NREM sleep, blunts all four mechanisms of respiratory-related EEG arousal: UAO, increased respiratory effort, hypercarbia, and hypoxia. The speed of the EEG arousal in response to UAO during REM sleep and non-REM sleep is inversed between persons with or without OSA. In persons without OSA, UAO-induced EEG arousal is faster during REM sleep than non-REM sleep. In patients with OSA, UAO-induced EEG arousal is slower during

REM sleep than non-REM sleep. This difference in speed of EEG arousal response contributes to the increased severity of OSA during REM sleep and adds to other deleterious effects of REM sleep on respiratory modulation, including blunting of neural and chemical modulation of breathing and the decreased contribution of accessory respiratory muscles due to REM sleep–induced skeletal muscle hypotonia.

PERIOPERATIVE CONSIDERATIONS IN PATIENTS WITH SRBD

The prevalence of OSA among surgical patients is higher than the overall prevalence of 2% to 4% in the general population, and it can approach 8%. The perioperative period can exacerbate SRBD due to sleep deprivation and disruption due to anxiety, pain, alterations in circadian rhythms, and nursing interventions; REM sleep rebound, which worsens OSA; and the suppressant effects of anesthetics, sedatives, and analgesics on airway patency, respiratory drive, and EEG arousal. The effect of sleep-disordered breathing on perioperative outcomes has been the subject of many observational studies and systematic reviews, with conflicting findings based on study population, examined outcomes, and study design. The evidence is, however, mostly negative.

PRACTICE GUIDELINES FOR PERIOPERATIVE MANAGEMENT OF PATIENTS WITH OSA

The American Academy of Sleep Medicine, the American Society of Anesthesiologists (ASA), the Society for Ambulatory Anesthesia (SAMBA), and the Society of Anesthesia and Sleep Medicine (SASM) have all created practice parameters for the perioperative management of patients with OSA.

In 2006, the ASA developed comprehensive practice guidelines for the perioperative management of OSA patients and updated them in 2014. These guidelines provide a checklist for preoperative identification and assessment of OSA and detailed recommendations covering the areas of preoperative evaluation, considerations for inpatient versus outpatient surgery, preoperative preparation, intraoperative management, postoperative management, and criteria for discharge to unmonitored settings. In 2012, SAMBA produced a consensus statement on preoperative selection of adult patients with OSA scheduled for ambulatory surgery, which concluded that patients with known OSA might be considered for ambulatory surgery if they were medically optimized and could use their CPAP postoperatively, whereas patients with presumed OSA could be considered for ambulatory surgery if they could be managed with nonopioid analgesia perioperatively.

In 2016, SASM issued guidelines for preoperative screening and assessment of adult patients with OSA. It included three strong recommendations based on moderate evidence: (1) consider patients with OSA to be at increased risk of perioperative complications; (2) screening tools can be used to identify patients with suspected OSA; and (3) PAP devices should be used at appropriate times perioperatively.

The elements of the practice parameters for perioperative care of patients with OSA are noted in Table 1.1.

TABLE 1.1 Perioperative Management of the Patient With Obstructive Sleep Apnea (OSA)

Potential Source of Perioperative Risk	Perioperative Risk Mitigation
Lack of institutional protocol for perioperative management of sleep apnea patients	Develop and implement institutional protocol for perioperative management of sleep apnea patients
Diagnosed OSA patients	Know patient's polysomnography (PSG) study results Know patient's OSA therapy, including surgery, oral appliance (OA), or positive airway pressure (PAP) therapy, with settings (mode, pressure level, and O_2, if any) Consult sleep medicine specialist as needed
Undiagnosed OSA patient	Use a screening tool to determine the likelihood of OSA: AASM questionnaire, ASA checklist, Berlin questionnaire or STOP-Bang
Inpatient versus outpatient	Develop institutional protocol based on factors related to patient, procedure, facility, and postdischarge setting
Preoperative lack of optimization of therapy of OSA	Consult a sleep medicine specialist to optimize therapy
Preoperative sedative-induced airway compromise and respiratory depression	Use preoperative sedation only in monitored setting
Intraoperative sedative/opioid/anesthetic-induced upper airway compromise and respiratory depression during monitored anesthesia care (MAC) cases	Whenever possible, use topical, local, or regional anesthesia (RA) with minimal to no sedation Continuously monitor ventilation when sedation is used Allow patient to use own OSA therapy device during MAC with sedation Consider the option of general anesthesia with secure airway versus that of deep sedation with unsecure airway
At risk for oxygen desaturation	Optimize head and neck position to facilitate spontaneous ventilation/oxygenation Preoxygenate early and sufficiently Maintain oxygen insufflation by nasal cannula during endotracheal intubation
Possibly difficult mask ventilation or endotracheal intubation	Apply ASA difficult airway algorithm including the use of laryngeal mask airway (LMA), video laryngoscope (VL), fiber-optic bronchoscope (FOB), and transtracheal jet ventilation (TTJV), as indicated Optimize head/neck position for mask ventilation and endotracheal intubation Use two-person mask ventilation as needed

TABLE 1.1 Perioperative Management of the Patient With Obstructive Sleep Apnea (OSA)—cont'd

Potential Source of Perioperative Risk	Perioperative Risk Mitigation
Potential difficulty with noninvasive monitoring of blood pressure	Consider intraarterial catheter insertion for blood pressure monitoring and blood sampling for arterial blood gases analysis
Increased risk for cardiovascular complications	
Postextubation airway obstruction in the operating room or postanesthesia care unit with associated risk of negative pressure pulmonary edema	Whenever possible, elevate the head of the bed Extubate only after patient clearly meets objective extubation criteria Maintain oxygen insufflation by nasal cannula throughout extubation Maintain readiness for reintubation with the same devices used during induction, and expecting that the difficulty of intubation would be greater than previously
At risk for postoperative oxygen desaturation	Maintain supplemental oxygen therapy Consider nasal airway Consider PAP therapy, which can be initiated de novo in the postoperative setting
Communication failure during transfer of care	Communicate the patient's diagnosis of sleep apnea and its therapy Alert staff about expected problems and their management
Perioperative opioid-induced ventilatory impairment (OIVI) due to opioids administered by neuraxial route, intravenous route with bolus injection, or via intravenous patient-controlled analgesia (IV-PCA)	Use continuous electronic monitoring of oxygenation and ventilation when either neuraxial or IV-PCA opioids are used Use supplemental oxygen as needed Maintain patient's OSA device therapy as needed and use home settings as a guide Avoid background mode on IV-PCA Consider opioid-sparing analgesic techniques (transcutaneous electrical nerve stimulation) and use nonopioid analgesics (nonsteroidal antiinflammatory drugs, acetaminophen, tramadol, ketamine, gabapentin) whenever possible Have naloxone ready for the treatment of OIVI
Postdischarge OIVI and exacerbation of OSA	Ensure companionship and safe home settings for high-risk patients Consult sleep medicine specialist to optimize OSA therapy as needed

AASM, American Academy of Sleep Medicine; *ASA*, American Society of Anesthesiologists.

KEY POINTS

- The hallmark of obstructive sleep apnea (OSA) is sleep-induced and arousal-relieved upper airway obstruction (UAO).
- Functional collapse of the upper airway occurs when forces that can collapse the upper airway overcome the forces that can dilate the upper airway. Collapsing forces consist of intraluminal negative inspiratory pressure and extraluminal positive pressure. Dilating forces consist of pharyngeal dilating muscle tone and longitudinal traction on the upper airway by an increased lung volume, the so-called tracheal tug.
- Apneic and hypopneic episodes result in hypoxia, which can be prolonged and severe. OSA-induced hypoxia and reoxygenation cycles activate redox-sensitive genes, oxidative stress, inflammatory processes, the sympathetic nervous system, and the coagulation cascade, all of which can contribute to endothelial dysfunction and ultimately to systemic HTN, pulmonary HTN, atherosclerosis, right and left ventricular systolic and diastolic dysfunction, coronary artery disease, CHF, atrial fibrillation, stroke, and sudden cardiac death.
- Polysomnography can be used to differentiate CSA from OSA, assess its severity, detect associated hypoventilation and hypoxia, detect associated EEG, ECG, and limb movement events, and, when indicated, titrate positive airway pressure (PAP) therapy and perform follow-up assessment of any implemented therapy for the SRBD.
- Because of its high prevalence rate and a general lack of diagnosis, the first step in management of OSA is detection.
- Suggested mechanisms for the efficacy of continuous PAP therapy include (1) increasing the pharyngeal transmural pressure (pneumatic splint effect), (2) reducing pharyngeal wall thickness and airway edema, (3) increasing airway tone by mechanoreceptor stimulation, and (4) increasing end-expiratory lung volume and producing a tracheal tug effect.
- Central sleep apnea refers to sleep apnea that is not associated with respiratory efforts during the apnea event. This absence of respiratory effort could be due to instability of neural control of respiration, weakness of respiratory muscles, or both. Instability of respiratory control may include increased, decreased, or oscillating respiratory drive.
- The perioperative period can exacerbate SRBD because of (1) sleep deprivation due to anxiety, pain, alterations in circadian rhythms, and nursing interventions; (2) REM sleep rebound, which worsens OSA; and (3) the suppressant effects of anesthetics, sedatives, and analgesics on airway patency, respiratory drive, and arousal.

RESOURCES

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2

Anesthetic Considerations for Obstructive Lung Disease

Jing Tao, Viji Kurup

OUTLINE

Obstructive respiratory diseases are an important factor contributing to increased risk of perioperative pulmonary complications. There is increasing awareness of how these complications contribute to overall morbidity, mortality, and increased hospital length of stay. Perioperative pulmonary complications can also play an important role in determining long-term mortality after surgery. Modification of disease severity and patient optimization prior to surgery can significantly decrease the incidence of these complications.

Obstructive respiratory diseases can be divided into the following groups for discussion of their influence on anesthetic management:

1. Acute upper respiratory tract infection (URI)
2. Asthma
3. Chronic obstructive pulmonary disease (COPD)
4. Miscellaneous respiratory disorders

ACUTE UPPER RESPIRATORY TRACT INFECTION

There are approximately 37 million visits to ambulatory care centers because of URIs. Adults between the ages of 25 and 44 experience the "common cold" at a rate of 18.7/100 persons per year. Adults between the ages of 45 and 65 experience it at a rate of 16.4/100 persons per year. As such, it is likely there will be a population of patients scheduled for elective surgery who have an active URI.

Infectious (viral or bacterial) nasopharyngitis accounts for about 95% of all URIs, with the most common responsible viral pathogens being rhinovirus, coronavirus, influenza virus, parainfluenza virus, and respiratory syncytial virus (RSV). Noninfectious nasopharyngitis can be allergic or vasomotor in origin.

Signs and Symptoms

Most common symptoms of acute URI include nonproductive cough, sneezing, and rhinorrhea. A history of seasonal allergies may indicate an allergic cause of these symptoms rather than an infectious cause. Symptoms caused by bacterial infections will usually present with more serious signs and symptoms such as fever, purulent nasal discharge, productive cough, and malaise. Such patients may be febrile, tachypneic, wheezing, or have a toxic appearance.

Diagnosis

Diagnosis is usually based on clinical signs and symptoms. Viral cultures and laboratory tests lack sensitivity, are time and cost

consuming, and are therefore impractical in a busy clinical setting.

Management of Anesthesia

Most studies regarding the effects of URI on postoperative pulmonary complications have involved pediatric patients. It is well known that children with a URI are at much higher risk of perioperative respiratory adverse events (PRAE) such as transient hypoxemia and laryngospasm, breath holding, and cough if they are anesthetized while suffering a URI. However, there are limited data about the adult population in this regard. There is evidence to show an increased incidence of respiratory complications in pediatric patients with a history of copious secretions, prematurity, parental smoking, nasal congestion, reactive airway disease, endotracheal intubation, and in those undergoing airway surgeries. Those with clear systemic signs of infection such as fever, purulent rhinitis, productive cough, and rhonchi who are undergoing elective surgery (particularly airway surgery) are at considerable risk of PRAE. Other risk factors that increase incidence of PRAE are airway surgery, secondhand smoke exposure, history of prematurity, and endotracheal intubation. Consultation with the surgeon regarding the urgency of the surgery is necessary. A patient who has had a URI for days or weeks and is in stable or improving condition can be safely managed without postponing surgery. If surgery is to be delayed, patients should not be rescheduled for about 6 weeks because some studies indicate that airway hyperreactivity may persist for that duration. The economic and practical aspects of canceling surgery should also be taken into consideration before a decision is made to postpone surgery. A scoring system for risk stratification of these patients has been proposed. The COLDS scoring system includes current signs and symptoms (higher risk with severe symptoms), onset of symptoms (higher risk ⊥2 weeks ago), presence of lung diseases (higher risk with moderate or severe disease), airway device (higher risk with endotracheal tube [ETT]), and surgery (higher risk with major airway surgery). Initial studies demonstrate its utility in predicting PRAE and possibly as a decision aid in proceeding with surgery in a patient with URI.

Viral infections, particularly during the infectious phase, can cause morphologic and functional changes in the respiratory epithelium. The relationship between epithelial damage, viral infection, airway reactivity, and anesthesia remains unclear. Tracheal mucociliary flow and pulmonary bactericidal activity can be decreased by general anesthesia. It is possible that positive pressure ventilation could help spread infection from the upper to the lower respiratory tract. The immune response of the body is altered by surgery and anesthesia. A reduction in B-lymphocyte numbers, T-lymphocyte responsiveness, and antibody production may be associated with anesthesia, but the clinical significance of this remains to be elucidated.

The anesthetic management of a patient with URI should include adequate hydration, reducing secretions, and limiting manipulation of a potentially sensitive airway. Nebulized or topical local anesthetic applied to the vocal cords may reduce upper airway sensitivity. Use of a laryngeal mask airway (LMA) rather than an ETT may also reduce the risk of laryngospasm. URIs may increase the risk of PRAE during procedural sedation with an increased need for airway interventions in these patients. Considerations for induction and maintenance are similar to those for patients with asthma in this population of patients. When there are no contraindications, deep extubation may result in smoother emergence.

Adverse respiratory events in patients with URIs include bronchospasm, laryngospasm, airway obstruction, postintubation croup, desaturation, and atelectasis. Intraoperative and immediate postoperative hypoxemia are common and amenable to treatment with supplemental oxygen. Long-term complications have not been demonstrated.

ASTHMA

Asthma is one of the most common chronic medical conditions in the world and currently affects approximately 334 million people globally. Although prevalence continues to be highest in developed countries, occurrence is rapidly rising in developing countries due to urbanization and air pollution.

Asthma is a disease of reversible airflow obstruction characterized by bronchial hyperreactivity, bronchoconstriction, and chronic airway inflammation. Development of asthma is multifactorial and includes genetic and environmental causes. It seems likely that various genes contribute to development of asthma and determine the severity of asthma in an individual. A family history of asthma, maternal smoking during pregnancy, viral infections (especially with rhinovirus and infantile RSV), and limited exposure to highly infectious environments as a child (i.e., farms, daycare centers, and pets) all contribute to the development of asthma. A list of some stimuli that can provoke an episode of asthma is provided in Table 2.1.

The pathophysiology of asthma is a specific chronic inflammation of the mucosa of the lower airways. Activation of the inflammatory cascade leads to infiltration of the airway mucosa with eosinophils, neutrophils, mast cells, T cells, B cells, and leukotrienes. This results in airway edema, particularly in the bronchi. There is also airway remodeling that leads to thickening of the basement membrane and smooth muscle mass. The inflammatory mediators implicated in asthma include histamine, prostaglandin D_2, and leukotrienes.

TABLE 2.1 Stimuli Provoking Symptoms of Asthma

Allergens
Pharmacologic agents: aspirin, antagonists, some nonsteroidal antiinflammatory drugs, sulfiting agents
Infections: respiratory viruses
Exercise: attacks typically follow exertion rather than occurring during it
Emotional stress: endorphins and vagal mediation

Signs and Symptoms

Asthma is an episodic disease with acute exacerbations interspersed with symptom-free periods. Clinical manifestations of asthma include expiratory wheezing, productive or nonproductive cough, dyspnea, chest discomfort or tightness that may lead to air hunger, and eosinophilia. Most attacks are short lived, lasting minutes to hours, and clinically the person recovers completely after an attack. However, there can be a phase in which a patient experiences some degree of airway obstruction daily. This phase can be mild, with or without superimposed severe episodes, or much more serious, with significant obstruction persisting for days or weeks. Status asthmaticus is defined as life-threatening bronchospasm that persists despite treatment. When the history is elicited from someone with asthma, attention should be paid to factors such as previous intubation or admission to the intensive care unit (ICU), two or more hospitalizations for asthma in the past year, and the presence of significant coexisting diseases.

Diagnosis

The diagnosis of asthma depends on clinical history, symptoms, signs, and objective measurements of airway obstruction. Asthma is diagnosed when a patient reports symptoms such as wheezing, chest tightness, or shortness of breath and demonstrates airflow obstruction on pulmonary function testing that is at least partially reversible with bronchodilators. Classification of asthma severity depends on the clinical symptoms, pulmonary function test, and medication usage (Tables 2.2 and 2.3).

Pulmonary Function Testing

Forced expiratory volume in 1 second (FEV_1), forced expiratory flow (FEF), midexpiratory phase flow ($FEF_{25\%-75\%}$ [also called maximum midexpiratory flow rate]), and peak expiratory flow rate (PEFR) are direct measures of the severity of expiratory airflow obstruction (Fig. 2.1). These measurements provide objective data that can be used to assess the severity and monitor the course of an exacerbation of asthma. The typical asthmatic patient who comes to the hospital for treatment has an FEV_1 that is less than 35% of normal. Flow-volume loops show characteristic downward scooping of the expiratory limb of the loop. Flow-volume loops in which the inhaled or exhaled portion of the loop is flat help distinguish wheezing caused by airway obstruction (i.e., due to a foreign body, tracheal stenosis, or mediastinal tumor) from asthma (Figs. 2.2 and 2.3). During moderate or severe asthmatic attacks, the functional residual capacity (FRC) may increase substantially, but total lung capacity (TLC) usually remains within the normal range. Diffusing capacity for carbon monoxide is not changed. Bronchodilator responsiveness provides supporting evidence if asthma is suspected on clinical grounds. In patients with expiratory airflow obstruction, an increase in airflow after inhalation of a bronchodilator suggests asthma. Abnormalities in pulmonary function test (PFT) results may persist for several days after an acute asthmatic attack despite the absence of symptoms. Since asthma is an episodic illness, its diagnosis may be suspected even if PFT results are normal.

TABLE 2.2 Most Clinically Useful Spirometric Tests of Lung Function

Forced expiratory volume in 1 sec (FEV1): The volume of air that can be forcefully exhaled in 1 sec. Values between 80% and 120% of the predicted value are considered normal.

Forced vital capacity (FVC): The volume of air that can be exhaled with maximum effort after a deep inhalation. Normal values are ≈ 3.7 L in females and ≈ 4.8 L in males.

Ratio of FEV1 to FVC: This ratio in healthy adults is 75%–80%.

Forced expiratory flow at 25%–75% of vital capacity (FEF25%-75%): A measurement of airflow through the midpoint of a forced exhalation.

Maximum voluntary ventilation (MVV): The maximum amount of air that can be inhaled and exhaled within 1 min. For patient comfort, the volume is measured over a 15-sec time period and results are extrapolated to obtain a value for 1 min expressed as liters per minute. Average values for males and females are 140–180 and 80–120 L/min, respectively.

Diffusing capacity (DLCO): The volume of a substance (carbon monoxide [CO]) transferred across the alveoli into blood per minute per unit of alveolar partial pressure. CO is rapidly taken up by hemoglobin. Its transfer is therefore limited mainly by diffusion. A single breath of 0.3% CO and 10% helium is held for 20 sec. Expired partial pressure of CO is measured. Normal value is 17–25 mL/min/mm Hg.

Arterial Blood Gas Analysis

Mild asthma is usually accompanied by a normal Pao_2 and $Paco_2$. Tachypnea and hyperventilation observed during an acute asthmatic attack do not reflect arterial hypoxemia but rather neural reflexes in the lungs. Hypocarbia and respiratory alkalosis are the most common arterial blood gas findings in the presence of asthma. As the severity of expiratory airflow obstruction increases, the associated ventilation/perfusion mismatching may result in a Pao_2 of less than 60 mm Hg while breathing room air. The $Paco_2$ is likely to increase when the FEV_1 is less than 25% of the predicted value. Fatigue of the skeletal muscles necessary for breathing may contribute to the development of hypercarbia.

Chest Radiography and Electrocardiography

A chest radiograph in a patient with mild or moderate asthma even during an asthma exacerbation is often normal. Patients with severe asthma may demonstrate hyperinflation and hilar vascular congestion due to mucous plugging and pulmonary hypertension. Chest x-rays can be helpful in determining the cause of an asthma exacerbation and in ruling out other causes of wheezing. The electrocardiogram (ECG) may show evidence of right ventricular strain or ventricular irritability during an asthmatic attack.

The differential diagnosis of asthma includes viral tracheobronchitis, sarcoidosis, rheumatoid arthritis with bronchiolitis, extrinsic compression (thoracic aneurysm, mediastinal neoplasm) or intrinsic compression (epiglottitis, croup) of the upper airway, vocal cord dysfunction, tracheal stenosis, chronic bronchitis, COPD, and foreign body aspiration. Upper airway obstruction produces a characteristic flow-volume loop (see Fig. 2.3A). A history of recent trauma, surgery, or tracheal intubation may be present in patients with upper airway obstruction mimicking asthma. Congestive heart failure and pulmonary embolism may also cause dyspnea and wheezing.

TABLE 2.3 Classification of Asthma Severity in Youths Older Than 12 Years and in Adults

Components of Severity		Classification of Asthma Severity (Youths ≥ 12 years of age and adults)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment Normal FEV_1:FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%	Symptoms	≤ 2 days/week	> 2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤ 2x/month	3–4x/month	> 1x/week but not nightly	Often 7x/week
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤ 2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 > 80% predicted • FEV_1:FVC normal	• FEV_1 < 80% predicted • FEV_1:FVC normal	• FEV_1 > 60% but < 80% predictec • FEV_1:FVC reduced 5%	• FEV_1 < 60% predicted • FEV_1:FVC reduced > 5%
Risk	Exacerbations (consider frequency and severity)	0–2/year >2/year → ← Frequency and severity may fluctuate over time for patients in any severity category → Relative annual risk of exacerbations may be related to FEV_1.			

From National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (EPR3)*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007.

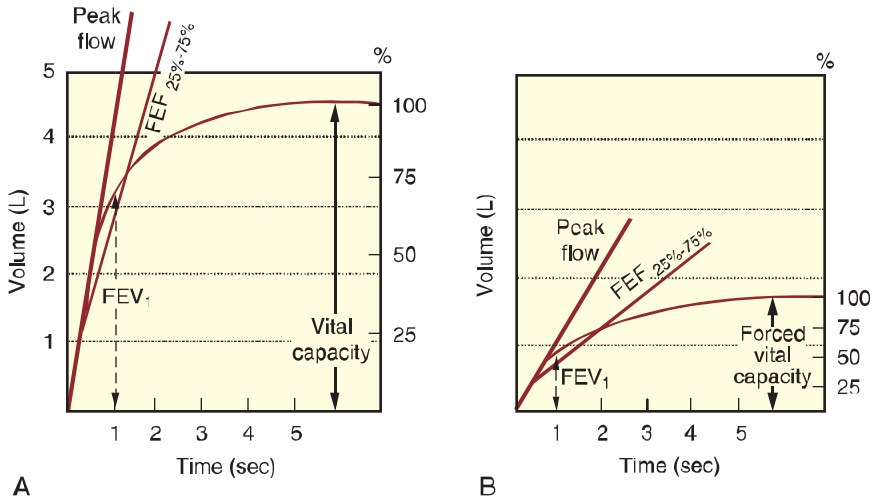

Fig. 2.1 Spirographic changes of a healthy subject (A) and a patient in bronchospasm (B). The forced expiratory volume in 1 second (FEV_1) is typically less than 80% of the vital capacity in the presence of obstructive airway disease. Peak flow and maximum midexpiratory flow rate ($FEF_{25\%-75\%}$) are also decreased in these patients (B). (Adapted from Kingston HGG, Hirshman CA. Perioperative management of the patient with asthma. *Anesth Analg*. 1984;63:844–855.)

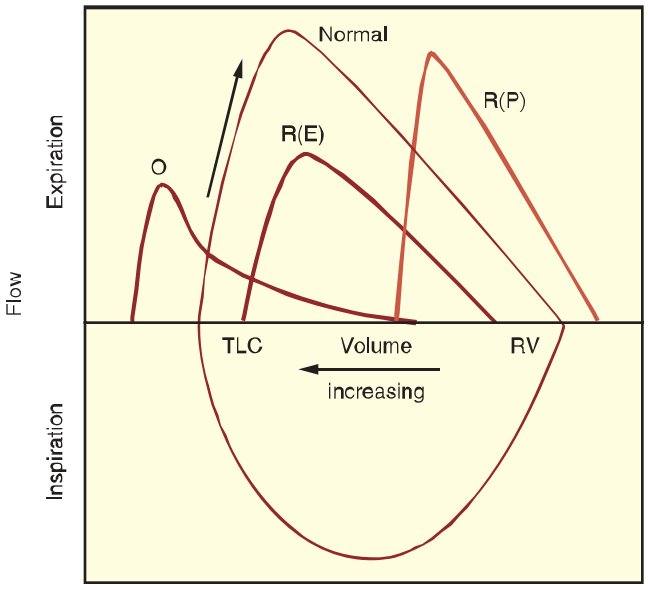

Fig. 2.2 Flow-volume curves in different conditions: obstructive disease *(O)*; extraparenchymal restrictive disease with limitation in inspiration and expiration *[R(E)]*; and parenchymal restrictive disease *[R(P)]*. Forced expiration is plotted for all conditions; forced inspiration is shown only for the normal curve. By convention, lung volume increases to the left on the abscissa. The arrow alongside the normal curve indicates the direction of expiration from total lung capacity *(TLC)* to residual volume *(RV)*. (Adapted from Weinberger SE. Disturbances of respiratory function. In: Fauci B, Braunwald E, Isselbacher KJ, et al., eds. *Harrison's Principles of Internal Medicine*. 14th ed. New York: McGraw-Hill; 1998.)

Treatment

Aim of asthma treatment lies in controlling symptoms and reducing exacerbations. Short-acting inhaled β_2 agonist (i.e., albuterol) is usually first-line treatment in patients with mild asthma. However, this is only recommended in patients with less than twice-a-month symptoms and who have no risk factors for exacerbations. Following short-acting β_2 agonist, daily inhaled corticosteroids have been shown to improve symptoms, reduce exacerbations, and decrease risk of hospitalization. If symptoms remain uncontrolled, daily inhaled β_2 agonist can be added to inhaled corticosteroids. Neither drug should be used in times of acute exacerbation. Other supplemental therapies include inhaled long-acting muscarinic antagonists, leukotriene modifiers, and mast cell stabilizers. Omalizumab, the first antiimmunoglobulin E (anti-IgE) monoclonal antibody approved for moderate to severe allergic asthma, has also been shown to reduce exacerbations and hospitalizations in adults and children. In patients with severe eosinophilic asthma, anti-interleukin-5 (anti-IL5) and anti-IL5 receptor medication can be used. Systemic corticosteroids are usually reserved for patients with severe asthma, uncontrolled with inhalational medication. Systematic reviews on the topic indicate that subcutaneous immunotherapy decreases use of long-term medications and may improve quality of life and subjective symptoms. A full list of pharmacologic therapy can be found in Tables 2.4 and 2.5.

Bronchial thermoplasty (BT) is a recently approved and only nonpharmacologic treatment used for refractory severe asthma. BT uses bronchoscopy guidance to deliver radiofrequency ablation of airway smooth muscles to all lung fields except the right middle lobe. The procedure is performed in three sessions and uses intense heat, which carries a risk of airway fire. Loss of airway smooth muscle mass is thought to lessen rates of bronchoconstriction. Serial determination of PFTs can be useful for monitoring the response to treatment. When the FEV_1 improves to about 50% of normal, patients usually have minimal or no symptoms.

Acute Severe Asthma

Acute severe asthma, previously called status asthmaticus, is defined as bronchospasm that does not resolve despite usual treatment and is considered life threatening. Emergency

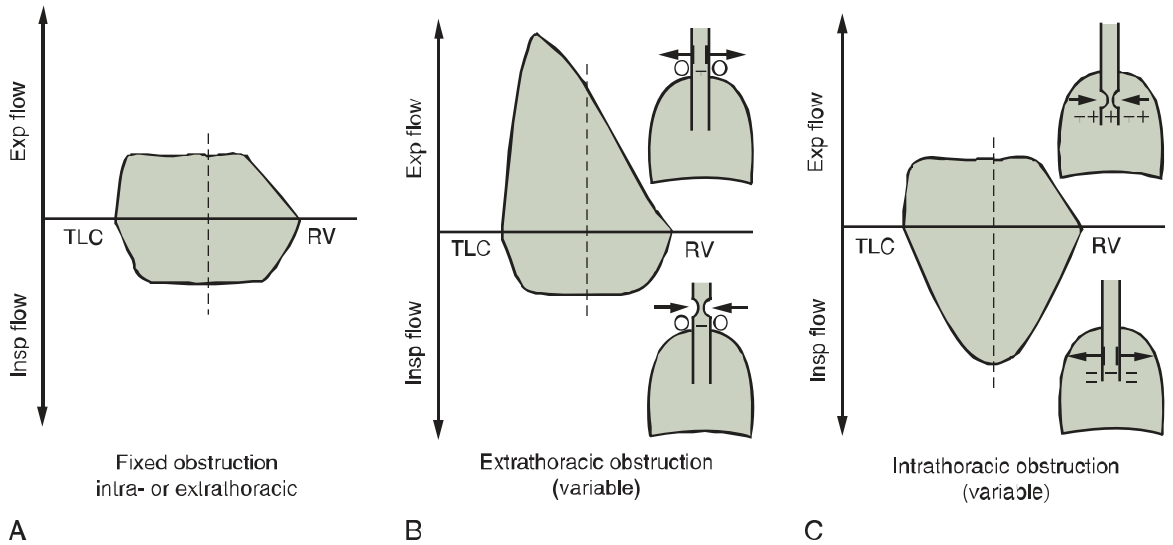

Fig. 2.3 Flow-volume curves in fixed and variable obstruction. (A) Fixed obstruction, intrathoracic or extrathoracic. (B) Extrathoracic obstruction (variable). (C) Intrathoracic obstruction (variable). *Exp*, Expiratory; *Insp*, inspiratory; *RV*, residual volume; *TLC*, total lung capacity. (Adapted from Benumof J, ed. *Anesthesia for Thoracic Surgery*. 2nd ed. Philadelphia: Saunders; 1995.)

TABLE 2.4 Short-Acting Bronchodilators Used for Immediate Relief of Asthma

Drug	Action	Adverse Effects
Albuterol (Proventil) Levalbuterol (Xopenex) Metaproterenol Pirbuterol (Maxair)	β_2-agonist: stimulates β_2 receptors in tracheobronchial tree	Tachycardia Tremors Dysrhythmias Hypokalemia

treatment consists of high-dose, short-acting β_2 agonists and systemic corticosteroids. β_2 agonists inhaled via a metered-dose inhaler (MDI) can be administered every 15 to 20 minutes for several doses without significant adverse hemodynamic effects, although patients may experience unpleasant sensations resulting from adrenergic overstimulation. Continuous administration of β_2 agonists by nebulizer may be more effective for delivery of these drugs to relieve airway spasm. Intravenous (IV) corticosteroids are administered early in treatment because it takes several hours for their effect to appear. The corticosteroids most commonly used are hydrocortisone and methylprednisolone (e.g., 80 mg IV q8h). Supplemental oxygen is administered to help maintain arterial oxygen saturation above 90%. If respiratory failure occurs, mechanical ventilation should be initiated. Other drugs used in more intractable cases include magnesium and oral leukotriene inhibitors. The National Asthma Education and Prevention Program Expert Panel always has the most recent evidence-based guidelines for treatment of asthma on its website (http://www.nhlbi.nih.gov/about/org/naepp/).

Measurements of lung function can be very helpful in assessing the severity of disease and the response to treatment. Patients whose FEV_1 or PEFR is decreased to 25% of normal or less are at risk of developing hypercarbia and respiratory failure. The presence of hypercarbia (defined as a $Paco_2$ > 50 mm Hg) despite aggressive antiinflammatory and bronchodilator therapy is a sign of respiratory fatigue that requires tracheal intubation

TABLE 2.5 Drugs Used for Long-Term Treatment of Asthma

Class	Drug	Action	Adverse Effects
Inhaled corticosteroids	Beclomethasone Budesonide (Pulmicort) Ciclesonice Flunisolide Fluticasone (Flovent) Mometasone Triamcinolone	Decrease airway inflammation Reduce airway hyperresponsiveness	Dysphonia Myopathy of laryngeal muscles Oropharyngeal candidiasis
Combined inhaled corticosteroids long-acting bronchodilators	Budesonide + formoterol (Symbicort) Fluticasone + salmeterol (Advair) Fluticasone furoate + vilanterol (Breo) Fluticasone + formoterol (Trimbrow)	Combination of long-acting bronchodilator and inhaled corticosteroid	Minimal
Leukotriene modifiers	Montelukast (Singulair) Zafirlukast (Accolate) Zileuton (Zyflo)	Reduce synthesis of leukotrienes by inhibiting 5-lipoxygenase enzyme	Minimal
Anti-IgE monoclonal antibody	Omalizumab (Xolair)	Decreases IgE release by inhibiting binding of IgE to mast cells and basophils	Injection site reaction Arthralgia Sinusitis Pharyngitis Headache
Anti-IL5 and anti-IL5 receptor monoclonal antibody	Mepolizumab Reslizumab Benralizumab	Targets IL5 to prevent activation of eosinophils	Injection site reaction Headache
Methylxanthines	Theophylline Aminophylline	Increase cAMP by inhibiting phosphodiesterase, block adenosine receptors, release endogenous catecholamines	Disrupted sleep cycle Nervousness Nausea/vomiting, anorexia Headache Dysrhythmias
Mast cell stabilizer	Cromolyn	Inhibit mediator release from mast cells, membrane stabilization	Cough Throat irritation

cAMP, Cyclic adenosine monophosphate; *IgE*, immunoglobulin E.

and mechanical ventilation. The pattern of mechanical ventilation can be particularly important in the patient with acute severe asthma. The expiratory phase must be prolonged to allow for complete exhalation and to prevent self-generated or intrinsic positive end-expiratory pressure (auto-PEEP). To prevent barotrauma, some recommend a degree of permissive hypercarbia. When the FEV_1 or PEFR improves to 50% of normal or higher, patients usually have minimal or no symptoms: at this point, the frequency and intensity of bronchodilator therapy can be decreased, and weaning from mechanical ventilation can ensue.

When asthma exacerbation is resistant to therapy, it is likely that the expiratory airflow obstruction is caused predominantly by airway edema and intraluminal secretions. Indeed, some patients may be at risk of asphyxia due to mucous plugging of the airways. In rare circumstances when life-threatening hypoxia persists despite aggressive pharmacologic therapy, it may be necessary to consider general anesthesia to produce bronchodilation. Isoflurane and sevoflurane are effective bronchodilators in this situation. Treatment of severe acute asthma is summarized in Table 2.6.

Management of Anesthesia

The occurrence of severe bronchospasm has been reported in 0.2% to 4.2% of all procedures involving general anesthesia performed in asthmatic patients. Factors that are more likely to predict the occurrence of severe bronchospasm include the type of surgery (risk is higher with upper abdominal surgery and oncologic surgery) and the proximity of the most recent asthmatic attack to the date of surgery.

Several mechanisms could explain the contribution of general anesthesia to increased airway resistance. Among these are depression of the cough reflex, impairment of mucociliary function, reduction of palatopharyngeal muscle tone, depression of diaphragmatic function, and an increase in the amount of fluid in the airway wall. In addition, airway stimulation by endotracheal intubation, parasympathetic nervous system activation, and/or release of neurotransmitters of pain such as substance P and neurokinins may also play a role.

Preoperative evaluation of patients with asthma requires an assessment of disease severity, the effectiveness of current pharmacologic management, and the potential need for additional therapy before surgery. The goal of preoperative evaluation is to formulate an anesthetic plan that prevents or blunts expiratory airflow obstruction.

Preoperative evaluation begins with a history to elicit the severity and characteristics of the patient's asthma (Table 2.7). History of symptom control, frequency of exacerbation, need for hospitalization and endotracheal intubation, and previous tolerance of anesthesia and surgery should be noted. A list of asthma medications may also provide insight into asthma severity and control. On physical examination the general appearance of the patient and any use of accessory muscles of respiration should be noted. Auscultation of the chest to detect wheezing or crepitations is important. Blood eosinophil counts often parallel the degree of airway inflammation, and airway hyperreactivity provides an indirect assessment of the current status of the disease. PFTs (especially FEV_1) performed before and after bronchodilator therapy may be indicated in patients scheduled for major surgery. A reduction in FEV_1 or forced vital capacity (FVC) to less than 70% of predicted, as well as an FEV_1:FVC ratio that is less than 65% of predicted, is usually considered a risk factor for perioperative respiratory complications.

Chest physiotherapy, antibiotic therapy, and bronchodilator therapy during the preoperative period can often improve reversible components of asthma. Measurement of arterial blood gases is indicated if there is any question about the adequacy of ventilation or oxygenation.

Antiinflammatory and bronchodilator therapy should be continued until the time of anesthesia induction. If the patient is currently on or has been treated with high doses of systemic corticosteroids within the past 6 months, supplementation with stress-dose hydrocortisone or methylprednisolone may be indicated. However, hypothalamic-pituitary-adrenal suppression is very unlikely if only inhaled corticosteroids are used for asthma treatment. In selected patients a preoperative course of oral corticosteroids may be useful to improve overall lung function.

TABLE 2.6 Treatment of Acute Severe Asthma

Supplemental oxygen to maintain Sao_2 ⁻ 90%
Γ_2 agonists by metered-dose inhaler every 15–20 min or by continuous nebulizer administration
Intravenous corticosteroids (hydrocortisone or methylprednisolone)
Intravenous fluids to maintain euvolemia
Empirical broad-spectrum antibiotics
Anticholinergic (ipratropium) by inhalation
Intravenous magnesium sulfate
Tracheal intubation and mechanical ventilation (when $Paco_2$ _ 50 mm Hg)
Sedation and paralysis
Mechanical ventilation parameters:
High gas flows permit short inspiration times and longer expiration times
Expiration time must be prolonged to avoid air trapping and "auto-PEEP"
Permissive hypercarbia if needed to avoid barotrauma
General anesthesia with a volatile anesthetic to produce bronchodilation
Extracorporeal membrane oxygenation (ECMO) as a last resort

PEEP, positive end-expiratory pressure

TABLE 2.7 Characteristics of Asthma to Be Evaluated Preoperatively

Age at onset
Triggering events
Hospitalization for asthma
Frequency of emergency department visits
Need for intubation and mechanical ventilation
Allergies
Cough
Sputum characteristics
Current medications
Anesthetic history

Patients should be free of wheezing and have a PEFR of either greater than 80% of predicted or at the patient's personal best value before surgery.

During induction and maintenance of anesthesia in asthmatic patients, airway reflexes must be suppressed to avoid bronchoconstriction in response to mechanical stimulation of these hyperreactive airways. Stimuli that do not ordinarily evoke airway responses can precipitate life-threatening bronchoconstriction in patients with asthma.

Because it avoids instrumentation of the airway and tracheal intubation, regional anesthesia is an attractive option when the operative site is suitable. Concerns that high sensory levels of anesthesia will lead to sympathetic blockade and consequent bronchospasm are unfounded.

When general anesthesia is selected, induction of anesthesia is most often accomplished with an IV induction drug. Propofol is often used for induction in a hemodynamically stable asthmatic patient. It produces smooth muscle relaxation and contributes to decreased airway resistance. Ketamine is a preferred induction drug in a hemodynamically unstable patient with asthma.

After general anesthesia is induced, the lungs are often ventilated for a time with a gas mixture containing a volatile anesthetic. The goal is to establish a depth of anesthesia that depresses hyperreactive airway reflexes sufficiently to permit tracheal intubation without precipitating bronchospasm. Sevoflurane is the preferred inhalational anesthetic agent as it produces more profound bronchodilation compared to isoflurane and desflurane. An alternative method to suppress airway reflexes before intubation is IV or intratracheal injection of lidocaine (1–1.5 mg/kg) several minutes before endotracheal intubation.

Opioids should also be administered to suppress the cough reflex and to achieve deep anesthesia. However, prolongation of opioid effects can cause postoperative respiratory depression. Remifentanil may be particularly useful because it is an ultrashort-acting opioid and does not accumulate. Most opioids have some histamine-releasing effects, but fentanyl and analogous drugs can be used safely in asthmatic patients. Administration of opioids prior to intubation can help prevent increased airway resistance, but muscle rigidity caused by an opioid could decrease lung compliance and impair ventilation. Opioid-induced muscle rigidity can be decreased by the combined use of IV anesthetics and neuromuscular blocking drugs.

Insertion of an LMA is less likely to result in bronchoconstriction than insertion of an ETT. Therefore use of an LMA is often a better method of airway management in asthmatic patients who are not at increased risk of reflux or aspiration. Supraglottic airway devices can be especially useful during airway-sharing procedures in severe asthmatics such as BT. Here, LMA combined with controlled ventilation and low Fio_2 to minimize airway fire from intense procedural heat may confer a significantly better safety profile. During maintenance of general anesthesia, it may be difficult to differentiate light anesthesia from bronchospasm as the cause of a decrease in pulmonary compliance. Administration of a neuromuscular blocker will relieve the ventilatory difficulty resulting from light anesthesia but has no effect on bronchospasm.

Intraoperatively the desired level of arterial oxygenation and carbon dioxide removal is typically provided via mechanical ventilation. In asthmatic patients, sufficient time must be provided for exhalation to prevent air trapping. Humidification and warming of inspired gases may be especially useful in patients with exercise-induced asthma in whom bronchospasm may be due to transmucosal loss of heat. Adequate administration of fluids during the perioperative period is important for maintaining adequate hydration and ensuring that airway secretions are less viscous and can be removed easily. Skeletal muscle relaxation is usually provided with nondepolarizing muscle relaxants. Neuromuscular blockers with limited ability to evoke the release of histamine should be selected.

Theoretically, antagonism of neuromuscular blockade with anticholinesterase drugs could precipitate bronchospasm due to stimulation of postganglionic cholinergic receptors in airway smooth muscle. However, such bronchospasm does not predictably occur due to the protective bronchodilation effects provided by the simultaneous administration of anticholinergic drugs. The newest neuromuscular blockage reversal agent, sugammadex, does not possess any muscarinic properties and may be used as an alternative to anticholinesterase drug reversal. However, bronchospasm has been reported in 2.6% of patients in this population as well.

At the conclusion of surgery it may be prudent to remove the ETT while anesthesia is still sufficient to suppress hyperreactive airway reflexes, a technique referred to as deep extubation. When it is deemed unwise to extubate the trachea before the patient is fully awake, suppressing airway reflexes and/or the risk of bronchospasm by administration of IV lidocaine or treatment with inhaled bronchodilators should be considered.

During surgery, bronchospasm may be due to light anesthesia rather than asthma itself (Table 2.8). Signs may include high peak airway pressure, upsloping of the end-tidal carbon dioxide ($ETCO_2$) waveform, wheezing, and desaturation. Treatment of intraoperative bronchospasm and wheezing will depend on its cause. Deepening anesthesia with either volatile agents or IV injections of propofol and administration of a rapid-acting β_2 agonist such as albuterol via the ETT are common first steps. Because the vast majority of albuterol delivered into an ETT

TABLE 2.8 Differential Diagnosis of Intraoperative Bronchospasm and Wheezing

Mechanical obstruction of endotracheal tube
Kinking
Secretions
Overinflation of tracheal tube cuff
Inadequate depth of anesthesia
Active expiratory efforts
Decreased functional residual capacity
Endobronchial intubation
Pulmonary aspiration
Pulmonary edema
Pulmonary embolus
Pneumothorax
Acute asthmatic attack

by MDI does not reach the patient, other methods of delivery should be considered. These include increasing the number of puffs and delivery via nebulizer attached to the circuit. If bronchospasm continues despite these initial therapies, other drugs (e.g., IV corticosteroids, epinephrine, magnesium) may be necessary.

Emergency surgery in the asthmatic patient introduces a conflict between protection of the airway in someone at risk of aspiration and the possibility of triggering significant bronchospasm. In addition, there may not be sufficient time to optimize bronchodilator therapy prior to surgery. Regional anesthesia may be a good option in this situation if the site of surgery is suitable.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a disease of chronic airflow obstruction. It includes emphysema characterized by lung parenchymal destruction, chronic bronchitis characterized by cough and sputum production, and small airway disease. Pulmonary elastic recoil is lost as a result of bronchiolar and alveolar destruction, often from inhaling toxic chemicals such as cigarette smoke and biomass fuel. As of 2017, COPD has a worldwide prevalence of 10.1% and is the third leading cause of death. Although cigarette smoking contributes to the majority of COPD development, multiple other risk factors exist, including occupational exposure to dust and chemicals, especially in coal mining, gold mining, and the textile industry, biomass fuel, air pollution, genetic factors such as $_1$-antitrypsin deficiency, age, female sex, lung development during gestation and childhood such as maternal smoking, low birth weight, and recurrent childhood respiratory infections, lower socioeconomic class, and asthma. Patients with COPD pose a challenge to the anesthesiologist as perioperative pulmonary complication, hospital length of stay, and mortality are significantly increased in this patient population.

COPD causes (1) pathologic deterioration in elasticity or recoil within the lung parenchyma, which normally maintains the airways in an open position; (2) pathologic changes that decrease the rigidity of the bronchiolar wall and thus predispose them to collapse during exhalation; (3) an increase in gas flow velocity in narrowed bronchioli, which lowers the pressure inside the bronchioli and further favors airway collapse; (4) active bronchospasm and obstruction resulting from increased pulmonary secretions; and (5) destruction of lung parenchyma, enlargement of air sacs, and development of emphysema.

Signs and Symptoms

Signs and symptoms of COPD vary with disease severity but usually include dyspnea at rest or on exertion, chronic cough, and chronic sputum production. COPD exacerbations are periods of worsening symptoms as a result of an acute worsening in airflow obstruction. As expiratory airflow obstruction increases in severity, tachypnea and a prolonged expiratory time are evident. Breath sounds are likely to be decreased, and expiratory wheezes are common. As the disease progresses, patients get exacerbations more frequently, and these are often triggered by respiratory infections with a bacterial component.

Diagnosis

Providers should have a high degree of suspicion and low threshold to test for COPD in patients with symptoms such as dyspnea and chronic cough and/or lifestyle and environmental exposures, which places them at risk (Singh et al, 2019). Definitive diagnosis of COPD is made with spirometry.

Pulmonary Function Tests

Results of PFTs in COPD reveal a decrease in the FEV_1:FVC ratio and an even greater decrease in the FEF between 25% and 75% of vital capacity ($FEF_{25\%–75\%}$). An FEV_1:FVC less than 70% of predicted, an increased FRC and TLC, as well as reduced diffusing capacity for carbon monoxide (DLCO) are usually seen in these patients (Fig. 2.4). Slowing of expiratory airflow and gas trapping behind prematurely closed airways are responsible for the increase in residual volume (RV). The pathophysiologic advantage of an increased RV and FRC in patients with COPD is related to an enlarged airway diameter and increased elastic recoil for exhalation. The cost is the greater work of breathing at the higher lung volumes.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) works with healthcare professionals and public health officials around the world to raise awareness of COPD and improve treatment. GOLD was launched in 1997 in collaboration with the National Heart, Lung, and Blood Institute of the US National Institutes of Health and the World Health Organization. GOLD developed a classification/severity grading system that is now widely used by physicians around the world (Table 2.9).

Chest Radiography

Radiographic abnormalities may be minimal even in the presence of severe COPD. Hyperlucency due to arterial vascular deficiency in the lung periphery and hyperinflation (flattening of the diaphragm with loss of its normal domed appearance

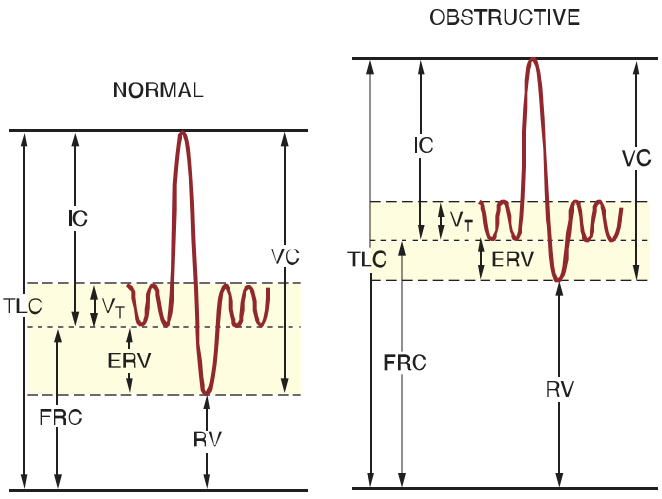

Fig. 2.4 Lung volumes in chronic obstructive pulmonary disease *(COPD)* compared with normal values. In the presence of obstructive lung disease, the vital capacity *(VC)* is normal to decreased, the residual volume *(RV)* and functional residual capacity *(FRC)* are increased, the total lung capacity *(TLC)* is normal to increased, and the RV:TLC ratio is increased. *ERV,* Expiratory reserve volume; *IC,* inspiratory capacity; *VT,* tidal volume.

TABLE 2.9 GOLD Spirometric Criteria for Chronic Obstructive Pulmonary Disease (COPD) Severity (Based on Postbronchodilator FEV_1 Measurement)

Stage	Characteristics
I: Mild COPD	FEV_1 ≥ 80% predicted
II: Moderate COPD	50% ≤ FEV_1 < 80% predicted
III: Severe COPD	30% ≤ FEV_1 < 50% predicted
IV: Very severe COPD	FEV_1 < 30% predicted

Adapted from Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of COPD: update 2020. http://www.goldcopd.com.

and a very vertical cardiac silhouette) suggest the diagnosis of emphysema. If bullae are present, the diagnosis of emphysema is certain. However, only a small percentage of patients with emphysema have bullae.

Computed Tomography

Computed tomography (CT) is much more sensitive at diagnosing COPD than chest radiograph. Airspace enlargement and alveolar destruction accompanied by loss of bone, muscle, and fat tissue are suggestive of the multiorgan loss of tissue (MOLT) phenotype, which is associated with higher rates of lung cancer, while bronchiolar narrowing and wall thickening indicate the bronchitic phenotype that is usually accompanied by metabolic syndrome and high rates of cardiac disease. CT also has the ability to reveal other disease states such as pulmonary fibrosis and coronary artery disease, which may affect COPD treatment. Although CT scan is not routinely used for COPD diagnosis, the plethora of information it can gather has prompted some to advocate its use in all patients with COPD.

Physiologic Testing

The BODE index is a grading system that takes into account the patient's body mass index, degree of airflow obstruction, level of dyspnea, and exercise tolerance to assess overall prognosis. Higher BODE scores indicate greater risk of COPD exacerbations, hospitalizations, and death as a result of pulmonary complications.

Blood Testing

α_1-antitrypsin deficiency is an inherited disorder associated with premature development of COPD. Low levels of plasma α_1-antitrypsin indicate a treatable genetic disease and the need for lifelong replacement therapy.

Plasma eosinophil should be measured in patients with uncontrolled disease despite adequate bronchodilator treatment. High levels of eosinophil indicate the need for inhaled glucocorticoids while low levels are associated with poor response and increased risk of pneumonia.

Arterial blood gas measurements often remain relatively normal until COPD is severe. The Pao_2 does not usually decrease until the FEV_1 is less than 50% of predicted, and the $Paco_2$ may not increase until the FEV_1 is even lower.

Treatment

Treatment of COPD is designed to relieve symptoms and to slow the progression of the disease.

The first and most important step in treating COPD is reducing exposure to smoking and environmental pollutants. Smoking cessation in particular can significantly decrease disease progression and lower mortality by as much as 18%. Symptoms of chronic bronchitis can diminish or entirely disappear. Accelerated loss of lung as seen in those who continue to smoke is also reduced.

Pharmacologic treatment usually begins with inhalers, specifically long-acting muscarinic antagonist. If dyspnea persists, long-acting β_2 agonist can be added. A third therapy with inhaled glucocorticoids is most effective when symptoms are associated with asthma, rhinitis, elevated serum eosinophil, and history of exacerbations (Table 2.10). Correctly using inhaled therapies can improve clinical symptoms, improve FEV_1, and reduce the number of exacerbations. Other pharmacologic treatments include vaccinations against influenza and pneumococcus, and diuretics in patients with cor pulmonale and right-sided heart failure with peripheral edema. During periods of exacerbation, antibiotics, systemic corticosteroids, and theophylline may become necessary additional treatments (Table 2.11). Exacerbations of COPD may be due to viral or bacterial infection of the upper respiratory tract or may be noninfective, so antibiotic treatment is not always warranted. Diuretic-induced chloride depletion may produce a hypochloremic metabolic alkalosis that depresses the ventilatory drive and aggravates chronic CO_2 retention. Pulmonary rehabilitation programs can increase exercise capacity of patients with COPD despite the

TABLE 2.10 Treatment of Patients With Chronic Obstructive Pulmonary Disease (COPD)

Smoking cessation
Annual vaccination against influenza
Vaccination against pneumococcus
Inhaled long-acting bronchodilators
Inhaled corticosteroids
Inhaled long-acting anticholinergic drugs
Home oxygen therapy if Pao_2 ≤ 55 mm Hg, hematocrit ≥ 55%, or there is evidence of cor pulmonale
Diuretics if evidence of right heart failure with peripheral edema
Lung volume reduction surgery
Lung transplantation

TABLE 2.11 Treatment of Patients With a Chronic Obstructive Pulmonary Disease (COPD) Exacerbation

Supplemental oxygen ± noninvasive positive pressure ventilation or mechanical ventilation
Increased dose and frequency of bronchodilator therapy
Systemic corticosteroids
Antibiotics

absence of detectable effects on PFTs. However, prompt deconditioning occurs when the exercise program is discontinued.

To decrease the risk of death, long-term oxygen administration (home oxygen therapy) is recommended if the Pao_2 is less than 55 mm Hg, the hematocrit is above 55%, or there is evidence of cor pulmonale. The goal of supplemental oxygen administration is to achieve a Pao_2 greater than 60 mm Hg, which can usually be accomplished by prescribing nasal cannula at 2 L/min. The flow rate of oxygen can be titrated as needed according to arterial blood gas or pulse oximetry measurements. It is important to note that relief of arterial hypoxemia with supplemental oxygen administration is more effective than any known drug therapy in decreasing pulmonary vascular resistance and pulmonary hypertension and in preventing erythrocytosis.

Lung Volume Reduction Surgery

In selected patients with severe COPD who are not responding to maximal medical therapy and who have regions of overdistended, poorly functioning lung tissue, lung volume reduction surgery may be considered. Surgical removal of these overdistended areas allows more areas of normal lung to expand and improves not only lung function but also quality of life. Lung volume reduction surgery is most commonly performed via either a median sternotomy or a video-assisted thoracoscopic surgery (VATS) approach. The proposed mechanisms for improvement in lung function after this surgery include (1) an increase in elastic recoil, which increases expiratory airflow; (2) a decrease in the degree of hyperinflation, which results in improved diaphragmatic and chest wall mechanics; and (3) a decrease in the inhomogeneity of regional ventilation and perfusion, which results in improved alveolar gas exchange and increased effectiveness of ventilation. Management of anesthesia for lung volume reduction surgery includes use of a double-lumen endobronchial tube to permit lung separation, and avoidance of nitrous oxide and excessive positive airway pressure. Monitoring of central venous pressure as a guide to fluid management is unreliable in this situation.

Recently, a less invasive approach using endobronchial valves inserted during bronchoscopy has been shown to also improve long-term lung function, dyspnea, and quality of life. The valve occludes the emphysematous lobe, which leads to eventual lung collapse and volume reduction.

Management of Anesthesia

A complete history should be taken and geared toward investigating the causes, course, and severity of patient disease. Smoking history, current medications (including any recent use of systemic corticosteroids), exercise tolerance, frequency of exacerbations, timing of the most recent exacerbation, and need for hospitalization should all be noted in the preoperative evaluation. Any previous need for noninvasive positive pressure ventilation (NIPPV) or mechanical ventilation should also be determined. Because smoking and COPD are associated with a number of other comorbidities, patients should also be questioned on the presence and severity of concomitant diseases such as diabetes mellitus, hypertension, peripheral vascular disease, ischemic heart disease, heart failure, cardiac dysrhythmias, and lung cancer. Right ventricular function should be carefully assessed by clinical examination and echocardiography in patients with advanced pulmonary disease. Chronic inhaled therapies should be continued until the morning of surgery. Preoperative chest physiotherapy such as deep breathing exercises, coughing, incentive spirometry, and pulmonary physical therapy can reduce postoperative pulmonary complications when implemented preoperatively.

The value of routine preoperative pulmonary function testing remains controversial. The results of PFTs and arterial blood gas analysis may be useful for predicting pulmonary function after lung resection, but they do not reliably predict the likelihood of postoperative pulmonary complications after nonthoracic surgery. Clinical findings such as active smoking, diffuse wheezing, and productive cough are more predictive of pulmonary complications than spirometric tests. Even patients defined as high risk by spirometry (FEV_1 < 70% of predicted, FEV_1:FVC ratio ≥ 65%) or arterial blood gas ($Paco_2$ ≥ 45 mm Hg) are usually safe to undergo surgery, including lung resection, with an acceptable risk of postoperative pulmonary complications. Therefore PFTs should be viewed as a management tool to optimize preoperative pulmonary function but not as a means to predict risk.

Indications for preoperative pulmonary evaluation (which may include consultation with a pulmonologist and/or performance of PFTs) typically include (1) hypoxemia on room air or the need for home oxygen therapy without a known cause, (2) a bicarbonate greater than 33 mEq/L or Pco_2 greater than 50 mm Hg in patients whom pulmonary disease has not been previously evaluated, (3) a history of respiratory failure resulting from a problem that still exists, (4) severe shortness of breath attributed to respiratory disease, (5) planned pneumonectomy, (6) difficulty in assessing pulmonary function by clinical signs, (7) the need to distinguish among potential causes of significant respiratory compromise, (8) the need to determine the response to bronchodilators, and (9) suspected pulmonary hypertension. Patients with COPD undergoing peripheral surgery do not require preoperative pulmonary function testing. If doubt exists, simple spirometry with measurement of only the FEV_1 can be sufficient to assess the severity of the lung disease.

In addition to spirometry, ventilatory function can also be assessed under dynamic conditions by measuring airflow as it relates to lung volume. With this assessment, expiratory flow rates can be plotted against lung volumes to produce flow-volume curves. When flow rates during inspiration are added to these curves, flow-volume loops are obtained. The flow rate is zero at TLC before the start of expiration. Once forced expiration begins, the peak flow rate is achieved rapidly, and the flow rate then falls in a linear fashion as the lung volume decreases to RV. During maximal inspiration from RV to TLC, the inspiratory flow is most rapid at the midpoint of inspiration so that the inspiratory curve is U shaped.

In patients with COPD there is a decrease in the expiratory flow rate at any given lung volume. The expiratory curve is

TABLE 2.12 Major Risk Factors for Development of Postoperative Pulmonary Complications

Patient Related
Age ≥60 yr
American Society of Anesthesiologists class higher than II
Congestive heart failure
Preexisting pulmonary disease (chronic obstructive pulmonary disease)
Cigarette smoking
Procedure Related
Emergency surgery
Abdominal or thoracic surgery, head and neck surgery, neurosurgery, vascular/aortic aneurysm surgery
Prolonged duration of anesthesia (≥2.5 h)
General anesthesia
Test Predictors
Albumin level of ≤3.5 g/dL

Adapted from Smetana GW, Lawrence VA, Cornell JE. Preoperative pulmonary risk stratification for noncardiothoracic surgery: A systematic review for the American College of Physicians. *Ann Intern Med.* 2006;144:581–595.

TABLE 2.13 Strategies to Decrease Incidence of Postoperative Pulmonary Complications

Preoperative
Encourage cessation of smoking for at least 6 weeks.
Treat evidence of expiratory airflow obstruction.
Treat respiratory infection with antibiotics.
Initiate patient education regarding lung volume expansion maneuvers.
Intraoperative
Use minimally invasive surgery (endoscopic) techniques when possible.
Consider regional anesthesia.
Avoid surgical procedures likely to last longer than 3 hours.
Postoperative
Institute lung volume expansion maneuvers (voluntary deep breathing, incentive spirometry, continuous positive airway pressure).
Maximize analgesia (neuraxial opioids, intercostal nerve blocks, patient-controlled analgesia).

Adapted from Smetana GW. Preoperative pulmonary evaluation. *N Engl J Med.* 1999;340:937–944. Copyright 1999 Massachusetts Medical Society.

concave upward due to uniform emptying of the airways. The RV is increased because of air trapping (see Fig. 2.2).

The major risk factors for the development of postoperative pulmonary complications are shown in Table 2.12. Obesity and mild to moderate asthma have not been shown to be independent risk factors. An algorithm for reducing pulmonary complications in patients undergoing noncardiothoracic surgery is shown in Fig. 2.5.

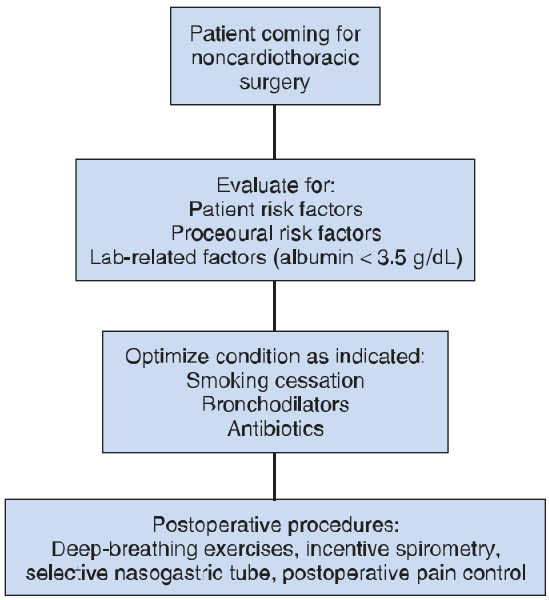

Fig. 2.5 Algorithm for decreasing pulmonary complications in patients undergoing noncardiothoracic surgery. (Adapted from Qaseem A, Snow V, Fitterman N, et al. Risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing noncardiothoracic surgery: a guideline from the American College of Physicians. *Ann Intern Med.* 2006;144:575-580.)

Risk Reduction Strategies

Strategies to decrease the incidence of postoperative pulmonary complications include preoperative, intraoperative, and postoperative interventions (Table 2.13).

Preoperative

Smoking cessation. Approximately 20% of American adults smoke, of whom 5% to 10% will annually undergo general anesthesia and/or surgery. These times of exposure to general anesthesia and/or surgery offer a window of opportunity for a smoking cessation intervention by a healthcare provider or other individual. This person can be the surgeon, anesthesiologist, nurse, or even a member of an active patient group or community group, who should encourage the patient to stop smoking at least temporarily before surgery or preferably permanently. The intervention can be carried out in the surgical clinic or anesthetic preadmission testing clinic, via phone calls by nurses or healthcare workers, or in a letter indicating the risks of postoperative complications caused by smoking. Recent evidence shows that the earlier the intervention before surgery, the more effective it is in reducing postoperative complications and maintaining cigarette abstinence.

Cigarette smoking is the single-most important risk factor for the development of COPD and death caused by lung disease. The effects of smoking on different organ systems are described in Table 2.14. Smoking cessation is strongly encouraged by the US Public Health Service. It recommends systematically identifying all tobacco users who come in contact with the healthcare system to urge and help them to quit smoking. The American Society of Anesthesiologists also has a Stop Smoking Initiative and provides resources to help practitioners encourage smoking cessation. The maximum benefit of smoking cessation is not usually seen unless smoking is stopped more than 8 weeks prior to surgery. However, patients should always be counseled to stop smoking irrespective of the time of encounter before surgery.

TABLE 2-14 Effects of Smoking on Different Organ Systems

Cardiac Effects of Smoking
Smoking is a risk factor for development of cardiovascular disease.
Carbon monoxide decreases oxygen delivery and increases myocardial work.
Smoking releases catecholamines and causes coronary vasoconstriction.
Smoking decreases exercise capacity.
Respiratory Effects of Smoking
Smoking is the major risk factor for development of chronic pulmonary disease.
Smoking decreases mucociliary activity.
Smoking results in hyperreactive airways.
Smoking decreases pulmonary immune function.
Other Organ System Effects
Smoking impairs wound healing.

Among smokers, predictive factors for the development of pulmonary complications include a lower diffusing capacity than predicted and a smoking history of more than 60 pack-years. Those who have smoked more than 60 pack-years have double the risk of any pulmonary complication and triple the risk of pneumonia compared with those who have smoked less than 60 pack-years.

Effects of smoking cessation. The adverse effects of carbon monoxide on oxygen-carrying capacity and of nicotine on the cardiovascular system are short lived. The sympathomimetic effects of nicotine on the heart are transient, lasting only 20 to 30 minutes. The elimination half-life of carbon monoxide is approximately 4 to 6 hours when breathing room air. Within 12 hours after cessation of smoking, the Pao_2 at which hemoglobin is 50% saturated with oxygen (P_{50}) increases from 22.9 to 26.4 mm Hg, and the plasma levels of carboxyhemoglobin decrease from 6.5% to 1%. However, despite the favorable effects on plasma carboxyhemoglobin concentration, short-term abstinence from cigarettes has not been proven to decrease the incidence of postoperative pulmonary complications.

Intermediate to long-term effects. Cigarette smoking causes mucous hypersecretion, impairment of mucociliary transport, and narrowing of small airways. In contrast to the rapid favorable effects of short-term abstinence from smoking on carboxyhemoglobin concentrations, improved ciliary and small airway function and decreased sputum production occur slowly over weeks after smoking cessation. Smoking may also interfere with normal immune responses and thus an ability to respond to pulmonary infection following surgery.

A decrease in postoperative pulmonary complications resulting from smoking cessation is thought to be related to the physiologic improvement in ciliary action, macrophage activity, and small airway function, as well as a decrease in sputum production. However, these changes take weeks to months to occur. Return of normal immune function requires at least 6 weeks of abstinence from smoking. In addition, some components of cigarette smoke stimulate hepatic enzymes. As with immune responses, it may take 6 weeks or longer for hepatic enzyme activity to return to normal following cessation of smoking.

The optimal timing of smoking cessation before surgery to reduce postoperative pulmonary complications is uncertain, but most data suggest that it is around 6 to 8 weeks. Smokers scheduled for surgery in less than 4 weeks should be advised to quit and should be offered interventions such as behavioral support and pharmacotherapy to help achieve this goal. Countless methods have been devised to aid in smoking cessation. Most involve some form of counseling and pharmacotherapy. Nicotine replacement therapy, with various delivery systems (including patches, inhalers, nasal sprays, lozenges, and gum), is generally well tolerated. The major side effect is local irritation at the site of drug delivery. The atypical antidepressant bupropion in a sustained-release formulation can also help. The drug is typically started 1 to 2 weeks before smoking is stopped.

Although long-term smoking cessation offers clear advantages, there can be disadvantages to smoking cessation in the immediate preoperative period. These include increase in sputum production, patient fear of the inability to handle stress, nicotine withdrawal, and symptoms such as irritability, restlessness, sleep disturbances, and depression.

Nutritional status. Poor nutritional status with a low serum albumin level (❑3.5 mg/dL) is a powerful predictor of postoperative pulmonary complications in COPD patients. Malnutrition can increase the risk of prolonged postoperative air leaks after lung surgery.

Preoperative incentive muscle training. Patients should be advised to do deep breathing exercises or incentive spirometry, which may improve respiratory function postoperatively.

Intraoperative

Regional anesthesia. Regional anesthesia is preferred over general anesthesia in patients with COPD. Intraoperatively, this technique can decrease the risk of laryngospasm, bronchospasm, barotrauma, and hypoxemia associated with positive pressure ventilation and endotracheal intubation. Recent data from the National Surgical Quality Improvement Program found regional anesthesia to also reduce postoperative rates of pneumonia, prolonged ventilatory dependence, and unplanned reintubation.

Regional anesthesia is suitable for procedures that do not invade the peritoneum, lower intraabdominal surgery, minimally invasive surgeries such as endovascular abdominal aortic aneurysm repair, and procedures performed on the extremities. General anesthesia is the usual choice for upper abdominal and intrathoracic surgery. Some studies in patients with COPD suggest a higher incidence of postoperative respiratory failure in patients who undergo general anesthesia, but whether this reflects the nature and complexity of the surgery and/or the operative site or the selection of anesthetic drugs or technique is unclear.

In general, regional anesthesia via peripheral nerve blockade carries a low risk of pulmonary complications. However, an interscalene block can cause ipsilateral phrenic nerve palsy and should be avoided in patients with severe COPD. In addition, techniques that produce sensory anesthesia above T6 is not recommended because such high blocks can impair the ventilatory functions requiring active exhalation; this affects parameters

such as expiratory reserve volume, PEFR, and maximum minute ventilation. Clinically this is manifested as an inadequate cough.

Regional anesthesia is a useful choice in patients with COPD only if large doses of sedative and anxiolytic drugs will not be needed. It must be appreciated that COPD patients can be extremely sensitive to the ventilatory depressant effects of sedative drugs. Elderly patients may be especially susceptible. Nevertheless, small doses of a benzodiazepine such as midazolam can be administered without producing undesirable degrees of ventilatory depression.

General anesthesia. General anesthesia is often accomplished with volatile anesthetics. Volatile anesthetics (especially desflurane and sevoflurane) are useful due to their rapid elimination and thus minimizing residual ventilatory depression. Volatile anesthetics are also known to cause bronchodilation and have been used to treat bronchospasm in status asthmaticus. However, desflurane may cause irritation of the bronchi and increased airway resistance, thereby limiting its usefulness during induction and emergence in patients with severe airway reactivity.

Emerging from anesthesia using inhalational agents can be significantly prolonged, since air trapping as a result of COPD may also trap anesthesia gas as it diffuses from various body compartments into the lungs during elimination. An alternative method to emerge is using IV anesthesia such as propofol. Short-acting analgesic such as remifentanil can also be added to relieve ETT irritation.

Nitrous oxide should be used with great caution in COPD patients owing to the possibility of enlargement or rupture of bullae, resulting in development of a tension pneumothorax. Another potential disadvantage is the limitation on inspired oxygen concentration it imposes. It is important to remember that inhaled anesthetics may attenuate regional hypoxic pulmonary vasoconstriction and produce more intrapulmonary shunting. Increasing the fraction of inspired oxygen (Fio_2) may be necessary to offset this loss of hypoxic pulmonary vasoconstriction.

Opioids may be less useful than inhaled anesthetics for maintenance of anesthesia in patients with COPD because they can be associated with prolonged ventilatory depression as a result of their slow rate of metabolism or elimination. Even the duration of ventilatory depression may be prolonged in patients with COPD compared to healthy individuals.

An ETT bypasses most of the natural airway humidification system, so humidification of inspired gases and use of low gas flows are needed to keep airway secretions moist.

Patients with COPD are at increased risk of lung injury during mechanical ventilation in the perioperative period. Goals of mechanical ventilation should be to avoid dynamic hyperinflation of the lungs and prevent development of auto-PEEP. Multiple studies show that protective ventilation with low tidal volumes (6–8 mL/kg), peak airway pressures less than 30 cm H_2O, and Fio_2 titrated to keep Spo_2 greater than 90% result in lower levels of inflammatory biomarkers. Patients with moderate to severe COPD can have cystic air spaces in the lungs that carry a risk of rupture once positive pressure ventilation is instituted. As such, in patients with COPD who become hemodynamically unstable during mechanical ventilation, the differential diagnosis must, importantly, include tension pneumothorax and bronchopleural fistula.

The phenomenon of air trapping, also called auto-PEEP or dynamic hyperinflation, occurs when positive pressure ventilation is applied and insufficient expiratory time is allowed. This contributes to increased intrathoracic pressure, impedes venous return, and transmits the elevated intrathoracic pressure to the pulmonary artery. Severe air trapping can significantly increase pulmonary vascular resistance and lead to right ventricular strain. Hyperinflated lungs can also exert direct pressure on the heart, limiting its ability to expand fully during diastole even with adequate preload. Shift of the ventricular septum and ventricular interdependence due to the shared pericardium may cause a distended right ventricle to impinge on filling of the left ventricle.

Air trapping can be detected during mechanical ventilation intraoperatively by the following methods:

1. Capnography shows that the carbon dioxide concentration does not plateau but is still upsloping at the time of the next breath. This indicates that there is still admixture of air from dead space reducing the $ETCO_2$.
2. Direct measurement of flow may be displayed graphically by the ventilator, showing that the expiratory flow has not reached baseline (zero) before initiation of the next breath.
3. Direct measurement of the resulting PEEP can be performed using more advanced ventilators that are capable of an expiratory hold.

Air trapping can cause serious hemodynamic instability by increasing intrathoracic pressure and decreasing preload. Immediate intervention includes disconnecting the patient from the ventilator to allow for complete exhalation. Decreasing respiratory rate and increasing expiratory time can help prevent auto-PEEP in the future.

Much like patients with asthma, patients with COPD are prone to bronchospasm. Triggering events are often due to airway manipulation during induction and light anesthesia during maintenance. Treatments include deepening anesthesia with either a volatile anesthetic or propofol, short-acting bronchodilator through the ETT, suctioning secretions, and IV corticosteroids and/or epinephrine if initial management options fail.

Although traditionally most anesthesiologists have used high inspired oxygen concentrations in the perioperative setting, a number of studies have questioned this practice. Oxygen can be split in tissues to produce reactive oxygen species (ROS), which can have a deleterious effect on nuclear and cell membranes. In addition, surgery, anesthesia, and patient positioning induces airway closure and atelectasis. The time from airway occlusion to atelectasis is dependent on the composition of the alveolar gas and is faster in lung units containing 100% oxygen.

The hazard of pulmonary barotrauma in the presence of bullae should be appreciated, particularly when high positive airway pressures are required to provide adequate ventilation. If spontaneous breathing is permitted during anesthesia in patients with COPD, it should be appreciated that the ventilatory depression produced by volatile anesthetics may be greater in these patients than in individuals without COPD.

Postoperative

Prevention of postoperative pulmonary complications is based on maintaining adequate lung volumes, especially FRC, and facilitating an effective cough. Identification of the FRC as the most important lung volume during the postoperative period provides a specific goal for therapy.

Lung expansion maneuvers. Lung expansion maneuvers (deep breathing exercises, incentive spirometry, chest physiotherapy, positive pressure ventilation) have proven benefits in preventing postoperative pulmonary complications in high-risk patients. These techniques decrease the risk of atelectasis by increasing lung volumes. Incentive spirometry is simple, inexpensive, and provides an objective goal for patient performance. By providing patients with a particular inspired volume to achieve and hold, incentive spirometry improves lung inflation and reexpansion of collapsed alveoli. A major disadvantage is the need for patient understanding and cooperation. Providing education in lung expansion maneuvers before surgery decreases the incidence of pulmonary complications to a greater degree than beginning education after surgery.

Continuous positive airway pressure (CPAP) is reserved for the prevention of postoperative pulmonary complications in patients who are not able to perform deep-breathing exercises or incentive spirometry.

Neuraxial analgesia has been proven to decrease the incidence of postoperative pneumonia when compared to parenteral opioids. It is recommended after high-risk thoracic, abdominal, and major vascular surgery. Intermittent or continuous intercostal nerve or paravertebral nerve blocks may be alternatives if neuraxial analgesia is contraindicated or technically difficult. Postoperative neuraxial analgesia with opioids alone may also permit early tracheal extubation. The sympathetic blockade, muscle weakness, and loss of proprioception that are produced by local anesthetics are not produced by neuraxial opioids. However, sedation may accompany neuraxial opioid administration, and delayed respiratory depression can be seen when poorly lipid-soluble opioids such as morphine are used.

Ambulation serves to increase FRC and improve oxygenation, presumably by improving ventilation/perfusion matching. Neuraxial opioids may be especially useful after intrathoracic and upper abdominal surgery. Breakthrough pain may require treatment with systemic opioids.

Continued mechanical ventilation during the immediate postoperative period may be necessary in patients with severe COPD who have undergone major abdominal or intrathoracic surgery. Patients with preoperative FEV_1:FVC ratios of less than 0.5 or with a preoperative $Paco_2$ of more than 50 mm Hg are likely to need a period of postoperative mechanical ventilation. In cases of chronic CO_2 retention, it becomes important to not correct hypercarbia too quickly as this will result in a significant metabolic alkalosis, which can be associated with cardiac dysrhythmias, central nervous system irritability, and even seizures.

When continued mechanical ventilation is necessary, Fio_2 and ventilator settings should be adjusted to keep the Spo_2 around 90% and the $Paco_2$ in a range that maintains normal arterial pH (7.35–7.45). Reduction of the respiratory rate or the I:E ratio allows more time for exhalation and may reduce the likelihood of air trapping. Resulting tidal volume and minute ventilation should be monitored as a result to prevent hypercapnia, hypoxia, and acidosis.

Extubation of high-risk COPD patients to CPAP or bilevel positive airway pressure (BiPAP) can reduce work of breathing and risk of reintubation. However, use of positive airway pressure in the setting of an unprotected airway raises concern about insufflation of the stomach and the risk of vomiting and aspiration. Treatment with sympathomimetic bronchodilators such as albuterol and inhaled anticholinergics such as ipratropium may improve airflow if a reactive component of air trapping is present.

Early mobilization postoperatively can decrease pulmonary complications by promoting deeper breathing, lung expansion, and cough.

MISCELLANEOUS RESPIRATORY DISORDERS

Bronchiectasis

Bronchiectasis is associated with irreversible airway dilation, inflammation, and chronic bacterial infection. Prevalence is highest in patients over the age of 60, those with concomitant chronic pulmonary disease such as COPD and asthma, and in women. Despite the availability of antibiotics, bronchiectasis is an important cause of chronic productive cough with purulent sputum and accounts for a significant number of cases of massive hemoptysis.

Pathophysiology

Bronchiectasis is characterized poor mucociliary activity and mucous pooling leading to a vicious cycle of recurrent bacterial and mycobacterial infection causing further inflammation, bronchial dilation, and eventual airway collapse, airflow obstruction, and the inability to clear secretions. Once bacterial superinfection is established, it is nearly impossible to eradicate, and daily expectoration of purulent sputum persists.

Diagnosis

The history of a chronic cough productive with purulent sputum is highly suggestive of bronchiectasis. Patients may also complain of hemoptysis, dyspnea, wheezing, and pleuritic chest pain. Clubbing of the fingers occurs in most patients with significant bronchiectasis and is a valuable diagnostic clue, especially since this change is not characteristic of COPD. Baseline chest x-ray and PFT should be obtained on all suspected patients, although results may vary widely. Sputum culture should be checked for any active infection. CT provides excellent images of bronchiectatic airways and is the gold standard for diagnosis. It will usually show dilated bronchi much larger in diameter than their adjacent blood vessels.

Treatment

Because sputum production and bacterial pulmonary infections are the hallmark of bronchiectasis, key treatments involve antibiotics and chest physiotherapy to improve expectoration of secretions. Other treatments include yearly immunization

against influenza, bronchodilators, systemic corticosteroids, and oxygen therapy. Results of periodic sputum cultures guide antibiotic selection. *Haemophilus influenzae* and *Pseudomonas* are the most common organisms cultured. Chest physiotherapy with chest percussion and vibration can aid bronchopulmonary drainage. Surgical resection has played a declining role in the management of bronchiectasis and is considered only in the rare instance in which severe symptoms persist or recurrent complications occur.

Management of Anesthesia

Much like caring for patients with other types of obstructive airway disease, a detailed history should be elicited from the patient, including severity of disease, frequency of exacerbations, and the date of the most recent exacerbation. Home medications should be continued until the morning of surgery. Elective procedures should be delayed if there are signs of active pulmonary infection with respiratory compromise or systemic involvement. During general anesthesia, the patient may need to be suctioned frequently through the ETT to manage secretions. If the patient is undergoing surgery for management of an empyema or hemoptysis, lung isolation may need to be achieved to prevent spillage of purulent sputum into normal areas of the lungs. Nasal endotracheal intubation should be avoided because of the high rate of concurrent chronic sinusitis in these patients.

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder of chloride channels that leads to alterations in secretion production and clearance. It affects an estimated 30,000 persons in the United States.

Pathophysiology

CF is caused by a mutation of a single gene on chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator *(CFTR)*. Normally, *CFTR* produces a protein, which aids in salt and water movement in and out of cells. However, in CF, the mutated *CFTR* gene results in the production of abnormally thick mucus outside of epithelial cells. Decreased chloride transport is accompanied by decreased transport of sodium and water, which leads to dehydrated viscous secretions, luminal obstruction, and destruction and scarring of various glands and tissues. The end result of CF can lead to severe organ damage manifested as bronchiectasis, COPD and sinusitis, diabetes mellitus, cirrhosis, meconium ileus in children, and azoospermia. Pancreatic insufficiency manifests with malabsorption of fat and fat-soluble vitamins. The primary cause of morbidity and mortality in patients with CF is chronic pulmonary infection. The CF Foundation patient registry has documented substantial improvement in life expectancy of patients with CF. This has been largely attributed to improved treatment of lung disease, antibiotics, and emphasis on nutrition.

Diagnosis

The presence of a sweat chloride concentration greater than 60 mEq/L plus the characteristic clinical manifestations (cough, chronic purulent sputum production, exertional dyspnea) or family history of the disease confirms the diagnosis of CF. Deoxyribonucleic acid (DNA) analysis can identify more than 90% of patients with *CFTR* mutation. Chronic pansinusitis is almost universal. The presence of normal sinuses on radiographic examination is strong evidence that CF is not present. Malabsorption with a response to pancreatic enzyme treatment is evidence of the exocrine insufficiency associated with CF. Positive sputum culture for *Pseudomonas aeruginosa* is common. Obstructive azoospermia confirmed by testicular biopsy is also strong evidence of CF. Bronchoalveolar lavage typically shows a high percentage of neutrophils, which is a sign of airway inflammation. COPD is present in virtually all adult patients with CF and follows a relentless downhill course.

Treatment

Treatment of CF is mainly directed toward symptom alleviation (mobilization and clearance of lower airway secretions and treatment of pulmonary infection), supportive care of various organ dysfunction (pancreatic enzyme replacement, oxygen therapy), nutrition, and prevention of intestinal obstruction. Gene therapy is currently being investigated as a treatment for CF.

Clearance of airway secretions. The abnormal viscoelastic properties of the sputum in patients with CF lead to sputum retention resulting in airway obstruction. The principal nonpharmacologic approach to enhancing clearance of pulmonary secretions is chest physiotherapy with postural drainage. High-frequency chest compression with an inflatable vest and airway oscillation with a flutter valve are alternative methods of physiotherapy that are less time consuming and do not require trained personnel.

Bronchodilator therapy. Bronchial reactivity to histamine and other provocative stimuli is greater in patients with CF than in individuals without the disease. Bronchodilator therapy can be considered if patients are known to have a response to inhaled bronchodilators. A response is defined as an increase of 10% or more in FEV_1 after bronchodilator administration.

Reduction in viscoelasticity of sputum. The abnormal viscosity of airway secretions is due primarily to the presence of neutrophils and their degradation products. DNA released from neutrophils forms long fibrils that contribute to the viscosity of the sputum. Recombinant human deoxyribonuclease I (dornase alfa [Pulmozyme]) can cleave this DNA and increase the clearance of sputum.

Antibiotic therapy. Patients with CF have periodic exacerbations of pulmonary infection that are recognized primarily by an increase in symptoms and in sputum production. Antibiotic therapy is based on identification and susceptibility testing of bacteria isolated from the sputum. In patients in whom cultures yield no pathogens, bronchoscopy to remove lower airway secretions may be indicated. Many patients with CF are given long-term maintenance antibiotic therapy in the hope of suppressing chronic infection and development of bronchiectasis.

Management of Anesthesia

Management of anesthesia in patients with CF follows the same principles as outlined for patients with COPD and bronchiectasis. Elective surgical procedures should be delayed

until optimal pulmonary function can be ensured by controlling bronchial infection and facilitating removal of airway secretions. Vitamin K treatment may be necessary if hepatic function is poor or if absorption of fat-soluble vitamins from the gastrointestinal tract is impaired. Maintenance of anesthesia with volatile anesthetics permits the use of high inspired concentrations of oxygen, decreases airway resistance by decreasing bronchial smooth muscle tone, and reduces airway hyperreactivity. Humidification of inspired gases, hydration, and avoidance of anticholinergic drugs are important steps in maintaining secretions in a less viscous state. Frequent tracheal suctioning may be necessary. Patients should regain their full airway reflexes and ventilatory abilities before extubation to decrease risk of aspiration. Postoperative pain control is extremely important to allow for deep breathing, coughing, and early ambulation so that pulmonary complications such as pneumonia, hypoxia, and atelectasis can be prevented.

Primary Ciliary Dyskinesia

Primary ciliary dyskinesia is characterized by congenital impairment of ciliary activity in respiratory tract epithelial cells and sperm tails (spermatozoa are alive but immobile). As a result of impaired ciliary activity in the respiratory tract, chronic sinusitis, recurrent respiratory infections, and bronchiectasis develop. Not only is there infertility in males, but fertility is also decreased in females because oviducts have ciliated epithelium. The triad of chronic sinusitis, bronchiectasis, and situs inversus is known as Kartagener syndrome. It is speculated that the normal asymmetric positioning of body organs is dependent on normal ciliary function of the embryonic epithelium. In the absence of normal ciliary function, placement of organs to the left or the right is random. As expected, approximately half of patients with congenitally nonfunctioning cilia exhibit situs inversus. In addition, isolated dextrocardia is almost always associated with congenital heart disease.

Preoperative preparation is directed at treating active pulmonary infection and determining whether any significant organ inversion is present. Regional anesthesia is preferable to general anesthesia in these patients to help decrease postoperative pulmonary complications. In the presence of dextrocardia, it is necessary to reverse the position of the ECG leads to permit their accurate interpretation. Inversion of the great vessels is a reason to select the left internal jugular vein for central venous cannulation. Uterine displacement in parturient women is logically to the right in these patients. Should a double-lumen endobronchial tube be considered, it is necessary to appreciate the altered anatomy introduced by pulmonary inversion. In view of the high incidence of sinusitis, nasopharyngeal airways should be avoided.

Bronchiolitis Obliterans

Bronchiolitis obliterans results from epithelial and subepithelial inflammation leading to bronchiolar destruction and narrowing. Multiple risk factors exist, including respiratory viral infections, environmental exposure to pollutants and toxins, lung transplantation, and stem cell transplant. Clinical manifestations are nonspecific and include dyspnea and nonproductive cough. PFT usually shows obstructive disease and includes a reduced FEV_1 and FEV_1:FVC ratio not responsive to bronchodilators. High-resolution CT scan shows air trapping and bronchiectasis in severe cases. Cryptogenic organizing pneumonia (formerly known as bronchiolitis obliterans with organizing pneumonia [BOOP]) is a clinical entity that shares certain features of interstitial lung disease and bronchiolitis obliterans. Treatment of bronchiolitis obliterans is usually ineffective, although chronic Macrobid antibiotics, systemic corticosteroids, and immunosuppressants may be useful. Cryptogenic organizing pneumonia, however, responds well to corticosteroid therapy.

Central Airway Obstruction

This category includes obstruction of airflow in the tracheal and mainstem bronchi. Approximately 20% to 30% of patients with lung cancer can be affected by airflow obstruction. They could be caused by airway compression by benign or malignant tumors, granulation from chronic infection, airway thinning from cartilage destruction, or infection. Tracheal stenosis can develop after prolonged intubation of the trachea either with an ETT or a tracheostomy tube. Tracheal mucosal ischemia can progress to destruction of cartilaginous rings, and subsequent circumferential constricting scar formation is minimized by the use of high-volume, low-pressure cuffs on tracheal tubes. Infection and hypotension may also contribute to events that culminate in tracheal stenosis.

Diagnosis

Tracheal stenosis becomes symptomatic when the lumen of the adult trachea is decreased to less than 5 mm in diameter. Symptoms may not develop until several weeks after tracheal extubation. Dyspnea is prominent even at rest. These patients must use accessory muscles of respiration during all phases of the breathing cycle and must breathe slowly. PEFRs are decreased. Stridor is usually audible. Flow-volume loops typically display flattened inspiratory and expiratory curves characteristic of a fixed airway obstruction (see Fig. 2.3A). CT of the trachea will demonstrate tracheal narrowing.

Management of Anesthesia

Tracheal dilation can be used as a temporizing measure to treat tracheal stenosis in some patients. This can be done bronchoscopically using balloon dilators or surgical dilators or laser resection of the tissue at the stenotic site. A tracheobronchial stent could also be inserted as either a temporary or longer-term solution to this problem. The most successful treatment is surgical tracheal resection and reconstruction with primary reanastomosis. This produces excellent long-term results. For this procedure, translaryngeal endotracheal intubation is accomplished. After surgical exposure, the distal normal trachea is opened, and a sterile cuffed tube is inserted and attached to the anesthetic circuit. Maintenance of anesthesia with volatile anesthetics is useful for ensuring a maximum inspired concentration of oxygen. High-frequency ventilation can be helpful in selected patients. Anesthesia for tracheal resection may be facilitated by the addition of helium to the inspired gases. This decreases the density of the gas mixture and may improve flow through the area of tracheal narrowing.

KEY POINTS

- Surgical patients with preexisting respiratory disease are at increased risk of respiratory complications both during and after surgery.
- The anesthetic management of a patient with a recent upper respiratory tract infection (URI) should focus on reducing secretions and limiting manipulation of a potentially hyperresponsive airway.
- If a patient with a URI appears toxic, elective surgery should be delayed.
- Asthma treatment is classified into immediate and long-term therapy. Immediate therapy for bronchospasm consists mainly of short-acting ¯-adrenergic agonists, whereas long-term relief includes inhaled corticosteroids, combined inhaled corticosteroids and long-acting bronchodilators, leukotriene modifiers, anti-IgE monoclonal antibody, monoclonal antibodies, and/or bronchial thermoplasty.
- In asthmatic patients the goal during induction and maintenance of anesthesia is to depress airway reflexes sufficiently to avoid bronchoconstriction in response to mechanical stimulation of the airway.
- In chronic obstructive pulmonary disease (COPD), smoking cessation and long-term oxygen therapy are the only two interventions that may decrease disease progression and mortality. Drug therapies, including inhaled -adrenergic agonists, inhaled corticosteroids, and anticholinergic drugs, are managed with a goal of decreasing exacerbation frequency.
- Pulmonary function tests (PFTs) have limited value in predicting the likelihood of postoperative pulmonary complications, and the results of PFTs in isolation should not be used to deny a patient access to surgery/anesthesia.
- Regional anesthesia, if indicated, is preferred over general anesthesia in patients with COPD, because this technique may decrease complications such as bronchospasm, barotrauma, and the need for positive pressure ventilation.
- COPD patients receiving general anesthesia should be ventilated at slow respiratory rates to allow sufficient time for full exhalation to occur. This minimizes the risk of air trapping and auto-PEEP.
- Prophylaxis against the development of postoperative pulmonary complications is based on restoring diminished lung volumes, especially functional residual capacity, and facilitating production of an effective cough to remove airway secretions.
- Intraoperative bronchospasm due to obstructive lung disease should be treated by deepening the anesthetic, administering bronchodilators (including -adrenergic agonists, corticosteroids, and epinephrine), and suctioning secretions as needed.

RESOURCES

American Society of Anesthesiologists. Stop Smoking Initiative. https://www.asahq.org/resources/clinical-information/asa-stop-smoking-initiative.

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3

Restrictive Respiratory Diseases and Lung Transplantation

Ranjit Deshpande, Viji Kurup

OUTLINE

The perioperative management of patients with restrictive lung disease presents unique challenges to the anesthesiologist. Although these patients are at increased risk of perioperative respiratory complications with all surgeries, their incidence is higher in patients undergoing cardiac, thoracic, vascular, and trauma surgeries. Restrictive lung disease is associated with increased perioperative morbidity and mortality. Although several conditions can cause restrictive lung disease, all share some common characteristics, and they differ from obstructive lung disease in several key features. Restrictive lung diseases affect both lung expansion and lung compliance ($\Delta V/\Delta P$). The hallmark of restrictive lung disease is an inability to increase lung volume in proportion to an increase in pressure in the alveoli. These disorders can result from connective tissue diseases, environmental factors, and other conditions that lead to pulmonary fibrosis, conditions that increase alveolar or interstitial fluid, and diseases that limit the appropriate excursion of the chest/diaphragm during breathing. These derangements lead to a reduction in available surface area for gas diffusion, leading to ventilation/perfusion mismatching and hypoxia. Intrinsic or extrinsic pathologies can affect the ability of the lung to expand. As the elasticity of the lungs worsens, patients become symptomatic owing to hypoxia, inability to clear lung secretions, and hypoventilation. This leads to a restrictive lung disease manifested by a reduced forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC), with a normal or increased FEV_1:FVC ratio and a reduced diffusing capacity for carbon monoxide (DLCO). A decrease in all lung volumes characterizes restrictive lung diseases, especially total lung capacity (TLC), a reduction in lung compliance, and preservation of expiratory flow rates (Fig. 3.1).

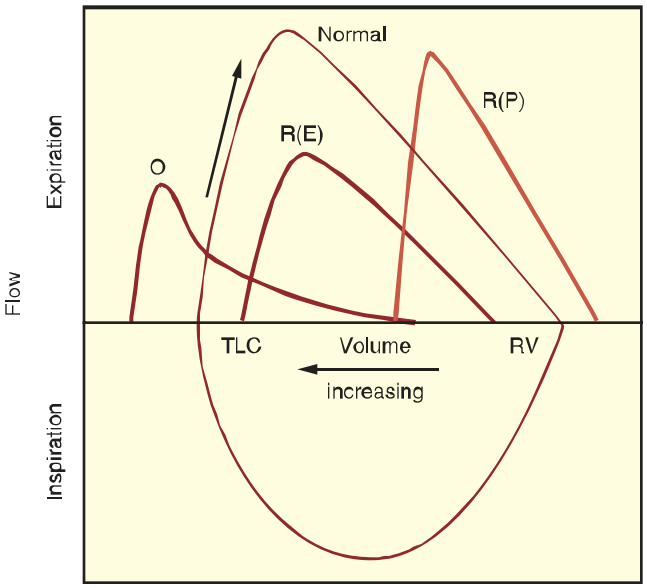

Fig. 3.1 Flow-volume curves in different conditions: obstructive disease *(O)*; extraparenchymal restrictive disease with limitation in inspiration and expiration *[R(E)]*; and parenchymal restrictive disease *[R(P)]*. Forced expiration is plotted for all conditions; forced inspiration is shown only for the normal curve. By convention, lung volume increases to the left on the abscissa. The arrow alongside the normal curve indicates the direction of expiration from total lung capacity *(TLC)* to residual volume *(RV)*. (Adapted from Weinberger SE. Disturbances of respiratory function. In: Fauci B, Braunwald E, Isselbacher KJ, et al., eds. *Harrison's Principles of Internal Medicine*. 14th ed. New York: McGraw-Hill; 1998.)

However, the principal feature of these diseases is a decrease in TLC (Fig. 3.2). TLC is used to classify restrictive lung disease as mild, moderate, or severe:

- Mild disease: TLC 65% to 80% of the predicted value
- Moderate disease: TLC 50% to 65% of the predicted value
- Severe disease: TLC less than 50% of the predicted value

Restrictive lung disease can be further classified according to its causes (Table 3.1).

ACUTE INTRINSIC RESTRICTIVE LUNG DISEASE (ALVEOLAR AND INTERSTITIAL PULMONARY EDEMA)

Pulmonary Edema

The leakage of intravascular fluid into the interstitium and the alveolar space leads to pulmonary edema. Acute pulmonary edema can be caused by increased capillary pressure (hydrostatic or cardiogenic pulmonary edema) or by increased capillary permeability. Both of these lead to a condition called capillary stress failure. Pulmonary edema typically appears as bilateral, symmetric perihilar opacities on chest radiography. This so-called butterfly fluid pattern is more commonly seen with increased capillary pressure than with increased capillary permeability. The presence of air bronchograms suggests increased-permeability pulmonary edema. Pulmonary edema caused by increased capillary permeability is characterized by a high concentration of protein and secretory products in the edema fluid. Diffuse alveolar damage is typically present with the increased-permeability pulmonary edema associated with acute respiratory distress syndrome (ARDS). Recently bedside lung ultrasound has emerged as a new modality to help diagnose pulmonary edema (Fig. 3.3).

Cardiogenic Pulmonary Edema

Cardiogenic pulmonary edema is characterized by marked dyspnea, tachypnea, and signs of sympathetic nervous system activation (hypertension, tachycardia, diaphoresis) that is often more pronounced than that seen in patients with increased-permeability pulmonary edema. This form of pulmonary edema is seen in acute decompensated heart failure and is characterized as dyspnea with elevated cardiac pressures. Cardiogenic pulmonary edema should be high in the differential if a patient has decrease in cardiac function either systolic or diastolic. One of the most underappreciated causes of cardiogenic pulmonary edema is diastolic dysfunction and should be actively sought after. Conditions that acutely increase preload such as acute aortic regurgitation and acute mitral regurgitation will also

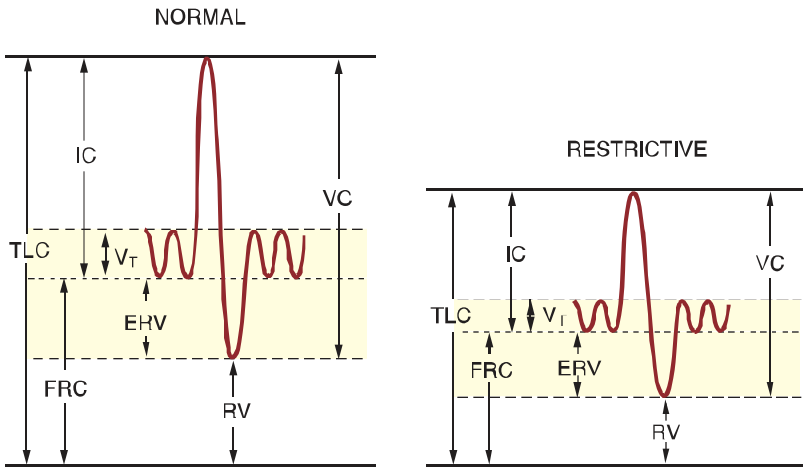

Fig. 3.2 Lung volumes in restrictive lung disease compared with normal values. *ERV*, Expiratory reserve volume; *FRC*, functional residual capacity; *IC*, inspiratory capacity; *RV*, residual volume; *TLC*, total lung capacity; *VC*, vital capacity; *VT*, tidal volume.

TABLE 3.1 Causes of Restrictive Lung Disease

Acute Intrinsic Restrictive Lung Disease (Pulmonary Edema)
Acute respiratory distress syndrome
Aspiration
Neurogenic problems
Opioid overdose
High altitude
Reexpansion of collapsed lung
Upper airway obstruction (negative pressure)
Congestive heart failure

Chronic Intrinsic Restrictive Lung Disease (Interstitial Lung Disease)
Sarcoidosis
Hypersensitivity pneumonitis
Eosinophilic granuloma
Alveolar proteinosis
Lymphangioleiomyomatosis
Drug-induced pulmonary fibrosis

Disorders of the Chest Wall, Pleura, and Mediastinum
Deformities of the costovertebral skeletal structures
- Kyphoscoliosis
- Ankylosing spondylitis

Deformities of the sternum
Flail chest
Pleural effusion
Pneumothorax
Mediastinal mass
Pneumomediastinum
Neuromuscular disorders
- Spinal cord transection
- Guillain-Barré syndrome
- Disorders of neuromuscular transmission
- Muscular dystrophies

Other
Obesity
Ascites
Pregnancy

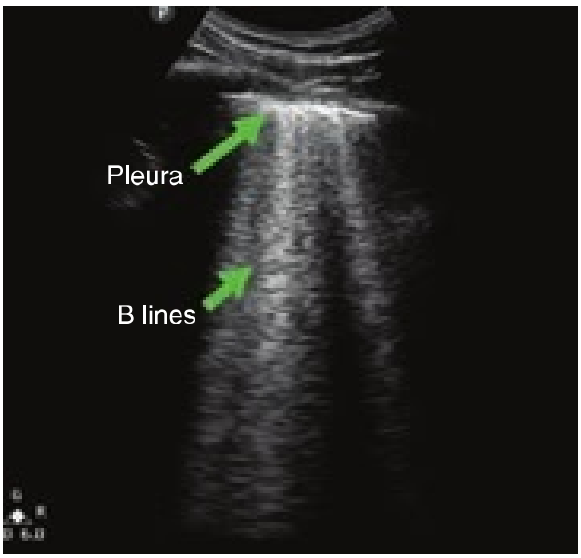

Fig. 3.3 Pulmonary edema.

predispose to cardiogenic pulmonary edema; conditions increasing afterload and systemic vascular resistance such as left ventricular outflow tract (LVOT) obstruction, mitral stenosis, and renovascular hypertension could also cause cardiogenic pulmonary edema.

Negative Pressure Pulmonary Edema

Negative pressure pulmonary edema follows the relief of acute upper airway obstruction. It is also called postobstructive pulmonary edema. It is caused by postextubation laryngospasm, epiglottitis, tumors, obesity, hiccups, or obstructive sleep apnea in spontaneously breathing patients. Spontaneous ventilation is necessary to create the marked negative pressure that causes this problem. The time to onset of pulmonary edema after relief of airway obstruction ranges from a few minutes to as long as 2 to 3 hours. Tachypnea, cough, and failure to maintain oxygen saturation above 95% are common presenting signs and may be confused with pulmonary aspiration or pulmonary embolism. Many cases of postoperative oxygen desaturation may be due to some degree of unrecognized negative pressure pulmonary edema.

The pathogenesis of negative pressure pulmonary edema is related to the development of high negative intrapleural pressure by vigorous inspiratory efforts against an obstructed upper airway (Mueller or reverse Valsalva maneuver). This high negative intrapleural pressure decreases the interstitial hydrostatic pressure, increases venous return, and increases left ventricular afterload. In addition, such negative pressure leads to intense sympathetic nervous system activation, hypertension, and central displacement of blood volume. Together these factors produce acute pulmonary edema by increasing the transcapillary pressure gradient.

Maintenance of a patent upper airway and administration of supplemental oxygen is usually sufficient treatment since this form of pulmonary edema is typically self-limited. Mechanical ventilation may occasionally be needed for a brief period. Hemodynamic monitoring reveals normal right and left ventricular function. Central venous pressure and pulmonary artery occlusion pressure are also normal. Radiographic evidence of this form of pulmonary edema resolves within 12 to 24 hours.

Neurogenic Pulmonary Edema

Neurogenic pulmonary edema develops in a small proportion of patients experiencing acute brain injury. Typically this form of pulmonary edema occurs minutes to hours after central nervous system (CNS) injury and may manifest during the perioperative period. There is a massive outpouring of sympathetic impulses from the injured CNS that results in generalized vasoconstriction and a shift of blood volume into the pulmonary circulation. Presumably the increased pulmonary capillary pressure from this acute translocation of blood volume leads to transudation of fluid into the interstitium and alveoli. Pulmonary hypertension and hypervolemia can also injure blood vessels in the lungs.

The association of pulmonary edema with a recent CNS injury should suggest the diagnosis of neurogenic pulmonary

edema. The principal entity in the differential diagnosis is aspiration pneumonitis. Unlike neurogenic pulmonary edema, chemical pneumonitis resulting from aspiration frequently persists longer and is often complicated by a bacterial infection.

Reexpansion Pulmonary Edema

The rapid expansion of a collapsed lung may lead to pulmonary edema in that lung. The risk of reexpansion pulmonary edema after relief of pneumothorax or pleural effusion is related to the amount of air or liquid that was present in the pleural space (>1 L increases the risk), the duration of collapse (>24 hours increases the risk), and the rapidity of reexpansion. The finding of high protein content in the pulmonary edema fluid suggests a role of enhanced capillary membrane permeability as a mechanism for the development of pulmonary edema. Treatment of reexpansion pulmonary edema is supportive.

Drug-Induced Pulmonary Edema

Acute noncardiogenic pulmonary edema can occur after the administration of several drugs, but especially opioids (heroin) and cocaine. The high protein concentration in the pulmonary edema fluid would suggest high-permeability pulmonary edema. Cocaine can also cause pulmonary vasoconstriction, acute myocardial ischemia, and myocardial infarction. There is no evidence that the administration of naloxone speeds the resolution of opioid-induced pulmonary edema. Another condition that needs to be in the differential is diffuse alveolar hemorrhage (DAH). If pulmonary edema on chest x-ray does not respond to diuretics, then this should be considered DAH. Treatment of patients who develop drug-induced pulmonary edema is supportive and may include tracheal intubation for airway protection and mechanical ventilation.

High-Altitude Pulmonary Edema (HAPE)

HAPE may occur at heights ranging from 2500 to 5000 m and is influenced by the rate of ascent to that altitude. The onset of symptoms is often gradual but typically occurs within 48 to 72 hours at high altitude. Fulminant pulmonary edema may be preceded by the less severe symptoms of acute mountain sickness. The cause of this high-permeability pulmonary edema is presumed to be hypoxic pulmonary vasoconstriction, which increases pulmonary vascular pressure. Treatment includes administration of oxygen and quick descent from the high altitude. Inhalation of nitric oxide may improve oxygenation.

Management of Anesthesia in Patients With Pulmonary Edema

Elective surgery should be delayed in patients with pulmonary edema, and every effort must be made to optimize cardiorespiratory function before surgery. Large pleural effusions may need to be drained. Persistent hypoxemia may require mechanical ventilation and positive end-expiratory pressure (PEEP). Hemodynamic monitoring may be useful in both the assessment and treatment of pulmonary edema. Patients with pulmonary edema are critically ill. Intraoperative management should be a continuation of critical care management and include a plan for intraoperative ventilator management. Current evidence shows that it might be beneficial to ventilate with low tidal volumes (e.g., 6–8 mL/kg) with a ventilatory rate of 14 to 18 breaths per minute while attempting to keep the end-inspiratory plateau pressure at less than 30 cm H_2O. Careful titration of PEEP in conjunction with inspiratory pause is recommended to optimize lung compliance. Patients with restrictive lung disease typically have rapid, shallow breathing. Tachypnea is likely during the weaning process and should not be used as the sole criterion for delaying extubation if gas exchange and results of other assessments are satisfactory.

Chemical Pneumonitis

Patients with decreased airway reflexes either due to their disease process or medications are at risk for aspiration. Intubation and extubation are high-risk periods for aspiration. Some authors recommend keeping the head of the bed elevated for intubations to decrease the chance of aspiration. Chemical pneumonitis could manifest with abrupt onset of dyspnea, tachycardia, and decreased oxygen saturations. When gastric fluid is aspirated, it is rapidly distributed throughout the lungs and produces the destruction of surfactant-producing cells and damage to the pulmonary capillary endothelium. As a result, there is atelectasis and leakage of intravascular fluid into the lungs, producing capillary-permeability pulmonary edema. This acute lung injury (ALI) might present with tachypnea, bronchospasm, and acute pulmonary hypertension. Arterial hypoxemia is commonly present. Chest radiography may not demonstrate evidence of aspiration pneumonitis for 6 to 12 hours after the event. Evidence of aspiration, when it does appear, is most likely to be in the superior segment of the right lower lobe if the patient aspirated while in the supine position. If an aspiration event is noted, the oropharynx should be suctioned and the patient turned to the side. Trendelenburg position or head-down position will not stop gastric reflux. Trendelenburg position can prevent aspiration once gastric contents are in the pharynx. After an episode, patients may need to be monitored for 24 to 48 hours for development of symptoms.

Measurement of gastric fluid pH is useful, since it reflects the pH of the aspirated fluid. Measurement of tracheal aspirate pH is of no value because airway secretions rapidly dilute the aspirated gastric fluid. The aspirated gastric fluid is also rapidly redistributed to peripheral lung regions, so lung lavage is not useful unless there has been an aspiration of particulate material.

Aspiration pneumonitis is best treated by the delivery of supplemental oxygen and PEEP. Bronchodilation may be needed to relieve bronchospasm. There is no evidence that prophylactic antibiotics decrease the incidence of pulmonary infection or alter the outcome. Antibiotics may be considered if a patient remains symptomatic after 48 hours and narrowed to specific therapy based on culture results. Corticosteroid treatment of aspiration pneumonitis remains controversial.

E-Cigarette (or Vaping) Product Use–Associated Lung Injury (EVALI)

It is a well-known fact that interstitial lung disease (ILD) can be caused by several factors, including inhalation of dusts, gases or fumes, and drugs. This may present as desquamative interstitial pneumonia, respiratory bronchiolitis–associated ILD, pulmonary Langerhans cell histiocytosis (PLCH), and idiopathic pulmonary fibrosis. A relatively newer entity, EVALI is now seen in patients using e-cigarettes and vaping (Cherian et al, 2020). EVALI is a form of ALI and is commonly associated with pneumonia, diffuse alveolar damage, acute fibrinous pneumonitis, and bronchiolitis. There may be varied presentation, including DAH. Additives such as tetrahydrocannabinol (THC), vitamin E acetate, nicotine, cannabinoids (CBD), and (rarely) other oils have been associated with EVALI. Most commonly one can see dyspnea, cough, nausea, vomiting, diarrhea, abdominal pain, and pleuritic or nonpleuritic chest pain. Patients may be febrile with tachycardia and tachypnea. Hypoxia and hemoptysis may also be noted. Radiologic findings are similar to diffuse alveolar damage seen in ARDS. Empiric antibiotics, systemic steroids, and supportive care are mainstays of therapy.

COVID-19 Induced Restrictive Lung Disease

Survivors of severe acute SARS-CoV-2 infection have been noted to have persistent inflammatory interstitial lung disease. The spectrum of pulmonary manifestations ranges from dyspnea to failure to wean form ventilator and pulmonary fibrosis. In one study the median 6min walking distance was lower than the normal range for approximately 25% of patients at 6months very similar to that seen with SARS and MERS survivors (Huang et al, 2021). A drop in diffusion capacity is the most commonly reported finding and directly co-relates to the severity of initial disease process. Patients who needed invasive or noninvasive form of mechanical ventilation were at the highest risk for long term pulmonary complications (Nalbandian et al, 2021). Along with the above-mentioned findings the survivors have decreased exercise capacity, hypoxia requiring supplemental oxygen, ground glass opacities on Computed Tomography (CT) scan. There is a lot of ongoing research on survivors of COVID 19.

Some recommended assessment strategies for recovery include pulse oximetry, 6minute walk test, Pulmonary function testing, high-resolution computed tomography of the chest and computed tomography pulmonary angiogram as clinically appropriate. Without a data from large systematic trials, it would be difficult to predict how patients with SARS-CoV-2 related persistent lung disease will do in the perioperative period.

ACUTE RESPIRATORY FAILURE

Overview

Respiratory failure is the inability to provide adequate arterial oxygenation and/or elimination of carbon dioxide. It has a myriad of causes. Acute respiratory failure is considered to be present when the Pao_2 is below 60 mm Hg despite oxygen supplementation and in the absence of a right-to-left intracardiac shunt. In the presence of acute respiratory failure, $Paco_2$ can be increased, unchanged, or decreased depending on the relationship of alveolar ventilation to the metabolic production of carbon dioxide. A $Paco_2$ above 50 mm Hg in the absence of respiratory compensation for metabolic alkalosis is consistent with the diagnosis of acute respiratory failure.

Acute respiratory failure is distinguished from chronic respiratory failure based on the relationship of $Paco_2$ to arterial pH (pHa). Acute respiratory failure is typically accompanied by abrupt increases in $Paco_2$ and corresponding decreases in pHa. With chronic respiratory failure, the pHa is usually between 7.35 and 7.45 despite an increased $Paco_2$. This normal pHa reflects renal compensation for chronic respiratory acidosis via renal tubular reabsorption of bicarbonate.

Respiratory failure is often accompanied by a decrease in functional residual capacity (FRC) and lung compliance. Increased pulmonary vascular resistance and pulmonary hypertension are likely to develop if the respiratory failure persists. ARDS is a condition that falls within the spectrum of acute respiratory failure.

Treatment of acute respiratory failure is directed at initiating specific therapies that support oxygenation and ventilation. The three principal goals in the management of acute respiratory failure are (1) a patent upper airway, (2) correction of hypoxemia, and (3) removal of excess carbon dioxide.

Mechanical Support for Ventilation

Supplemental oxygen can be provided to spontaneously breathing patients via nasal cannula, Venturi mask, nonrebreathing mask, or T-piece. These devices seldom provide inspired oxygen concentrations higher than 50% and therefore are of value only in correcting hypoxemia resulting from mild to moderate ventilation/perfusion mismatching. When these methods of oxygen delivery fail to maintain the Pao_2 above 60 mm Hg, continuous positive airway pressure (CPAP) by face mask can be initiated. CPAP may increase lung volumes by opening collapsed alveoli and decreasing right-to-left intrapulmonary shunting. A disadvantage of CPAP by face mask is that the tight mask fit required may increase the risk of pulmonary aspiration should the patient vomit. Maintenance of the Pao_2 above 60 mm Hg is adequate because hemoglobin saturation with oxygen is over 90% at this level. In some patients, it may be necessary to perform tracheal intubation and institute mechanical ventilation to maintain acceptable oxygenation and ventilation. Typical devices that provide positive pressure ventilation include volume-cycled and pressure-cycled ventilators (Tobias, 2010).

Volume-Cycled Ventilation

Volume-cycled ventilation provides a fixed tidal volume with inflation pressure as the dependent variable. A pressure limit can be set; when inflation pressure exceeds this value, a pressure relief valve prevents further gas flow. This valve prevents the development of dangerously high peak airway and alveolar pressures and warns that a change in pulmonary compliance has occurred. Significant increases in peak airway pressure may reflect worsening pulmonary edema, development of a pneumothorax, kinking of the tracheal tube, or the presence of mucous plugs in the tracheal tube or large airways. Tidal volume is

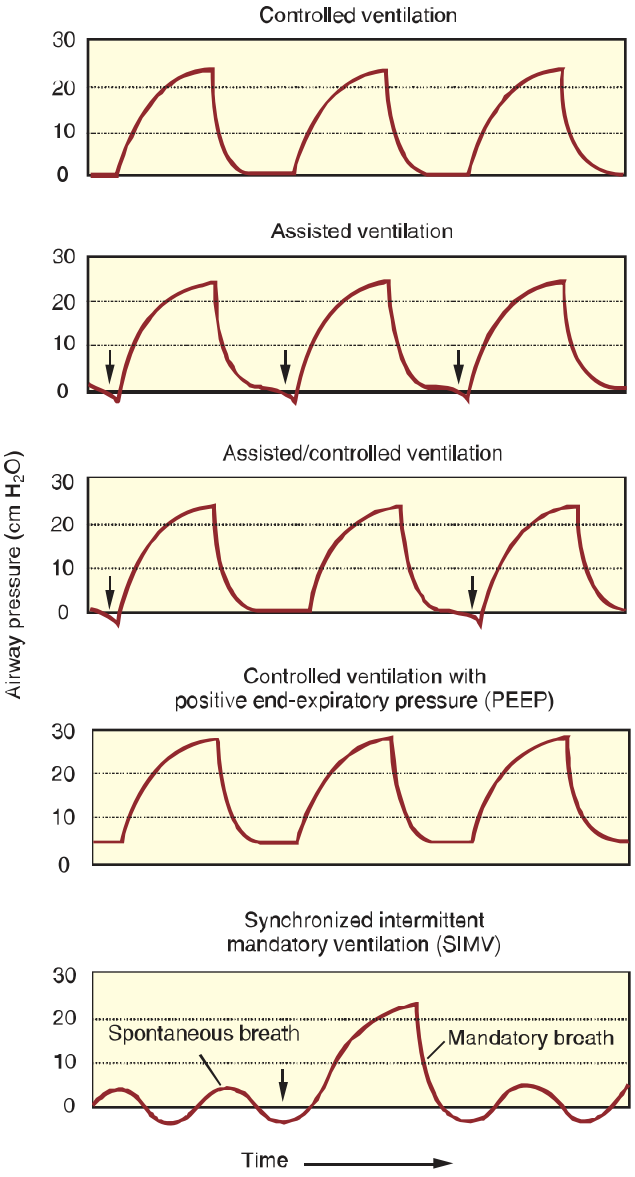

Fig. 3.4 Tidal volume and airway pressures produced by various modes of ventilation delivered through an endotracheal tube. Arrows indicate initiation of a spontaneous breath by the patient, who triggers the ventilator to deliver a mechanically assisted breath.

maintained despite small changes in peak airway pressure. A disadvantage of volume-cycled ventilation is the inability to compensate for leaks in the delivery system. The primary modalities of ventilation using volume-cycled ventilation are assisted/controlled (A/C) ventilation and synchronized intermittent mandatory ventilation (SIMV) (Fig. 3.4).

A/C ventilation. In the assist control mode, a preset respiratory rate ensures that a patient receives a predetermined number of mechanically delivered breaths even if there are no inspiratory efforts. In the assist mode, however, if the patient can create some negative airway pressure, a breath at the preset tidal volume will be delivered.

SIMV. The SIMV technique allows patients to breathe spontaneously at any rate and tidal volume, while the ventilator provides predefined minute ventilation. The gas delivery circuit is modified to provide sufficient gas flow for spontaneous breathing and permit periodic mandatory breaths that are synchronous with the patient's inspiratory efforts. Theoretical advantages of SIMV compared with A/C ventilation include continued use of respiratory muscles, lower mean airway and mean intrathoracic pressure, prevention of respiratory alkalosis, and improved patient–ventilator coordination.

Pressure-Cycled Ventilation

Pressure-cycled ventilation provides gas flow to the lungs until a preset airway pressure is reached. Tidal volume is the dependent variable and varies with changes in lung compliance and airway resistance.

Newer modes of mechanical ventilation are beyond the scope of this chapter.

Management of Patients Receiving Mechanical Support for Ventilation

Critically ill patients who require mechanical ventilation may benefit from a continuous infusion of sedative drugs to treat anxiety and agitation and to facilitate coordination with ventilator-delivered breaths. Inadequate sedation or agitation can lead to life-threatening problems such as self-extubation, acute deterioration in gas exchange, and barotrauma. The optimum use of sedation can reduce the need for neuromuscular blockade. However, when acceptable sedation without hemodynamic compromise cannot be achieved, it may be necessary to produce skeletal muscle paralysis to ensure appropriate ventilation and oxygenation.

Sedation. Benzodiazepines, propofol, dexmedetomidine, and opioids are the drugs most commonly administered to decrease anxiety, produce amnesia, increase patient comfort, and provide analgesia during mechanical ventilation. Continuous infusion of drugs rather than intermittent injection provides a more constant and desirable level of sedation. Daily interruption of sedative infusions to allow the patient to "awaken" may facilitate the evaluation of mental status and ultimately shorten the period of mechanical ventilation. Continuous infusion of propofol is uniquely attractive for this purpose because of the brief context-sensitive halftime of this drug, and rapid awakening is predictable. Prompt recovery from the effects of a remifentanil infusion is also not affected by the duration of the drug infusion. Dexmedetomidine is already considered preferable to benzodiazepines for intensive care unit (ICU) sedation, and multiple studies have shown a reduction in ICU delirium with dexmedetomidine.

Muscle relaxants. When sedation is inadequate, hypotension accompanies the administration of drugs used for sedation, or in cases of early moderate to severe ARDS the use of nondepolarizing neuromuscular blocking drugs to produce skeletal muscle relaxation may be necessary to permit optimal mechanical ventilation (Papazian et al, 2010). The dependence of some of these drugs on renal clearance should be considered. It is better to use intermittent rather than continuous skeletal muscle paralysis to allow periodic assessment of the adequacy of sedation and the need for ongoing paralysis. Monitoring of neuromuscular blockade and titration of muscle relaxant doses so that two twitch responses remain in the train-of-four is prudent.

Patients who need neuromuscular blockade must be monitored for adequate depth of anesthesia, especially if using total

intravenous anesthesia. Monitoring with electroencephalography (EEG), such as bispectral index (BIS), entropy, and cerebral state index, should be available. Neuromuscular weakness and neuropathy (ICU-acquired weakness [ICU-AW]) can present as critical illness polyneuropathy, critical illness myopathy, or critical illness neuromyopathy based on nerve conduction studies. Neuromuscular blocking agents, especially steroidal agents, have been implicated in this disorder.

Complications of Mechanical Ventilation

Infection. In mechanically ventilated patients with acute respiratory failure, tracheal intubation is the single most important predisposing factor for the development of nosocomial pneumonia (ventilator-associated pneumonia). The primary pathogenic mechanism is the microaspiration of contaminated secretions around the tracheal tube cuff. Diagnosis of pneumonia in the presence of acute respiratory failure may be difficult since fever and pulmonary infiltrates may already be present in association with the cause of acute respiratory failure.

Nosocomial sinusitis is strongly related to the presence of a nasotracheal tube. Treatment of nosocomial sinusitis includes administration of antibiotics, replacement of nasal tubes with oral tubes, and use of decongestants and head elevation to facilitate sinus drainage.

Barotrauma. Barotrauma may present as subcutaneous emphysema, pneumomediastinum, pulmonary interstitial emphysema, pneumoperitoneum, pneumopericardium, arterial gas embolism, or tension pneumothorax. These examples of extraalveolar air almost always reflect dissection or passage of air from overdistended and ruptured alveoli. Infection increases the risk of barotrauma, presumably by weakening pulmonary tissue. Barotrauma severe enough might manifest as a tension pneumothorax. Hypotension, worsening hypoxemia, and increased airway pressure suggest the presence of a tension pneumothorax.

Atelectasis. Atelectasis is a common cause of hypoxemia that develops during mechanical ventilation. Migration of the tracheal tube into the left or right main bronchus or development of mucous plugs should be considered when abrupt worsening of oxygenation occurs in the absence of hypotension. Arterial hypoxemia resulting from atelectasis is not responsive to an increase in Fio_2. Other causes of sudden hypoxemia in mechanically ventilated patients include tension pneumothorax and pulmonary embolism, but in contrast to atelectasis these are usually accompanied by hypotension. Bronchoscopy may be necessary to remove mucous plugs responsible for persistent atelectasis. Atelectasis may be identified on bedside lung ultrasound (LUS) by presence of static air bronchograms.

Monitoring of Treatment

Monitoring the progress of treatment of acute respiratory failure includes evaluation of pulmonary gas exchange (arterial and venous blood gases, pHa) and cardiac function (cardiac output, cardiac filling pressures, intrapulmonary shunt). Pao_2 reflects the adequacy of oxygen exchange across alveolar capillary membranes. The efficacy of this exchange is paralleled by the difference between the calculated alveolar Po_2 (Pao_2) and the measured Pao_2. Calculation of $Pao_2 - Pao_2$ is useful for evaluating the gas exchange function of the lungs and for distinguishing among the various causes of arterial hypoxemia (Table 3.2).

Significant desaturation of arterial blood occurs only when the Pao_2 is less than 60 mm Hg. Ventilation/perfusion mismatching, right-to-left intrapulmonary shunting, and hypoventilation are the principal causes of arterial hypoxemia. Increasing the inspired oxygen concentration is likely to improve Pao_2 in all of these conditions, except for a significant right-to-left intrapulmonary shunt.

Compensatory responses to arterial hypoxemia vary. As a general rule, these responses are stimulated by an acute decrease in Pao_2 below 60 mm Hg. Compensatory responses are also present in chronic hypoxemia when Pao_2 is less than 50 mm Hg. These responses to arterial hypoxemia include:

1. Carotid body–induced increase in alveolar ventilation
2. Regional pulmonary artery vasoconstriction (hypoxic pulmonary vasoconstriction) to divert pulmonary blood flow away from hypoxic alveoli
3. Increased sympathetic nervous system activity to enhance tissue oxygen delivery by increasing cardiac output

Chronic hypoxemia leads to an increase in red blood cell mass to improve the oxygen-carrying capacity of the blood. The adequacy of alveolar ventilation relative to the metabolic production of carbon dioxide is reflected by the $Paco_2$ (Table 3.3). The efficacy of carbon dioxide transfer across alveolar capillary membranes is reflected by the dead space–to–tidal volume ratio (V_D:V_T). This ratio indicates areas in the lungs that receive adequate ventilation but inadequate or no pulmonary blood flow. Ventilation to these alveoli is described as wasted or dead space ventilation. Normally the V_D:V_T is less than 0.3, but it may increase to 0.6 or more when there is an increase in dead space ventilation. An increased V_D:V_T occurs in the presence of acute

TABLE 3.2 Mechanisms of Arterial Hypoxemia

Mechanism	Pao_2	$Paco_2$	$Pao_2 - Pao_2$	Response to Supplemental Oxygen
Low inspired oxygen concentration (altitude)	Decreased	Normal to decreased	Normal	Improved
Hypoventilation (drug overdose)	Decreased	Increased	Normal	Improved
Ventilation/perfusion mismatching (chronic obstructive pulmonary disease, pneumonia)	Decreased	Normal to decreased	Increased	Improved
Right-to-left intrapulmonary shunt (pulmonary edema)	Decreased	Normal to decreased	Increased	Poor to none
Diffusion impairment (pulmonary fibrosis)	Decreased	Normal to decreased	Increased	Improved

TABLE 3.3 Mechanisms of Hypercarbia

Mechanism	$Paco_2$	V_D/V_T	$Pao_2 - Pao_2$
Drug overdose	Increased	Normal	Normal
Restrictive lung disease (kyphoscoliosis)	Increased	Normal to increased	Normal to increased
Chronic obstructive pulmonary disease	Increased	Increased	Increased
Neuromuscular disease	Increased	Normal to increased	Normal to increased

respiratory failure, a decrease in cardiac output, and pulmonary embolism.

Hypercarbia is defined as a $Paco_2$ above 45 mm Hg. Permissive hypercapnia is the strategy of allowing $Paco_2$ to increase to up to 55 mm Hg or more in spontaneously breathing patients to avoid or delay the need for tracheal intubation and mechanical ventilation. Symptoms and signs of hypercarbia depend on the rate of increase and the ultimate level of $Paco_2$. Acute increases in $Paco_2$ are associated with increased cerebral blood flow and increased intracranial pressure. Extreme increases in $Paco_2$ to over 80 mm Hg result in CNS depression.

Mixed Venous Partial Pressure of Oxygen

The mixed venous partial pressure of oxygen (Pvo_2) and the arterial venous oxygen content difference ($Cao_2 - Cvo_2$) reflect the overall adequacy of the oxygen transport system (cardiac output) relative to tissue oxygen extraction. For example, a decrease in cardiac output that occurs in the presence of unchanged tissue oxygen consumption causes Pvo_2 to decrease and $Cao_2 - Cvo_2$ to increase. These changes reflect the continued extraction of the same amount of oxygen by the tissues during a time of decreased tissue blood flow. A Pvo_2 below 30 mm Hg or a $Cao_2 - Cvo_2$ above 6 mL/dL indicates the need to increase cardiac output to facilitate tissue oxygenation. A pulmonary artery catheter permits sampling of mixed venous blood, measurement of Pvo_2, and calculation of Cvo_2.

Arterial pH

Measurement of pHa is necessary to detect acidemia or alkalemia. Metabolic acidosis predictably accompanies arterial hypoxemia and inadequate delivery of oxygen to tissues. Acidemia caused by respiratory or metabolic derangements is associated with dysrhythmias and pulmonary hypertension.

Alkalemia is often associated with mechanical hyperventilation and diuretic use, which leads to loss of chloride and potassium ions. The incidence of dysrhythmias may be increased by respiratory alkalosis. The presence of alkalemia in patients recovering from acute respiratory failure can delay or prevent successful weaning from mechanical ventilation because of the compensatory hypoventilation that will occur to correct the pH disturbance.

Intrapulmonary Shunt

Right-to-left intrapulmonary shunting occurs when there is perfusion of nonventilated alveoli (West zone 3). The net effect is a decrease in Pao_2, reflecting dilution of oxygen in blood exposed to ventilated alveoli with blood containing little oxygen coming from unventilated alveoli. Calculation of the shunt fraction provides a reliable assessment of ventilation/perfusion matching and serves as a useful estimate of the response to various therapeutic interventions during the treatment of acute respiratory failure.

A physiologic shunt typically comprises 2% to 5% of cardiac output. This degree of right-to-left intrapulmonary shunting reflects the passage of pulmonary arterial blood directly to the left side of the circulation through the bronchial and thebesian veins. It should be appreciated that the determination of the shunt fraction in patients breathing less than 100% oxygen reflects the contribution of ventilation/perfusion mismatching as well as right-to-left intrapulmonary shunting. Calculation of the shunt fraction from measurements obtained when the patient breathes 100% oxygen eliminates the contribution of ventilation/perfusion mismatching.

Weaning From the Ventilator

Mechanical ventilatory support is withdrawn when a patient can maintain oxygenation and carbon dioxide elimination without assistance. When determining whether the patient can be safely weaned from mechanical ventilation and will tolerate extubation, essential considerations include that the patient is alert and cooperative and can tolerate a trial of spontaneous ventilation without excessive tachypnea, tachycardia, or respiratory distress. Some of the guidelines that have been proposed for indicating the feasibility of discontinuing mechanical ventilation include:

- Vital capacity of more than 15 mL/kg
- Alveolar-arterial oxygen difference of less than 350 cm H_2O while breathing 100% oxygen
- Pao_2 of more than 60 mm Hg with an Fio_2 of less than 0.5
- Negative inspiratory pressure of more than −20 cm H_2O
- Normal pHa
- Respiratory rate lower than 20 breaths per minute
- $V_D:V_T$ of less than 0.6

Breathing at rapid rates with low tidal volumes usually signifies an inability to tolerate extubation. Ultimately the decision to attempt withdrawal of mechanical ventilation is individualized and considers not only pulmonary function but also the presence of coexisting medical problems.

When a patient is ready for a trial of withdrawal from mechanical support of ventilation, three options may be considered:

1. SIMV, which allows spontaneous breathing amid progressively fewer mandatory breaths per minute until the patient is breathing unassisted
2. Intermittent trials of total removal of mechanical support and breathing through a T-piece
3. Use of decreasing levels of pressure support ventilation

Overall, correcting the underlying condition responsible for the need for mechanical ventilation is more important for successful extubation than the weaning method. Deterioration in oxygenation after the withdrawal of mechanical ventilation may reflect progressive alveolar collapse, which can be responsive to treatment with CPAP or noninvasive positive pressure ventilation (NIPPV) rather than the reinstitution of mechanical ventilation.

Several things may interfere with successful withdrawal from mechanical ventilation and extubation. Excessive workload on the respiratory muscles imposed by hyperinflation, copious secretions, bronchospasm, increased lung water, or increased carbon dioxide production from fever or parenteral nutrition greatly decreases the likelihood of successful tracheal extubation. The use of noninvasive ventilation (NIV) as a bridge to discontinuation of mechanical ventilation may be considered. This involves early extubation with the immediate application of a form of NIV. This method of weaning may be associated with a decreased incidence of nosocomial pneumonia, a shorter ICU stay, and a reduction in mortality. However, NIV may impair the ability to clear airway secretions if the patient does not have a good cough, and there may be inadequate minute ventilation. Careful patient selection is required if this modality is being considered.

Tracheal Extubation

Tracheal extubation should be considered when patients tolerate 30 minutes of spontaneous breathing with CPAP of 5 cm H_2O without deterioration in arterial blood gas concentrations, mental status, or cardiac function. The Pao_2 should remain above 60 mm Hg with Fio_2 less than 0.5. Likewise, the $Paco_2$ should remain below 50 mm Hg, and the pHa should remain above 7.30. Additional criteria for tracheal extubation include the need for less than 5 cm H_2O PEEP, spontaneous breathing rates lower than 20 breaths per minute, and a vital capacity above 15 mL/kg. Patients should be alert, with active laryngeal reflexes and the ability to generate an effective cough and clear secretions. Protective glottic closure function may be impaired following tracheal extubation, which results in an increased risk of aspiration.

Oxygen Supplementation

Oxygen supplementation is often needed after tracheal extubation. This need reflects the persistence of ventilation/perfusion mismatching. Weaning from supplemental oxygen is accomplished by gradually decreasing the inspired concentration of oxygen, as guided by measurements of Pao_2 and/or monitoring of oxygen saturation by pulse oximetry.

ACUTE RESPIRATORY DISTRESS SYNDROME

Adult ARDS is caused by inflammatory injury to the lung and is manifested clinically as acute hypoxemic respiratory failure. Events that can cause direct or indirect lung injury and lead to ARDS are listed in Table 3.4. Sepsis is associated with the highest risk of progression to ARDS. Rapid-onset respiratory failure accompanied by refractory arterial hypoxemia, with radiographic findings indistinguishable from cardiogenic pulmonary edema, are the hallmarks of ARDS. Proinflammatory cytokines lead to the increased alveolar capillary membrane permeability and alveolar edema seen in this condition. The acute phase of ARDS usually resolves completely, but in some patients it may progress to fibrosing alveolitis with persistent arterial hypoxemia and decreased pulmonary compliance.

TABLE 3.4 Clinical Disorders Associated With Acute Respiratory Distress Syndrome

Direct Lung Injury
Pneumonia
Aspiration of gastric contents
Pulmonary contusion
Fat emboli
Near drowning
Inhalational injury
Reperfusion injury
Indirect Lung Injury
Sepsis
Trauma associated with shock
Multiple blood transfusions
Cardiopulmonary bypass
Drug overdose
Acute pancreatitis

TABLE 3.5 The Berlin Definition of Acute Respiratory Distress Syndrome

Lung injury of acute onset with 1 week of an apparent clinical insult and with progression of pulmonary symptoms
Bilateral opacities on lung imaging not explainable by other lung pathology
Respiratory failure not explained by heart failure or volume overload
Decreased arterial Pao_2/Fio_2 ratio:
Mild ARDS: ratio is 201–300
Moderate ARDS: ratio is 101–200
Severe ARDS: ratio is <101

From the ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307:2526-2533.

Diagnosis

The previous definition of ARDS came from the American-European Consensus Conference of 1994, but this has now been supplanted by the Berlin definition of ARDS (Force et al, 2012), which is the result of the work of a task force empowered by critical care societies from several countries (Table 3.5). The focus of the new definition is on oxygenation, the timing of disease onset, and imaging results. The term *acute lung injury* is no longer used.

ARDS is now classified as follows:

- Mild (200 mm Hg $<$ Pao_2/Fio_2 $\leq$ 300 mm Hg)
- Moderate (100 mm Hg $<$ Pao_2/Fio_2 $\leq$ 200 mm Hg)
- Severe (Pao_2/Fio_2 $\leq$ 100 mm Hg)

The calculation of the Pao_2/Fio_2 ratios must be calculated with CPAP or PEEP of at least 5 cm H_2O. Pulmonary artery occlusion pressure is no longer a part of the definition of ARDS. Bilateral findings on chest radiography in at least three lung quadrants not explained by pleural effusion or atelectasis are seen. Echocardiography helps rule out a cardiogenic cause of pulmonary edema.

Pulmonary hypertension can be due to pulmonary artery vasoconstriction and obliteration of portions of the pulmonary capillary bed and, when severe, can cause acute right-sided heart failure. Death from ARDS is most often a result of sepsis or multiple organ failure rather than respiratory failure, although some deaths are directly related to lung injury.

Clinical Management

Management of a patient with ARDS is mainly supportive. Supportive care consists of mechanical ventilation, antibiotics, stress ulcer prophylaxis, venous thromboembolism prophylaxis, and early enteral feeding (Table 3.6).

Mechanical ventilation in patients with ARDS has been a topic of great debate. Two schools of thought exist: low tidal protective ventilation and open lung ventilation. Low tidal volume ventilation (6 mL/kg of predicted body weight) has shown to reduce 28-day mortality and total hospital mortality. Overinflation of the lungs is deleterious because it appears to be the primary mechanism of ventilator-induced lung injury. Limiting end-inspiratory lung stretch to minimize mortality in ARDS patients has been evaluated, and a mortality benefit of 22% was noted in patients ventilated with "low" (6 mL/kg) tidal volumes compared to higher lung volumes. This mortality benefit did not appear to have any relationship to baseline lung compliance or the underlying factor responsible for the development of ARDS. It was noted that inflammatory mediators' concentrations, especially those of interleukin-6 (IL6), were lower in the survival group.

Other studies addressed the potential superiority of an open lung ventilation approach in which PEEP was titrated to the highest value possible while keeping plateau pressure below 28 to 30 cm H_2O. Patients treated according to the open lung approach had significantly more ventilator-free days and organ failure–free days, but in-hospital mortality, 28-day mortality, and 60-day mortality were not improved. In addition to lung overdistension, cyclic opening and closing of small airways and alveolar units during tidal mechanical ventilation can lead to a form of lung injury called atelectrauma. Several trials have examined the effects of open lung ventilation and protective lung ventilation in limiting atelectrauma. Open lung ventilation strategy such as airway pressure release ventilation (APRV) might improve oxygenation while minimizing ventilator-associated lung injury (VALI). Given that the recruitability of alveoli is extremely difficult to gauge and changes with the extent of disease, open lung strategies work best in early diffuse ARDS versus late ARDS or focal ARDS. If the alveoli are difficult to recruit, open lung strategy may induce VALI. Open lung strategy might increase afterload to the right ventricle and cause hemodynamic impairment.

TABLE 3.6 Treatment of Acute Respiratory Distress Syndrome

Oxygen supplementation
Tracheal intubation
Mechanical ventilation
Positive end-expiratory pressure
Optimization of intravascular fluid volume
Diuretic therapy
Inotropic support
Glucocorticoid therapy
Neuromuscular blockers
Prone positioning
Removal of secretions
Control of infection
Nutritional support
Administration of inhaled β_2-adrenergic agonists

Prone positioning and extracorporeal membrane oxygenation (ECMO) have been proposed as therapies for the life-threatening refractory hypoxemia in patients with severe ARDS. Both strategies have demonstrated improvement in oxygenation. Prone positioning exploits gravity and repositioning of the heart in the thorax to recruit lung units and improve ventilation/perfusion matching. It appears that prone position ventilation is beneficial in selected patients with severe ARDS, as indicated by an improvement in oxygenation as well as a mortality benefit.

Extracorporeal lung support (ECLS) techniques like ECMO can be considered in patients with severe hypoxemic and/or hypercapnic respiratory failure as possible rescue therapy. The aim of this strategy is to rest the lungs until severe hypoxemia, and respiratory acidosis has resolved. The benefits and timing of venovenous ECMO in ARDS remain controversial.

Additional supportive therapies are crucial in the management of ARDS. Optimal fluid management, neuromuscular blockade, inhaled nitric oxide, prostacyclin (PGI_2) administration, recruitment maneuvers, surfactant replacement therapy, glucocorticoids, and ketoconazole have all been implicated in improved outcomes in ARDS.

A positive fluid balance is an independent risk factor for mortality in critically ill patients. Conservative fluid therapy is considered the mainstay in managing pulmonary issues despite the lack of evidence showing mortality benefit. Hypervolemia can lead to increased vascular permeability in already damaged lung tissue. Negative euvolemia is preferred and is associated with lower mortality. We prefer conservative therapy as long as there is adequate perfusion pressure. Some data suggest a combination of albumin and furosemide may improve fluid balance, oxygenation, and hemodynamics.

The use of neuromuscular blockers has been associated with less barotrauma and less secretion of both pulmonary and systemic proinflammatory mediators. However, given the potential adverse effect of these medications in terms of causing ICU-acquired myopathy, their use should be limited to severely hypoxemic patients for as brief a period as possible.

Pulmonary vasodilators such as inhaled nitric oxide (NO) and inhaled epoprostenol (iEPO) have been proposed to treat refractory hypoxemia, owing to its vasodilatory effects on vascular smooth muscle. It can help improve ventilation/perfusion matching and decrease pulmonary vascular resistance and pulmonary artery pressure. Several studies have noted a transient improvement in oxygenation but no reduction in mortality.

Other therapies that have been used to manage ARDS are continuous high-volume hemofiltration, aspirin, and glucocorticoids. Some promising therapies that are being researched are cell-based therapy with mesenchymal cells and statin therapy.

CHRONIC INTRINSIC RESTRICTIVE LUNG DISEASE (INTERSTITIAL LUNG DISEASE)

ILD is a term used for a group of diseases with similar presentation and radiographic findings, leading to restrictive physiology from diffuse parenchymal disease. Patients usually present with dyspnea and nonproductive cough. This leads to a chronic restrictive form of lung disease. Pulmonary hypertension and cor pulmonale develop as progressive pulmonary fibrosis results in the loss of pulmonary vasculature. Clubbing of the digits is common in some ILDs such as asbestosis and idiopathic pulmonary fibrosis. It is important to look for extrapulmonary involvement of systemic disease associated with ILD in all these patients (Table 3.7).

Sarcoidosis

Sarcoidosis is a systemic granulomatous disorder that involves many tissues but has a predilection for intrathoracic lymph nodes and the lungs. Many patients have no symptoms at the time of presentation, and the disease is often identified only because of abnormal findings on chest radiography. Crackles are not common even in the presence of parenchymal disease. Wheezing may be present if there is involvement of the bronchioles. Some patients may have respiratory symptoms such as dyspnea and cough. Ocular sarcoidosis may produce uveitis; myocardial sarcoidosis may produce conduction defects and dysrhythmias. The most common form of neurologic involvement in sarcoidosis is unilateral facial nerve palsy. Endobronchial sarcoid is common. Laryngeal sarcoidosis occurs in up to 5% of patients and may interfere with the passage of adult-size tracheal tubes. Cor pulmonale may develop. Hypercalcemia occurs in fewer than 10% of patients but is a classic manifestation of sarcoidosis.

Angiotensin-converting enzyme (ACE) activity is increased in patients with sarcoidosis and is presumably due to the production of this enzyme by cells within the granuloma. However, this increase in ACE activity does not have useful diagnostic or prognostic significance. Other markers that have been studied include serum amyloid A, serum and bronchoalveolar lavage levels of adenosine deaminase, and serum soluble IL2 receptor. Kveim test is used to detect sarcoidosis and is similar to a tuberculin test. This is essentially a research tool. Procedures such as mediastinoscopy, endobronchial/transbronchial ultrasound, and bronchoscopy may be necessary to provide tissue or bronchoalveolar lavage for the diagnosis of sarcoidosis. Corticosteroids are administered to suppress the manifestations of sarcoidosis and to treat the hypercalcemia. Advanced pulmonary fibrosis may lead to pulmonary hypertension in these patients.

TABLE 3.7 Interstitial Lung Disease

Diffuse parenchymal lung disease	Drugs
	Rheumatic disease
Idiopathic interstitial pneumonia	Chronic fibrosing, acute fibrosing or smoking related
Granulomatous lung disease	Sarcoidosis
Others	Lymphangioleiomyomatosis
	Pulmonary Langerhans cell histiocytosis or histiocytosis X

Hypersensitivity Pneumonitis (Extrinsic Allergic Alveolitis)

Hypersensitivity pneumonitis is characterized by diffuse interstitial granulomatous reactions in the lungs after inhalation of dust containing fungi, spores, and animal or plant material. This pneumonitis may present as an acute, subacute, or chronic form. Signs and symptoms of acute disease include the onset of dyspnea and cough 4 to 6 hours after inhalation of the antigens. This is followed by leukocytosis, eosinophilia, and often arterial hypoxemia. High-resolution computed tomography (CT) shows centrilobular ground-glass opacities in the mid to upper zones of the lung. Patients may present for procedures such as bronchoscopy, transtracheal or transbronchial biopsy, and cryobiopsy. Repeated episodes of hypersensitivity pneumonitis may lead to pulmonary fibrosis. Treatment consists of antigen avoidance, glucocorticoids, and lung transplantation.

Pulmonary Langerhans Cell Histiocytosis

Pulmonary fibrosis accompanies the disease process previously known as eosinophilic granuloma (histiocytosis X). In this disease the inflammation is usually around smaller bronchioles leading to destruction of bronchiolar wall and surrounding lung parenchyma. The disease usually affects the upper and middle zones of the lung. A strong association with smoking tobacco has been observed. High-resolution CT can be diagnostic, showing cysts or honeycombing in upper zones with costophrenic sparing. Lung biopsy shows pathognomonic inflammatory lesions around the bronchioles containing Langerhans cells, eosinophils, lymphocytes, and neutrophils. Treatment consists of smoking cessation, systemic glucocorticoid therapy, and symptomatic support.

Pulmonary Alveolar Proteinosis (PAP)

PAP is a disease characterized by the deposition of lipid-rich proteinaceous material in the alveoli. It usually presents in the fourth or fifth decade of life. Dyspnea and arterial hypoxemia are clinical manifestations. This process may occur independently or in association with chemotherapy, acquired immunodeficiency syndrome (AIDS), or inhalation of mineral dust. Chest x-ray shows batwing distribution of alveolar opacities in middle and lower lung zones. Smoking cessation is advised for all patients. Although spontaneous remission may occur, the treatment of severe cases requires whole-lung lavage under general anesthesia to remove the alveolar material and improve macrophage function. Lung lavage in patients with hypoxemia may temporarily decrease the level of oxygenation further. Airway management during anesthesia for lung lavage includes placement of a double-lumen endobronchial tube to facilitate lavage of each lung separately and to optimize oxygenation during the procedure.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis is a rare multisystem disease that results in proliferation of smooth muscle in airways, lymphatics,

and blood vessels mostly in women of reproductive age. Pulmonary function tests show restrictive and obstructive lung disease with a decrease in diffusing capacity. Lymphangioleiomyomatosis presents clinically as progressive dyspnea, hemoptysis, recurrent pneumothorax, and pleural effusions. Treatment with sirolimus is indicated in symptomatic patients with rapidly progressive disease.

Aging-Related Restrictive Physiology

Aging is associated with physiologic lung changes, chest wall compliance decreases, and decreased elastic recoil. This leads to increased residual volume and decreased vital capacity. Geriatric patients breathe at a higher lung volume with increased FRC. Respiratory muscle function from the changes in lung volume and geometry of the thoracic cage plays an important part in the lung physiology of aging. Kyphosis curvature and the anteroposterior (AP) diameter of the chest increase with aging, thus decreasing the efficiency of the diaphragm. There seems to be a rapid decline in FEV_1 and FVC with age and an even more rapid decline in patients with increased airway reactivity.

Management of Anesthesia in Patients With Chronic Interstitial Lung Disease

Patients with ILD tolerate apneic periods very poorly because of their small FRC and low oxygen stores. Preoperatively, lung function should be optimized. Any infection should be treated, secretions minimized, and smoking cessation advised. General anesthesia, the supine position, and controlled ventilation all contribute to further decreases in FRC. Alterations in FRC and the risk of hypoxia continue into the postoperative period. Uptake of inhaled anesthetics is faster in these patients because of the small FRC. Peak airway pressures should be kept as low as possible to minimize the risk of barotrauma.

CHRONIC EXTRINSIC RESTRICTIVE LUNG DISEASE

Thoracic Extrapulmonary Causes

Chronic extrinsic restrictive lung disease is often due to disorders of the thoracic cage (chest wall) that interfere with lung expansion. Deformities of the sternum, ribs, vertebrae, and costovertebral structures include conditions such as ankylosing spondylitis, flail chest, scoliosis, and kyphosis. The lungs are compressed, and lung volumes are reduced. The work of breathing is increased because of the abnormal mechanical properties of the chest and the increased airway resistance that results from decreased lung volumes. Any thoracic deformity may cause compression of the pulmonary vasculature and lead to right ventricular dysfunction. Recurrent pulmonary infection resulting from a poor cough is common.

The two basic types of costovertebral skeletal deformity are scoliosis (lateral curvature with the rotation of the vertebral column) and kyphosis (anterior flexion of the vertebral column). They may present in combination as kyphoscoliosis, which leads to severe restrictive impairment of lung function. Kyphoscoliosis may be idiopathic, due to a neuromuscular disorder, or associated with congenital vertebral malformations.

Idiopathic kyphoscoliosis accounts for 80% of cases. This commonly begins during late childhood or early adolescence and may progress in severity during the years of rapid skeletal growth. Patients with neuromuscular disorders producing kyphoscoliosis have more respiratory compromise than those with idiopathic kyphoscoliosis. This deformity of the spine results in a decrease in ventilatory capacity of the lung and an increase in the work of breathing. The deformity also leads to a raised hemidiaphragm on the side of the concavity. The severity of this disorder is usually measured by the degree of spinal curvature (Cobb angle). The greater the Cobb angle, the greater the respiratory compromise. Mild to moderate kyphoscoliosis (scoliotic angle <60 degrees) is associated with minimal to mild restrictive ventilatory defects. A Cobb angle of more than 70 degrees puts the patient at an increased risk of respiratory dysfunction. Dyspnea may occur during exercise, but as the skeletal deformity worsens, the vital capacity declines and dyspnea becomes a common complaint even with moderate exertion. Severe deformities (scoliotic angle >100 degrees) can lead to chronic alveolar hypoventilation, hypoxemia, secondary erythrocytosis, pulmonary hypertension, and cor pulmonale. Respiratory failure is most likely in patients with kyphoscoliosis associated with a vital capacity of less than 45% of the predicted value and a scoliotic angle of more than 100 degrees.

An increase in alveolar-arterial oxygen difference could result from the compression of underlying lung tissue. It is important to note that during the nonphasic period of rapid eye movement (REM) sleep, these patients are at increased risk of hypoventilation. Nocturnal hypoventilation may sometimes be the presenting feature of this condition. NIV strategies can be used to help manage this problem. Indications for NIV in these patients include symptoms suggestive of nocturnal hypoventilation, signs of cor pulmonale, nocturnal oxygen desaturation, or an elevated daytime $Paco_2$. Perioperatively, patients with severe kyphoscoliosis are at increased risk of developing pneumonia and hypoventilation when exposed to CNS depressant drugs. Supplemental oxygen therapy augmented by nocturnal ventilatory support may be needed.

Pectus excavatum, also called funnel chest or concave chest, is a deformity in which the body of the sternum, mostly the lower end, is curved inward. This deformity can restrict chest expansion and reduce vital capacity. In most patients with pectus excavatum, there are no significant functional limitations. Lung volumes and cardiovascular function are preserved. Surgical correction is indicated when the sternal deformity is accompanied by evidence of pulmonary restriction or cardiovascular dysfunction.

Pectus carinatum, also called pigeon chest, is a deformity of the sternum characterized by the outward protuberance of the sternum and ribs. The etiology is unknown, though it does run in families. This is usually a condition of cosmetic concern, but some children display respiratory symptoms or asthma.

Multiple rib fractures, especially when they occur in a parallel vertical orientation, can produce a flail chest characterized by paradoxic inward movement of the unstable portion of the thoracic cage while the remainder of the thoracic cage moves outward during inspiration. At least three or more anteriorly or posteriorly fractured ribs must be present to have a flail

chest. The flail portion of the chest moves outward during exhalation. A flail chest results in pain, increased work of breathing, inability to cough and clear secretions, and splinting of the injured hemithorax, resulting in atelectasis and delayed healing. There is also underlying lung contusion that results in low compliance and FRC. Flail chest can also result from the dehiscence of a median sternotomy. Tidal volumes are diminished because the region of the lung associated with the chest wall abnormality paradoxically increases its volume during exhalation and deflates during inspiration. The result is progressive hypoxemia, alveolar hypoventilation, and increased work of breathing. Treatment of a flail chest includes positive pressure ventilation until a definitive stabilization procedure can be carried out.

Pleural disorders include conditions such as trapped lung syndrome, pleural effusion, empyema, and pneumothorax. The pleura is a thin membrane that covers the entire surface of the lung, inner rib cage, diaphragm, and mediastinum. There are two pleural membranes: the visceral pleura, which covers the lungs, and the parietal pleura, which underlies the rib cage, diaphragm, and mediastinum.

Pleural effusion refers to the accumulation of fluid in the pleural space. Diagnosis can be made with chest radiography, CT scan of the chest, or bedside ultrasonography. Chest radiography will reveal blunting of the costophrenic angle and a characteristic homogeneous opacity that forms a concave meniscus with the chest wall. Apparent elevation or changes in the contour of the diaphragm may signify a subpulmonic effusion. However, chest radiography is not a very sensitive tool for diagnosis of pleural effusion since there must be at least 250 mL of effusion before it can be detected by this method. The sensitivity and specificity of ultrasound for diagnosing pleural effusion is much better and approaches 100% in experienced hands. This methodology can also reveal septae within the effusion and can distinguish between transudates and exudates.

Various types of fluid may accumulate in the pleural space, including blood (hemothorax), pus (empyema), lipids (chylothorax), and serous liquid (hydrothorax). The diagnosis is possible by the analysis of pleural fluid after a thoracentesis. The distinction between transudate and exudate points to potential diagnoses and the need for further evaluation. Bloody pleural effusion is common in patients with malignant disease, trauma, or pulmonary infarction. Surgical treatment is usually required for an effusion that cannot be drained by needle/small catheter thoracentesis. Pleurodesis, decortication, pleuroperitoneal shunts, and closure of diaphragmatic defects are some of the surgical options for treating recurrent effusions.

Pneumothorax is the presence of gas in the pleural space caused by disruption of either the parietal pleura (from an external penetrating injury) or visceral pleura (from a tear or rupture in the lung parenchyma). The visceral pleura usually separates from the parietal pleura, and the air can be seen between the visceral pleural lining and the rib cage. When the gas originates from the lung itself, the rupture may occur in the absence of known lung disease (spontaneous pneumothorax) or as a result of some known parenchymal lung pathology (secondary pneumothorax).

Idiopathic spontaneous pneumothorax occurs most often in tall, thin men aged 20 to 40 years and is due to rupture of apical subpleural blebs. Smoking cigarettes increases the risk of spontaneous pneumothorax several-fold. Most episodes of spontaneous pneumothorax occur while patients are at rest. Women with subpleural and diaphragmatic endometriosis can have rupture of these nodules at the time of menstruation, causing a pneumothorax. This particular kind of pneumothorax is termed catamenial pneumothorax.

Underlying lung diseases associated with secondary pneumothorax include chronic obstructive lung disease, pulmonary malignancies, cystic fibrosis, and lung abscess. As the air that is trapped in the thoracic cavity continues to expand, it leads to an increase in intrathoracic pressure and can cause compromise of cardiac function (i.e., tension pneumothorax).

Tension pneumothorax is a medical emergency and develops when gas enters the pleural space during inspiration and is prevented from escaping during exhalation. The result is a progressive increase in the amount and pressure/tension in the trapped air (Fig. 3.6). Patients are usually in respiratory distress, with an increased respiratory rate, shortness of breath, hypoxia, and pleuritic chest pain. The trachea may be deviated away from the pneumothorax. Auscultation reveals decreased/absent breath sounds on the side of the pneumothorax, with hyperresonance on percussion. Vital signs show tachycardia and hypotension. If the patient is mechanically ventilated, increased airway pressures and decreased tidal volumes can be observed. Tension pneumothorax occurs in fewer than 2% of patients experiencing idiopathic spontaneous pneumothorax but can occur with rib fractures, insertion of central lines, and barotrauma in patients undergoing mechanical ventilation. More than 30% of the pneumothoraces that develop in patients on mechanical ventilation are tension pneumothoraces. Dyspnea, hypoxemia, and hypotension may be severe. Immediate evacuation of gas through a needle or a small-bore catheter placed into the second anterior intercostal space can be lifesaving. Bedside ultrasonography can be diagnostic when available in expert hands (Fig. 3.5).

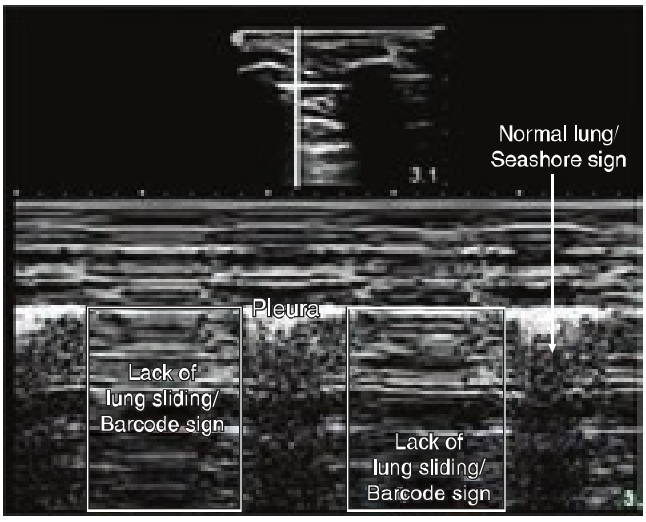

Fig. 3.5 Pneumothorax.

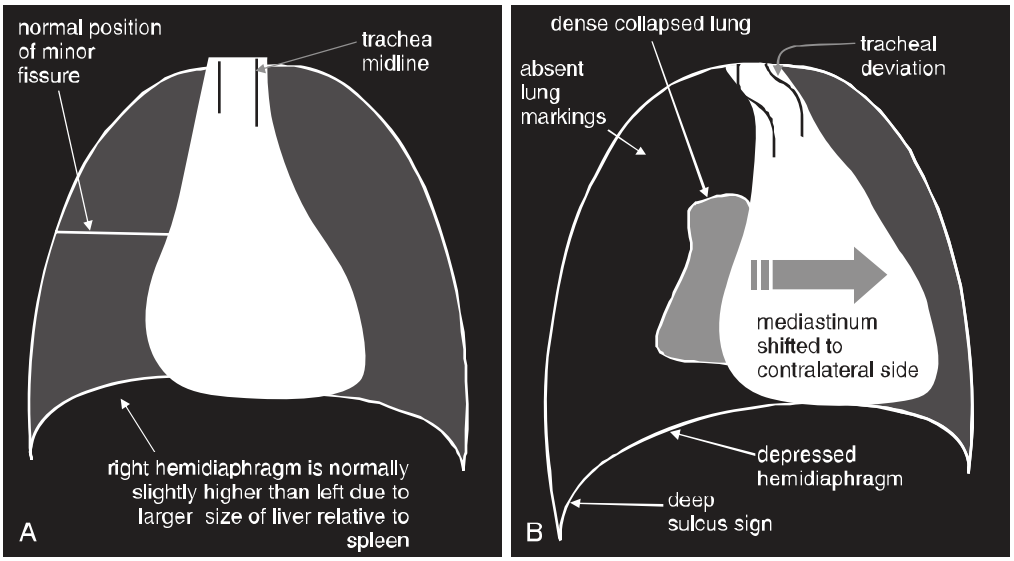

Fig. 3.6 Changes in pressure and volume on chest x-ray. (A) Lungs and mediastinum under normal conditions of pressure and volume. The heart and airway are near the midline. The minor fissure is in normal position. The right diaphragm is usually slightly higher than the left, because of the larger size of the liver relative to the spleen. (B) Increased pressure results in mediastinal shift and tracheal deviation to the opposite side. In the case of a right-sided tension pneumothorax, the right hemidiaphragm may be displaced in a caudad direction and may be lower than the left hemidiaphragm—the reverse of their normal positions. In addition, in any tension pneumothorax the costophrenic angle may be extremely deep on the abnormal side owing to a hyperinflated pleural space—the deep sulcus sign. (From Broder JS. *Diagnostic Imaging for the Emergency Physician*. Philadelphia, PA: Saunders; 2011.)

Treatment of symptomatic pneumothorax requires evacuation of air from the pleural space by aspiration through a needle or small-bore catheter or placement of a chest tube. Aspiration of a pneumothorax followed by catheter removal is successful in most patients with a small to moderate-sized primary spontaneous pneumothorax. When the pneumothorax is small (<15% of the volume of the hemithorax or pleural space to apex <2 cm) and symptoms are absent, observation may suffice.

When a pneumothorax occurs during anesthesia, immediate discontinuation of nitrous oxide and administration of 100% oxygen must commence. If the patient has a tension pneumothorax, needle/catheter decompression must be performed, followed by chest tube placement. Oxygen supplementation accelerates reabsorption of air from the pleural space.

Pneumomediastinum may follow a tear in the esophagus or tracheobronchial tree or alveolar rupture, although it most often occurs without a known cause. Spontaneous pneumomediastinum has been observed after recreational cocaine use. Symptoms of retrosternal chest pain and dyspnea are typically abrupt in onset and usually follow an exaggerated breathing effort, such as a cough, emesis, or Valsalva maneuver. Subcutaneous emphysema may be extensive in the neck, arms, abdomen, and scrotum. Pneumomediastinum may decompress into the pleural space, leading to pneumothorax, and both can be diagnosed by chest radiography. Spontaneous pneumomediastinum resolves without specific therapy. When pneumomediastinum is a result of organ rupture, surgical drainage and repair may be necessary.

Pleural fibrosis may follow hemothorax, empyema, or surgical pleurodesis for the treatment of recurrent pneumothorax. Despite obliteration of the pleural space, functional restrictive lung abnormalities remain but are usually minor. Surgical decortication to remove thick fibrous pleura is considered if the restrictive lung disease is very symptomatic.

Acute mediastinitis usually results from bacterial contamination after esophageal perforation. Symptoms include chest pain and fever. It is treated with broad-spectrum antibiotics and surgical drainage.

The anterior mediastinal compartment is anterior to the pericardium and includes lymphatic tissue, the thymus, and potentially the thyroid (Fig. 3.7). Mediastinal masses most commonly found in the anterior mediastinum are thymomas, germ cell tumors, lymphomas, intrathoracic thyroid tissue, and parathyroid lesions. Thymomas comprise 20% of mediastinal neoplasms in adults and are the most common primary anterior mediastinal neoplasms in this patient population. Symptoms due to myasthenia gravis affect one-third of patients with thymomas. Middle mediastinal lesions include tracheal masses, bronchogenic and pericardial cysts, enlarged lymph nodes, and proximal aortic disease (i.e., aneurysm or dissection). Posterior mediastinal masses include neurogenic tumors and cysts, meningocele, lymphoma, descending aortic aneurysm, and esophageal disorders such as diverticula and neoplasms.

Patients with systemic lymphoma often have involvement of the mediastinum, and 5% to 10% of patients with lymphoma have primary mediastinal lesions at clinical presentation. Mediastinal cysts can arise in the pericardium, bronchi, esophagus, stomach, thymus, and thoracic duct, and although benign they can produce compressive symptoms. Lung cancer can manifest with mediastinal adenopathy, a sign of advanced-stage disease. In the evaluation of mediastinal widening, contrast-enhanced CT can distinguish between vascular structures, soft tissues, and calcifications. Large mediastinal tumors may be associated with progressive airway obstruction, loss of lung volumes,

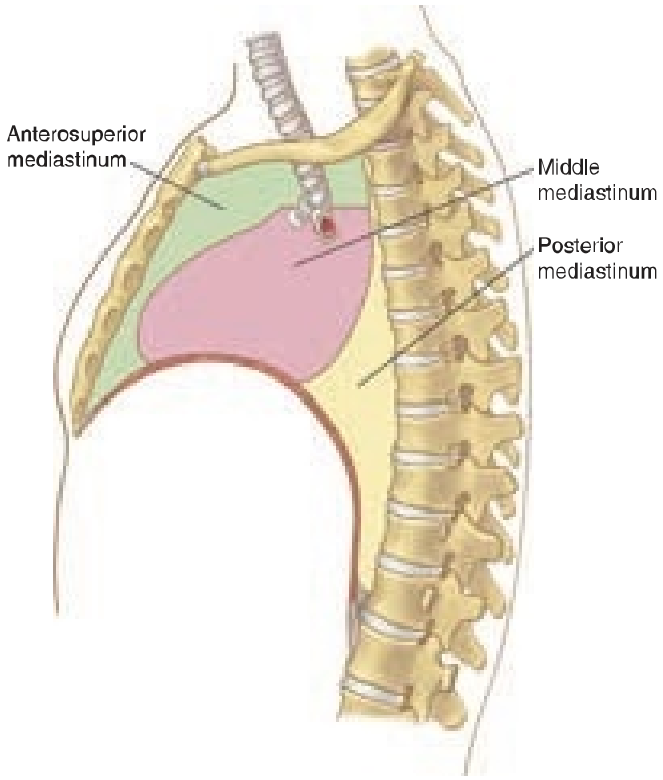

Fig. 3.7 Anatomic location of the mediastinal compartments in the three-compartment model. (This model has no specific superior compartment.) (From Liu W, Deslauriers J. Mediastinal divisions and compartments. *Thorac Surg Clin.* 2011;21:183–190.)

pulmonary artery and/or cardiac compression, and superior vena cava obstruction.

Treatment of a mediastinal mass depends on the underlying pathology. Many require surgical resection, radiation, chemotherapy, or careful surveillance over time.

Anesthetic management of patients with mediastinal masses can present significant challenges. Preoperative evaluation of such patients includes measurement of a flow-volume loop, chest imaging studies, and clinical evaluation for evidence of tracheobronchial compression. The size of the mediastinal mass and the degree of tracheal compression can be established by CT scan, and this study is also a useful predictor of whether airway difficulties during anesthesia are likely. Flexible fiberoptic bronchoscopy under topical anesthesia can be a useful tool for evaluating the degree of airway obstruction. Unfortunately, the severity of preoperative pulmonary symptoms has no relationship to the degree of respiratory compromise that can be encountered during anesthesia. Indeed, several asymptomatic patients have developed severe airway obstruction during anesthesia. Preoperative radiation of a malignant mediastinal mass to decrease its size should be considered whenever possible. A local anesthetic technique is best for symptomatic patients requiring a diagnostic tissue biopsy. During anesthesia, the tumor may increase in size because of venous engorgement, and its position may shift somewhat. As a result, it can compress the airway, vena cava, pulmonary artery, or atria and create life-threatening hypoxemia, hypotension, or even cardiac arrest.

The method of induction of anesthesia and tracheal intubation in the presence of mediastinal tumors depends on the preoperative assessment of the airway. Visible external edema associated with superior vena cava syndrome is likely to be accompanied by similar edema inside the mouth and hypopharynx. If edema resulting from venocaval obstruction is severe, it may be necessary to establish intravenous access in the legs rather than in the arms. Invasive blood pressure monitoring should be established. Symptomatic patients may need to be in the sitting position to breathe adequately. If so, anesthetic induction should proceed in the sitting position until the airway has been secured. Topical anesthesia of the airway, with or without light sedation, can be used to facilitate fiberoptic laryngoscopy. If severe airway obstruction occurs, it can be alleviated by placing the patient in the lateral or prone position. Spontaneous ventilation throughout surgery is recommended whenever possible. Worsening of superior vena cava syndrome may occur as a result of excessive fluid administration. Diuretics may decrease the tumor volume, but the reduction in preload in these patients with already compromised venous return can result in significant hypotension. Surgical bleeding is often more than expected because of the increased central venous pressure. Postoperatively, tumor swelling as a result of partial resection or biopsy may increase symptoms of airway obstruction and require reintubation of the trachea.

Bronchogenic cysts are fluid-filled or air-filled cysts arising from the primitive foregut that is lined with respiratory epithelium. They are typically located in the mediastinum or lung parenchyma. These cysts may be asymptomatic, the focus of recurrent pulmonary infection, or the cause of life-threatening airway obstruction. Cysts located in the mediastinum are more likely to be filled with fluid than air and are usually not in direct communication with the airways. These masses cause symptoms of airway compression as they grow. Surgical excision may be necessary.

Theoretical concerns in patients with bronchogenic cysts include hazards related to nitrous oxide administration and the use of positive pressure ventilation. Nitrous oxide can diffuse into air-filled bronchogenic cysts and cause their expansion, with associated life-threatening respiratory or cardiovascular compromise. Institution of positive pressure ventilation in patients with cysts that extrinsically compress the tracheobronchial tree may have a ball-valve effect resulting in air trapping. Despite these concerns, clinical experience confirms that nitrous oxide and positive pressure ventilation are often safely used in patients with bronchogenic cysts.

Other thoracic nonpulmonary causes of restrictive physiology include the following:

- Asphyxiating thoracic dystrophy, also called Jeune syndrome, is an autosomal recessive disorder with skeletal dysplasia and multiorgan dysfunction. This condition is associated with cysts in kidney, pancreas, and liver. Retinal abnormality with short ribs, narrow thorax, short limbs, and polydactyly are hallmarks of this condition. Patients may come for surgeries such as lateral limb expansion, dynamic thoracoplasty, and chest wall reconstruction. Asphyxiating thoracic dystrophy may be seen in adults after pectus excavatum surgery.

- Fibrodysplasia ossificans is a hereditary disorder caused by genetic variation in a bone morphogenetic protein (BMP) type 1.
- Poland syndrome or sequence is the partial or complete absence of pectoral muscles commonly affecting only one side. Most patients do not have respiratory symptoms, but some may have paradoxic respiratory motion due to the absence of multiple ribs.

Extrathoracic Causes

Neuromuscular disorders that interfere with the transfer of CNS input to the skeletal muscles necessary for inspiration and exhalation can result in restrictive lung disease. These abnormalities of the spinal cord, peripheral nerves, neuromuscular junction, or skeletal muscles may result in restrictive pulmonary defects characterized by an inability to generate normal inspiratory and expiratory respiratory pressures.

In contrast to mechanical disorders of the thoracic cage, in which an effective cough is typically preserved, the expiratory muscle weakness characteristic of neuromuscular disorders prevents the generation of a sufficient expiratory airflow velocity to provide a forceful cough. Acute respiratory failure is likely when pneumonia occurs (caused by retained secretions resulting from this ineffective cough) or central or respiratory depressant drugs are administered. Patients with neuromuscular disorders are dependent to some degree on their state of wakefulness to maintain adequate ventilation. During sleep, hypoxemia and hypercapnia may develop and contribute to the development of cor pulmonale. Vital capacity is an important indicator of the total impact of the neuromuscular disease on ventilation.

Breathing is maintained solely or predominantly by the diaphragm in quadriplegic patients with spinal cord injury at or below C4. Higher levels of injury result in diaphragmatic paralysis. Because the diaphragm is active only during inspiration, coughing, which requires activity by the muscles involved in exhalation, including those of the abdominal wall, is almost totally absent. Normally, intercostal muscles are required to stabilize the upper rib cage against inward collapse when the descent of the diaphragm produces negative intrathoracic pressure. With diaphragmatic breathing there is a paradoxic inward motion of the upper thorax during inspiration. This results in a diminished tidal volume. When quadriplegic patients are in the upright position, the weight of the abdominal contents pulls on the diaphragm, and the absence of abdominal muscle tone results in less efficient function of the diaphragm. Abdominal binders can serve to replace lost abdominal muscle tone and may be useful whenever tidal volume decreases significantly in the upright position. Quadriplegic patients have mild degrees of bronchial constriction caused by the parasympathetic tone that is unopposed by sympathetic activity from the spinal cord. The use of anticholinergic bronchodilating drugs can reverse this abnormality. Respiratory failure rarely occurs in quadriplegic patients in the absence of complications such as pneumonia.

Respiratory insufficiency that requires mechanical ventilation occurs in 20% to 25% of patients with Guillain-Barré syndrome. Ventilatory support is needed on average for 2 months. A small number of patients have persistent skeletal muscle weakness and are susceptible to recurring episodes of respiratory failure in association with pulmonary infection.

Myasthenia gravis is the most common disease affecting neuromuscular transmission that may result in respiratory failure. Patients with myasthenia gravis are resistant to succinylcholine and sensitive to nondepolarizing muscle relaxants. Myasthenic syndrome (Eaton-Lambert syndrome) may be confused with myasthenia gravis. Prolonged skeletal muscle paralysis or weakness may occur following the administration of nondepolarizing neuromuscular blocking drugs.

Patients with Duchenne muscular dystrophy, myotonic dystrophy, and other forms of muscular dystrophy are predisposed to pulmonary complications and respiratory failure. Chronic alveolar hypoventilation caused by inspiratory muscle weakness may develop. Expiratory muscle weakness impairs cough. The weakness of the swallowing muscles may lead to pulmonary aspiration of gastric contents. As with all neuromuscular syndromes, CNS depressant drugs should be avoided or administered in minimal dosages. Nocturnal ventilation with noninvasive techniques such as nasal intermittent positive pressure or external negative pressure ventilation may be useful.

In the absence of complications, neuromuscular disorders rarely progress to the point of hypercapnic respiratory failure unless diaphragmatic weakness or paralysis is present. Thus quadriplegic patients who have preserved phrenic nerve function are unlikely to develop respiratory failure in the absence of pneumonia or administration of CNS depressants. In the supine position, patients with diaphragmatic paralysis may develop a ventilatory pattern similar to that seen with a flail chest. In the upright posture, these patients experience a significant increase in vital capacity and improved oxygenation and ventilation. Most cases of unilateral diaphragmatic paralysis are a result of neoplastic invasion of the phrenic nerve. In the absence of associated pleuropulmonary disease, most adult patients with unilateral diaphragmatic paralysis remain asymptomatic, and this defect is detected as an incidental finding on chest radiography. In contrast, infants are more dependent on bilateral diaphragmatic function for adequate respiratory function. In symptomatic infants and adults, plication of the hemidiaphragm may be necessary to prevent flail motion of the thoracic cage.

Transient diaphragmatic dysfunction may occur after abdominal surgery as lung volumes decrease, the alveolar-arterial oxygen difference increases, and the respiratory rate increases. These changes may be a result of irritation of the diaphragm, which causes reflex inhibition of phrenic nerve activity. As a result of this postoperative diaphragmatic dysfunction, atelectasis and arterial hypoxemia may occur. Incentive spirometry may alleviate these abnormalities.

Obesity is an increase in body mass index (BMI) and is associated with decreases in FEV_1, FVC, FRC, and expiratory reserve volume (ERV). With a BMI over 40 kg/m^2 there is also a decrease in residual volume and TLC. With extreme clinical obesity, FRC may exceed closing volume and approach residual volume. The FEV_1:FVC ratio is usually preserved. Chest wall compliance may be mildly reduced. Central obesity is associated with worse lung function and respiratory symptoms. An increased waist-to-hip ratio and/or abdominal girth has a good

correlation with impaired lung function. Buildup of adipose tissue in the anterior abdominal wall and viscera hinders diaphragmatic movement, diminishes basal lung expansion during inspiration, and causes closure of peripheral lung units. This leads to ventilation/perfusion abnormalities and arterial hypoxemia, which results in respiratory compromise, especially during sleep and in the perioperative period. Patients have an increased resting respiratory rate with a normal tidal volume. When adjusted for lean body weight, the respiratory rate is reduced. Adipose cells release adipocytokines that play a part in the systemic inflammation triggered by obesity-related hypoxemia and obesity-related respiratory disorders such as obstructive sleep apnea, obesity hypoventilation syndrome, and chronic obstructive pulmonary disease (COPD). Weight loss might help improve pulmonary function.

Changes associated with pregnancy can lead to restrictive lung physiology in several ways. The thorax undergoes structural changes, with the subcostal angle of the rib cage and the circumference of the lower chest wall increasing and the diaphragm moving cranially. Increased levels of the hormone relaxin cause stretching of the lower rib cage ligaments. The subcostal angle widens from 68 to 103 degrees (Fig. 3.8). The anteroposterior diameter and transverse diameter of the chest wall increases by 2 cm, leading to an increase in the circumference of the rib cage.

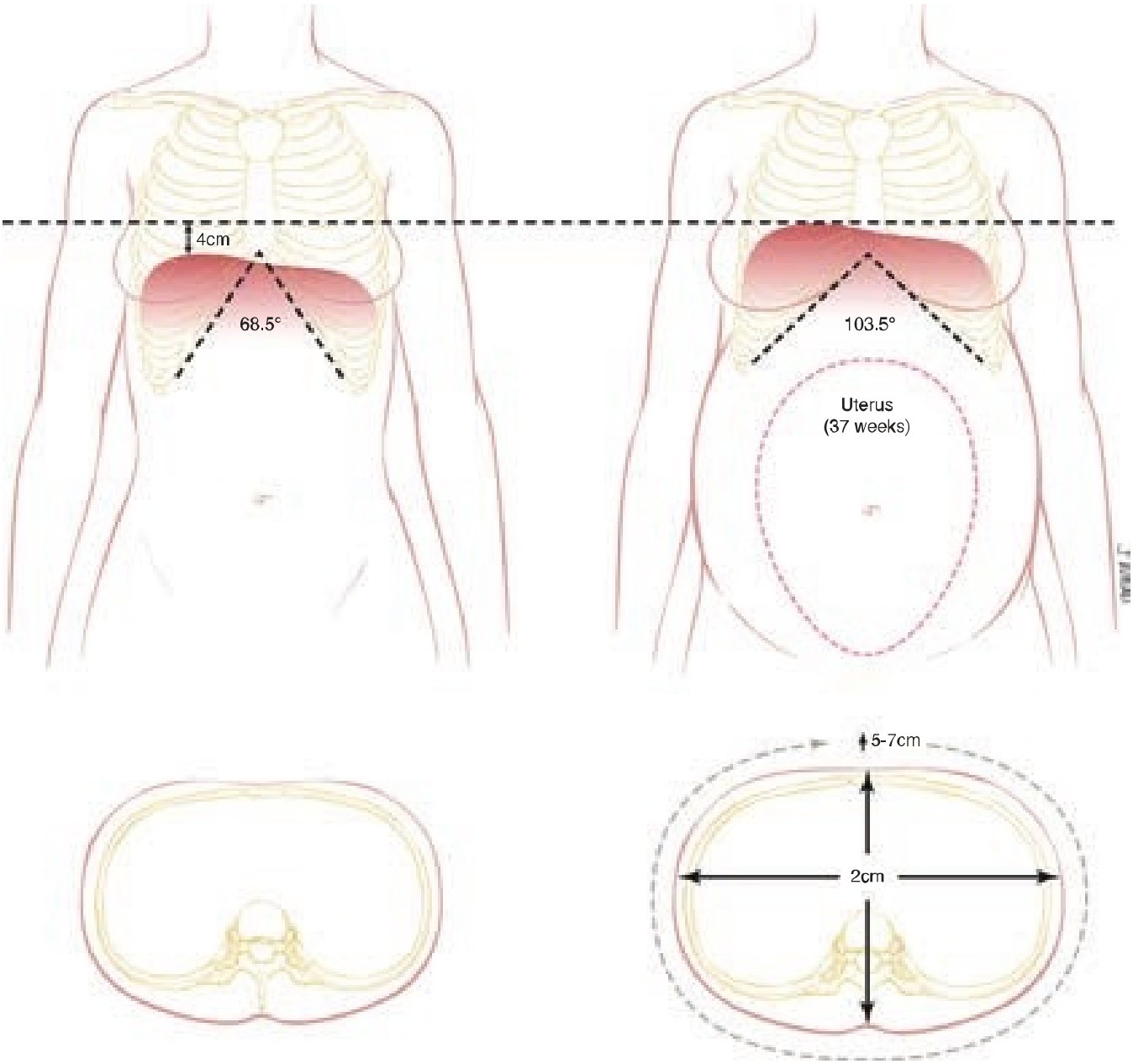

Fig. 3.8 Chest wall changes that occur during pregnancy. The subcostal angle increases, as does the anterior-posterior and transverse diameter of the chest wall and the chest wall circumference. These changes compensate for the 4-cm elevation of the diaphragm so that total lung capacity is not severely reduced. (From Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy. *Clin Chest Med.* 2011;32:1–13.)

These changes peak at the 37th week of pregnancy. Chest wall configuration normalizes about 6 months postpartum, except for the subcostal angle, which remains wider by about 20%. The enlarging uterus pushes the diaphragm up by about 4 cm.

Static lung function stays the same in pregnancy, except for a decrease in FRC and its component expiratory reserve and residual volumes. This reduction in FRC is expected secondary to the elevation of the diaphragm, downward pull of the abdomen, and changes in chest wall compliance. FRC typically decreases by 15% to 20%, or 200 to 300 mL. Intrinsic lung compliance is unaffected by pregnancy. At term, FRC decreases by another 25% in the supine compared to the sitting position. Although the FRC is decreased in obesity and pregnancy, the residual volume is *increased* in obesity but *decreased* in pregnancy.

Laparoscopic surgery is one of the most common surgical techniques and has several advantages over traditional surgery, including decreased postoperative pain, a shorter length of stay in the hospital, and cosmetic appeal. However, it requires a pneumoperitoneum to allow for visualization of intraabdominal structures. Carbon dioxide is the most commonly used gas for insufflation because it is extremely soluble and diffuses readily through biological membranes. This property of CO_2 helps it equilibrate but can also lead to hypercarbia and respiratory acidosis. Intraabdominal pressure (IAP) is raised from less than 5 mm Hg to approximately 15 mm Hg. Insufflation above 15 mm Hg pressure has significant effects on lung and chest wall compliance. Decreases in lung volume and the ventilation/perfusion mismatch can be offset to some degree by application of PEEP. Pneumothorax, pneumomediastinum, and pneumopericardium can be seen in a few patients. Auscultation or ultrasound can confirm diagnosis. The addition of Trendelenburg positioning worsens the effects of pneumoperitoneum.

Ascites is commonly seen in patients with portal hypertension and is associated with cirrhosis, heart failure, hypoalbuminemia, and some malignancies. FRC, TLC, FVC, DLCO, FEV_1, Pao_2, and ERV are reduced with accumulation of fluid within the peritoneum. These decreases might be obviated by paracentesis. Other important considerations in patients with ascites are a decrease in inspiratory muscle strength and increased elastic load on the lung. Increased intrapleural pressures lead to early closure of alveoli.

ANESTHETIC MANAGEMENT OF PATIENTS WITH RESTRICTIVE LUNG DISEASE

Restrictive lung disease does not influence the choice of drugs used for induction or maintenance of anesthesia. Drugs with prolonged respiratory depressant effects that may persist in the postoperative period should be avoided. Vigilance must be maintained for the development of pneumothorax and the need to avoid or discontinue nitrous oxide. Regional anesthesia can be considered for peripheral operations, but the involvement of sensory/motor levels above T10 can be associated with impairment of the respiratory muscle activity needed by these patients to maintain acceptable ventilation. Mechanical ventilation during the intraoperative period facilitates optimal oxygenation and ventilation. Since the lungs are poorly compliant, increased inspiratory pressures may be necessary. Postoperative mechanical ventilation is often needed in patients with significantly impaired pulmonary function. Restrictive lung disease also contributes to the risk of perioperative pulmonary complications.

DIAGNOSTIC PROCEDURES IN PATIENTS WITH LUNG DISEASE

Fiberoptic bronchoscopy has generally replaced rigid bronchoscopy for visualizing the airways and obtaining samples for culture, cytologic examination, and biopsy. Pneumothorax occurs in 5% to 10% of patients after transbronchial lung biopsy and in 10% to 20% after percutaneous needle biopsy of peripheral lung lesions. The major contraindication to pleural biopsy is a coagulopathy.

Mediastinoscopy is performed under general anesthesia through a small transverse incision just above the suprasternal notch. Blunt dissection along the pretracheal fascia is performed, which permits biopsy of paratracheal lymph nodes down to the level of the carina. Potential complications include pneumothorax, mediastinal hemorrhage, venous air embolism, and injury to the recurrent laryngeal nerve, leading to hoarseness and vocal cord paralysis. The mediastinoscope can also exert pressure on the right innominate artery, causing loss of pulses in the right arm and compromise of right carotid artery blood flow.

LUNG TRANSPLANTATION

Overview

The four principal approaches to lung transplantation are:

1. Single-lung transplantation
2. Bilateral sequential lung transplantation
3. Heart-lung transplantation
4. Transplantation of lobes from living donors

Table 3.8 lists the typical indications for lung transplantation.

Fibrotic lung disease responds well to single-lung transplantation because both ventilation and perfusion are distributed preferentially to the transplanted lung. Bilateral sequential lung transplantation involves the sequential performance of two single-lung transplants at one surgery. In the absence of severe pulmonary hypertension, cardiopulmonary bypass can usually be avoided by ventilating the contralateral lung during each implantation. The primary indications for double-lung transplantation are cystic fibrosis and other forms of bronchiectasis.

TABLE 3.8 Indications for Lung Transplantation

Chronic obstructive pulmonary disease
Cystic fibrosis
Idiopathic pulmonary fibrosis
Primary pulmonary hypertension
Bronchiectasis
Eisenmenger syndrome

Adapted from Singh H, Bossard RF. Perioperative anaesthetic considerations for patients undergoing lung transplantation. *Can J Anaesth.* 1997;44:284–299.

The presence of cor pulmonale is not an indication for heart-lung transplantation because recovery of right ventricular function is typically rapid and complete after lung transplantation alone. In patients with pulmonary hypertension, high pulmonary vascular resistance in the remaining native lung requires the allograft to handle nearly the entire cardiac output. This could result in reperfusion pulmonary edema and poor allograft function in the period immediately after surgery. Immunosuppression is initiated intraoperatively and continued for life.

Management of Anesthesia for Primary Lung Transplantation Surgery

Management of anesthesia for lung transplantation follows the same principles used when pneumonectomy is performed.

Patients selected for lung transplantation most often have restrictive lung disease and a large $Pao_2 - Pao_2$. They generally have progressive and/or irreversible pulmonary disease. Cancer is regarded as a contraindication to transplantation because of the risk of cancer recurrence with immunosuppression. Mild to moderate degrees of pulmonary hypertension and some degree of right-sided heart failure are often present. Smokers should have quit smoking at least 6 to 12 months before transplantation. The ability of the right ventricle to maintain an adequate stroke volume in the presence of the acute increase in pulmonary vascular resistance produced by clamping the pulmonary artery before the native lung is removed needs to be assessed. Evaluation of oxygen dependence and steroid use, hematologic and biochemical analyses, and tests of lung and other major organ system functions are also required prior to surgery. Posterolateral thoracotomy is performed for single-lung transplantation and a clam-shell thoracotomy for bilateral or sequential lung transplantation. Cardiopulmonary bypass may be needed if cardiac or respiratory instability develops during the procedure. The lung with worse perfusion is removed in single-lung transplantation. Monitoring includes placement of intraarterial and pulmonary artery catheters. Pulmonary artery pressure monitoring is especially important. During the surgery, the pulmonary artery catheter may need to be withdrawn from the native pulmonary artery to be stapled and refloated into the pulmonary artery of the nonoperative lung. Transesophageal echocardiographic monitoring can be used to evaluate the right and left ventricular function and fluid balance. There are no specific recommendations regarding drugs for the induction and maintenance of anesthesia and skeletal muscle paralysis for lung transplantation. Drug-induced histamine release is undesirable. Drug-induced bronchodilation is useful.

The trachea is intubated with a double-lumen endobronchial tube, and its proper placement is verified by fiberoptic bronchoscopy. Potential intraoperative problems include hypoxia, especially during one-lung ventilation. CPAP to the nondependent lung, PEEP to the dependent lung, or some form of differential lung ventilation may be needed to minimize intrapulmonary shunting and hypoxia. Severe pulmonary hypertension and right ventricular failure can occur when the pulmonary artery is clamped. Infusion of a pulmonary vasodilator (e.g., prostacyclin) or inhalation of nitric oxide may be helpful in controlling pulmonary hypertension in this situation. If hypoxia cannot be controlled despite all of these maneuvers, support with partial cardiopulmonary bypass is required. Connection of the donor's lung to the recipient is usually performed in the sequence of pulmonary veins to the left atrium, then anastomosis of the pulmonary artery, and finally anastomosis of the bronchus.

Postoperative mechanical ventilation is continued as needed. Some authors recommend mechanical ventilation strategy to be based on donor characteristics.

The principal causes of mortality with lung transplantation are bronchial dehiscence and respiratory failure due to sepsis or rejection. The denervation of the donor's lung deprives patients of normal cough reflexes of the lower airways and predisposes them to the development of pneumonia. In the absence of rejection, pulmonary function test results can be normal.

Management of Anesthesia for Patients With Prior Lung Transplantation

Anesthetic management of patients with a prior lung transplant should focus on the following:

1. Function of the transplanted lung
2. Possibility of rejection or infection in the transplanted lung
3. Effect of immunosuppressive therapy on other organ systems
4. Effect of other organ systems' dysfunction on the transplanted lung
5. Disease in the native lung
6. Planned surgical procedure and its effects on the lungs

Evaluation before surgery includes obtaining a history suggestive of rejection or infection, auscultation of the lungs, and evaluation of the results of pulmonary function tests, arterial blood gas analyses, and chest radiographs. If rejection or infection is suspected, elective surgery should be postponed. The side effects of immunosuppressive drugs should be noted. Hypertension and renal dysfunction related to cyclosporine therapy are present in many patients.

Because transplanted lungs may have ongoing rejection that can adversely affect pulmonary function, it is recommended that spirometry be performed preoperatively. However, it may be difficult to differentiate between chronic rejection and infection. With chronic rejection, the FEV_1, FVC, and TLC decrease, and arterial blood gas values show an increased alveolar-arterial oxygen gradient, but carbon dioxide retention is rare. Bronchiolitis obliterans, the lung disease caused by chronic rejection, usually presents as a nonproductive cough developing later than the third month following transplantation. Symptoms can mimic those of an upper respiratory tract infection and include fever and fatigue. Dyspnea occurs within months and is followed by a clinical course similar to that of COPD. Chest radiographs show peribronchial and interstitial infiltrates.

Premedication is acceptable if pulmonary function is adequate. Antisialagogues can be particularly useful since secretions can be excessive. Supplemental corticosteroids may be needed. A significant cause of morbidity and mortality in transplant recipients is infection. Prophylactic antibiotics are indicated, and strict aseptic technique is required for the placement of intravascular catheters. Lung denervation has limited effects on the pattern of breathing, but bronchial hyperreactivity and bronchoconstriction are common. Denervation ablates afferent sensation in the lung below the

level of the tracheal anastomosis. Patients lose the cough reflex and are prone to the retention of secretions and silent aspiration. The response to carbon dioxide rebreathing is normal.

Because lung transplant recipients lack a cough reflex, they do not clear secretions unless they are awake. Because of the diminished cough reflex, the potential for bronchoconstriction, and the increased risk of pulmonary infection, it is recommended that regional anesthesia be selected whenever possible. Epidural and spinal anesthesia are acceptable.

However, paralysis of intercostal muscle function may have implications in these patients. In addition, any nerve blockade procedure carries the risk of infection. The importance of using sterile technique in this high-risk population cannot be overemphasized. Fluid preloading before spinal or epidural anesthesia may be risky because disruption of the lymphatic drainage in the transplanted lung causes interstitial fluid accumulation. This is particularly problematic during the early posttransplantation period.

In heart-lung transplant recipients, fluid management may be particularly challenging because the heart requires adequate preload to maintain cardiac output, but the lungs have a lower-than-normal threshold for developing pulmonary edema. In this situation, invasive hemodynamic monitoring may be beneficial, but the benefits must be balanced against the risk of infection. Transesophageal echocardiography can be useful for monitoring volume status and cardiac function. If a central venous catheter is inserted via the internal jugular vein, it is prudent to select the internal jugular vein on the side of the native lung. Cardiac denervation is another consideration in patients who have undergone heart-lung transplantation. These patients may develop intraoperative bradycardia that does not respond to the administration of atropine. Epinephrine and/or isoproterenol may be required to increase the heart rate.

An essential goal of anesthetic management is the prompt recovery of adequate respiratory function and early tracheal extubation. Volatile anesthetics are well tolerated, and the use of nitrous oxide is acceptable in the absence of bullous lung disease. Immunosuppressive drugs may interact with neuromuscular blocking drugs, and the impaired renal function caused by immunosuppressive drugs may prolong the effects of certain muscle relaxants. The effects of nondepolarizing neuromuscular blockers are routinely antagonized pharmacologically at the conclusion of surgery because even minimal residual muscle weakness can compromise ventilation in these patients. When an endotracheal tube is positioned, it is best to place the cuff just below the vocal cords to minimize the risk of traumatizing the tracheal anastomosis. Inadvertent endobronchial intubation of the native or transplanted lung must be avoided. If the surgical procedure requires the use of a double-lumen endobronchial tube, it is preferable to place the endobronchial portion of the tube in the native bronchus to avoid contact with the tracheal anastomosis. In patients with a single-lung transplant, positive pressure ventilation may be complicated by differences in lung compliance between the native and the transplanted lung.

Physiologic Effects of Lung Transplantation

Single or bilateral lung transplantation in patients with end-stage lung disease can dramatically improve lung function. Peak improvement is usually achieved within 3 to 6 months. Arterial oxygenation rapidly returns to normal, and supplemental oxygen is no longer needed. In patients with pulmonary vascular disease, both single and bilateral lung transplantations result in immediate and sustained normalization of pulmonary vascular resistance and pulmonary artery pressure. This is accompanied by an immediate increase in cardiac output and a gradual remodeling of the right ventricle, with a decrease in right ventricular wall thickness. Exercise capacity improves sufficiently to permit most lung transplant recipients to resume an active lifestyle.

Donor pneumonectomy disrupts the innervation of the lung, its lymphatic drainage, and bronchial circulation. The principal effect of lung denervation is loss of the cough reflex, which places patients at risk of aspiration and pulmonary infection. A decrease in mucociliary clearance is noted in the early postoperative period. There might be some reestablishment of lymphatic drainage during the early postoperative period that was disrupted by the transection of the trachea and bronchi. Often a blunted ventilatory response to carbon dioxide persists even though pulmonary function improves.

Mild transient pulmonary edema is common in a newly transplanted lung. In some patients, however, pulmonary edema is sufficiently severe to cause a form of acute respiratory failure termed primary graft failure. This diagnosis is confirmed by the appearance of infiltrates on chest radiographs and severe hypoxemia during the first 72 hours postoperatively. Treatment is supportive and includes mechanical ventilation.

Focal wheezing, recurrent lower respiratory tract infection, and suboptimal pulmonary function could point toward significant airway stenosis. Stenosis of the bronchial anastomosis is the most common airway complication and typically occurs several weeks after transplantation. Dehiscence of the bronchial anastomosis mandates immediate surgical correction or retransplantation.

The rate of infection in lung transplant recipients is several times higher than that in recipients of other transplanted organs and is most likely related to exposure of the allograft to the external environment. Bacterial infection of the lower respiratory tract is the most common manifestation of pulmonary infection. A ubiquitous organism acquired by inhalation is *Aspergillus*, which frequently colonizes the airways of lung transplant recipients. However, clinical infection with *Aspergillus* develops in only a small number of patients.

One needs to have a high suspicion for acute rejection of the lung allograft as a third of patients will have this form of acute rejection within the first year of transplantation (Parulekar et al, 2019). One should have a high clinical suspicion as manifestations are nonspecific and include malaise, low-grade fever, dyspnea, impaired oxygenation, and leukocytosis. Management consists of a transbronchial lung biopsy for diagnosis and intravenous methylprednisolone for treatment. Most patients have a prompt clinical response, although histologic evidence of rejection may persist even in the absence of clinical symptoms and signs. Chronic rejection is sometimes used synonymously with bronchiolitis obliterans, a fibroproliferative process that targets the small airways and leads to submucosal fibrosis and luminal obliteration. Bronchiolitis obliterans is uncommon during the first 6 months following transplantation, but its incidence exceeds 60% in patients who survive at least 5 years. Bronchiolitis obliterans syndrome in lung transplant

recipients is characterized by progressive airflow obstruction. The onset of this syndrome is insidious and is associated with dyspnea, cough, and colonization of the airways with *Pseudomonas aeruginosa*, which produces recurrent bouts of purulent tracheobronchitis. The overall prognosis is poor. Retransplantation is the only definitive treatment for severe bronchiolitis obliterans.

KEY POINTS

- Surgical patients with restrictive lung disease are at increased risk of perioperative pulmonary complications.
- Increases in the interstitial and alveolar fluid can cause acute intrinsic restrictive lung disease. Cardiogenic and noncardiogenic pulmonary edema, pulmonary edema associated with acute neurologic injury, high-altitude pulmonary edema, pulmonary aspiration, reexpansion pulmonary edema, and negative pressure pulmonary edema can all be causes of this form of lung disease.
- Thoracic abnormalities such as those of the chest wall, pleura, and spine (e.g., pectus excavatum, kyphoscoliosis, pleural effusion, flail chest, bronchogenic cysts, pneumothorax, mediastinal tumors) can all cause extrinsic restrictive lung disease.
- Extrathoracic causes of restrictive lung disease include neuromuscular disorders associated with a limited or absent function of the respiratory muscles, including the diaphragm, obesity, and pneumoperitoneum during laparoscopic surgery.
- The most effective treatment for aspiration pneumonitis is the delivery of supplemental oxygen and initiation of therapy with positive end-expiratory pressure (PEEP).
- Adult ARDS is a syndrome with many risk factors that trigger the acute onset of respiratory insufficiency. Despite the diverse pathologic entities that can cause this syndrome, they all have in common the following features: significant hypoxemia, increased pulmonary capillary permeability causing alveolar edema, and neutrophil infiltration into the alveoli. The Berlin definition and criteria classify ARDS as mild, moderate, and severe based on the value of the Pao_2/Fio_2 ratios as measured with CPAP or PEEP of at least 5 cm H_2O.
- The major effect of lung denervation from lung transplantation is the loss of the cough reflex, which places patients at risk of aspiration and pulmonary infection. Only while awake will patients clear pulmonary secretions.
- In heart-lung transplant recipients, fluid management is a challenge because the heart requires adequate preload to maintain cardiac output, but the lungs have a low threshold for developing pulmonary edema.

RESOURCES

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4

Critical Illness

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OUTLINE

Critical illness has been documented since the beginning of recorded history, an inherent component of the human experience. However, critical care is a recent development made possible by the technical and scientific advances of the 20th century. If the whole of critical illness could be reduced to a single common element, that element would be disordered perfusion. Simply stated, our effort to correct this imbalance is critical care.

Patients who would have succumbed to their critical illness a century ago now have a chance to return to a state of health that allows them to enjoy additional years of productive and fulfilling life. Perhaps more than any other segment of society, the rapidly growing geriatric population will continue to produce an ever greater demand for critical care services. As the critically ill patient population grows, emphasis on patient safety, harm prevention, and improved outcomes must also grow. Over the course of recent decades, critical care has evolved into much more than a conglomeration of technology, pharmaceuticals, and policies. Rather, the subspecialty has become a multidisciplinary and interprofessional endeavor focused on the integration of clinicians with complementary fields of expertise working together to deliver the highest quality of care to our sickest patients. To provide maximum benefit with the least potential for harm, diverse expertise requires excellent communication among the practitioners rendering care. Just as disordered perfusion is the essence of critical illness, communication is the cornerstone of critical care.

Although crucial in every critical care environment, teamwork is of paramount importance in the surgical intensive care unit (SICU) and operating rooms (ORs). Critically ill individuals who require operative intervention comprise a unique patient population. Anesthesiologists and surgeons bring singular viewpoints and expertise to the shared management of these patients. This chapter will provide a unique perspective on the underlying pathophysiology of this patient population. In turn, this perspective will provide a framework for an enhanced understanding of the general management and special scenarios encountered in the care of critically ill surgical patients.

PATHOPHYSIOLOGY OF THE CRITICALLY ILL PATIENT UNDERGOING SURGERY

Shock: Disordered Perfusion

Shock is an abnormality of the circulatory system that causes inadequate organ perfusion and tissue oxygenation. No single parameter can diagnose shock. Rather, the initial diagnosis is based on clinically apparent inadequacy of tissue perfusion and oxygenation. Over 4 decades ago, Hinshaw and Cox proposed a classification of shock involving four subsets: hypovolemic, cardiogenic, obstructive, and distributive. These descriptors are further grouped into two categories based on hemodynamic profiles: hypodynamic shock and hyperdynamic shock. These classifications provide a basis for developing differential diagnoses and

management plans. However, the individual patient's clinical status may be much more complex, with overlapping types of shock physiology. For example, early in septic shock, a primarily distributive state, hypovolemia may be the primary clinical manifestation prior to the initiation of volume resuscitation.

Hypodynamic Shock

Hypodynamic shock is characterized by a low cardiac index and vasoconstriction. Decreased cardiac output results in increased oxygen extraction and lactic acidosis. Organ dysfunction is directly related to inadequate blood flow.

Hypovolemic shock. Common causes of hypovolemic shock include hemorrhage, dehydration, and massive capillary leak. Decreased cardiac filling pressures are the hallmark of these conditions.

Cardiogenic shock. The most common cause of cardiogenic shock is acute myocardial infarction (MI) involving 40% or more of the left ventricular mass. Cardiomyopathies and valvular lesions are other etiologies. In contrast to hypovolemic shock, cardiac filling pressures are increased in cardiogenic shock.

Obstructive shock. The most common causes of obstructive shock include pericardial tamponade, acute pulmonary embolism, and tension pneumothorax. Cardiac filling pressures are usually increased owing to outflow obstruction, impaired ventricular filling, or decreased ventricular compliance. Therefore the clinical manifestations of cardiogenic and obstructive shock may be similar.

Hyperdynamic Shock

Hyperdynamic shock is distributive shock characterized by a high cardiac index and vasodilation. Unlike hypodynamic shock, oxygen extraction may be normal or decreased despite clinically significant hypoperfusion. Filling pressures can be increased or normal, depending on volume status and myocardial performance. Maldistribution of blood flow, rather than inadequate blood flow, is the etiology of organ dysfunction. Common causes of hyperdynamic shock are sepsis, severe trauma, anaphylaxis, specific drug intoxications, neurogenic shock, adrenal insufficiency, and severe pancreatitis.

Septic shock. Sepsis is the most common etiology of hyperdynamic distributive shock. Direct mediators of the inflammatory response and tissue hypoperfusion result in cellular injury and organ dysfunction in septic patients.

Traumatic shock. Severe trauma may result in traumatic shock through an inflammatory mechanism that is similar to the genesis of septic shock on a molecular, cellular, and phenotypic level. Shock in trauma patients is especially likely to be multifactorial, including a distributive immunologically mediated response to injury as well as shock resulting from hemorrhage.

Inflammation: Sepsis and the Systemic Response to Trauma

Commonalities of Systemic Inflammation

Sepsis and severe trauma are two of the most common clinical diagnoses encountered in the SICU. Systemic inflammation is the common denominator in both sepsis and severe trauma. This inflammatory response results from local or systemic release of infection-associated or injury-associated molecules, which use similar signaling pathways to marshal the soluble and cellular effectors necessary to restore homeostasis. Minor infections and minimal traumatic insults cause a localized inflammatory response that is transient and usually beneficial. However, sepsis and major trauma may result in dysregulated amplified reactions, leading to systemic inflammation and multiple organ failure in a significant percentage of these patients. This detrimental amplification of inflammation occurs in up to one-third of severely injured patients. Damage-associated molecular patterns are molecules that result from tissue and cellular injury. They interact with various receptors to initiate a sterile systemic inflammatory response following severe traumatic injury. These receptors are the same receptors that sense invading microorganisms. Hence, a similar form of systemic inflammation occurs whether the patient is septic or severely injured.

Primary Goals: Surviving Sepsis

Autodysregulation in the infected patient can lead to sepsis or septic shock. New consensus definitions for sepsis and septic shock were established in 2016 (Sepsis-3 definitions). Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is characterized by circulatory and cellular/metabolic dysfunction resulting in a higher risk of mortality. When sepsis or septic shock are encountered in the perioperative period, or if an infection potentially amenable to surgical therapy is suspected, affected patients are admitted to the SICU for intensive management.

The Surviving Sepsis Campaign (SSC) was established in 2002 to facilitate a worldwide reduction in sepsis mortality. Initial priorities included (1) building awareness of sepsis, (2) improving the diagnosis, (3) increasing the use of appropriate treatments, (4) educating healthcare professionals, (5) improving post-ICU care, (6) developing guidelines of care, and (7) implementing performance improvement programs. The original SSC guidelines were published in 2004 and revised in 2008 and again in 2012. The most current iteration was established in 2016 and published in 2017 and is specifically directed toward the management of patients with sepsis and septic shock. These recommendations are not perfect with respect to scientific rigor, but the evidence-based recommendations regarding acute management of sepsis and septic shock provide the foundation for improved outcomes in this large subset of critically ill patients.

General resuscitative measures. The SSC guidelines recommend resuscitation of patients with sepsis and septic shock to begin immediately, at the time of diagnosis. For sepsis-induced hypoperfusion, at least 30 mL/kg of intravenous (IV) crystalloid is administered within the first 3 hours. Additional fluid administration is guided by serial reassessments, including physical examination; physiologic variables, including heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, and urine output; and noninvasive or invasive monitoring. The target mean arterial pressure (MAP) is 65 mm Hg. An additional end point is normalization of lactate in those patients who present with elevated lactate levels as markers

of tissue hypoperfusion. Resuscitative end points must be individualized.

Diagnosis of septic source. Hospitals and healthcare systems should establish performance improvement programs for sepsis, including screening algorithms. Blood cultures and other applicable cultures should be obtained prior to initiation of antibiotic therapy. If indicated, imaging studies should be performed to confirm potential sources of infection.

Empirical antibiotic therapy and infection source control. Administration of empirical broad-spectrum antimicrobials should occur within 1 hour of recognition of sepsis or septic shock. When appropriate, the choice of antimicrobial drugs should be reassessed daily for the potential to deescalate from broad-spectrum antibiotics to more specifically tailored antibiotics. Infection source control should occur as soon as possible.

Fluid resuscitation. Initial fluid resuscitation should be undertaken with crystalloid. Volume resuscitation should continue as long as the patient demonstrates volume responsiveness based on either dynamic or static variables. The addition of albumin to the resuscitation fluid can be considered in patients who continue to require substantial quantities of crystalloid to maintain an adequate MAP. *Hydroxyethyl starches should be avoided.*

Vasopressor and inotropic medications. Once intravascular volume is deemed to be optimal, vasopressors may be necessary to achieve adequate perfusion pressures, typically targeted to the aforementioned MAP of 65 mm Hg. However, if the degree of shock is profound, volume resuscitation may occur simultaneously with the initiation of vasopressor support, particularly if diastolic hypotension is severe. Norepinephrine is the first-line vasopressor for management of septic shock. Epinephrine can be added when an additional drug is required to maintain an adequate MAP. Low-dose vasopressin can also be added at the nontitratable sepsis dose (0.03 U/min) but should not be used as the initial vasopressor. Dopamine is not recommended as an alternative to norepinephrine except in selected patients such as those with a low risk of tachydysrhythmias and absolute or relative bradycardia. Dobutamine can be added to vasopressor support in the presence of myocardial dysfunction or when hypoperfusion persists despite adequacy of intravascular volume and MAP.

Steroid management. Empirical IV corticosteroids should be avoided if adequate volume resuscitation and vasopressor therapy restore hemodynamic stability. If this cannot be achieved, IV hydrocortisone 200 mg per day in four divided doses is recommended.

Hemoglobin target. In the absence of myocardial ischemia, severe hypoxemia, or acute hemorrhage, the transfusion trigger is generally less than 7.0 g/dL.

Ventilator measures for sepsis-induced acute respiratory distress syndrome. First and foremost, a low tidal volume and limitation of inspiratory plateau pressure are recommended for ventilator management of sepsis-induced acute respiratory distress syndrome (ARDS). The target tidal volume is 6 mL/kg, and the upper limit goal for plateau pressure is 30 cm H_2O. Application of at least a minimal amount of positive end-expiratory pressure (PEEP) is also advised; higher levels of PEEP are used for moderate or severe ARDS. Recruitment maneuvers can be used in patients with severe refractory hypoxemia. Prone positioning may be used in patients with a Pao_2/Fio_2 ratio of 150 mm Hg or less in critical care units familiar with this mode of hypoxemic rescue. A short course of neuromuscular blockade (≤48 hours) for adjunctive management of ARDS and a Pao_2/Fio_2 less than 150 mm Hg can be undertaken. The head of the bed should be elevated in all mechanically ventilated patients unless contraindicated. In patients with established ARDS who are adequately volume resuscitated, a conservative fluid strategy should be employed. Finally, protocols for spontaneous breathing trials, weaning, and minimizing of sedation should be used.

General critical care management. Protocols for blood glucose management are recommended, targeting a blood glucose level of 180 mg/dL or less. Continuous venovenous hemofiltration (CVVH) and intermittent hemodialysis are considered equivalent in patients with sepsis and acute renal failure (ARF) because they achieve similar short-term survival rates. However, CVVH is much better tolerated in hemodynamically unstable patients with septic shock. Additional recommendations call for venous thromboembolism prophylaxis, stress ulcer prophylaxis, and early enteral feeding initiation. Finally, the goals of care, including treatment plans and end-of-life discussions if appropriate, should occur as soon as possible, but within 72 hours of ICU admission.

A Genomic and Molecular Perspective

The systemic inflammatory response. The similarity between the pathophysiologic response to sepsis and to traumatic injury is immunologically mediated and, by extrapolation, is a genomic and molecular phenomenon. Both sepsis and traumatic injury activate the innate immune system, which results in a systemic inflammatory response that ideally limits damage and restores homeostasis. Sepsis requires an identifiable source of infection. Conversely, it is widely accepted that systemic inflammation following trauma is sterile.

The two general components of the systemic inflammatory response include (1) an acute proinflammatory response mediated by an increase in the expression of innate immunity genes and (2) an antiinflammatory response that modulates the proinflammatory phase to affect the restoration of homeostasis. It is likely that both components of the response occur simultaneously rather than sequentially following severe traumatic injury. The degree of systemic inflammation following trauma is proportional to the severity of the injury and is an independent predictor of organ dysfunction and mortality.

Compensatory antiinflammatory response syndrome (CARS). CARS is associated with the antiinflammatory component of systemic inflammation. It is a suppression of adaptive immunity mediated by suppression of associated genes. A major consequence of CARS is the enhanced susceptibility of critically ill patients to nosocomial infections. This has been demonstrated in animal "two-hit" models, manifested as an increased susceptibility to infection after a first insult.

Persistent inflammation, immunosuppression, and catabolism syndrome (PICS). Chronic critical illness describes patients

who survive their initial episode of critical illness but remain dependent on ICU care and never fully recover. PICS describes this form of chronic critical illness. Severely injured trauma patients with complicated outcomes are older and sicker and require more ventilator days compared to their "uncomplicated" counterparts. They have persistent leukocytosis and low lymphocyte and albumin levels. Genomic analysis of these complicated patients demonstrates persistent expression of changes consistent with defects in the adaptive immune response and increased inflammation. Clinically, this manifests as persistent inflammation, including a prolonged acute-phase response, immunosuppression, protein catabolism, malnutrition, and reduced functional and cognitive abilities. The unifying pathology is low-level inflammation inducing immune suppression and progressive protein catabolism. These patients typically have a long and complicated course culminating in transfer to a long-term acute care facility where they experience a further protracted decline and death.

Hemorrhage: The Exsanguinating Patient

Acute blood loss and its sequelae are the leading causes of early preventable death in surgical patients. Massive hemorrhage is typically associated with the severely injured trauma patient, but any operation can be complicated by intraoperative or postoperative hemorrhage. Additional clinical scenarios associated with life-threatening blood loss include gastrointestinal hemorrhage and obstetric hemorrhage. Management of these patients includes definitive control of the bleeding source in the OR or angiography suite and perioperative management in the SICU. Resuscitative strategies are used to keep the bleeding patient alive long enough to undergo hemorrhage control. Management of the exsanguinating patient is a prototype of multidisciplinary teamwork: surgeons, anesthesiologists, and intensivists work together to effect a life-saving intervention.

Classification of Hemorrhage

Hemorrhage is classified into four categories based on the initial clinical presentation. This allows estimation of the percentage of acute blood loss. Class I hemorrhage describes blood loss of up to 15% of blood volume or up to about 750 mL in a 70-kg male. Clinical symptoms may be minimal with no significant change in vital signs. Blood transfusion is typically not required in this circumstance. Class II hemorrhage describes blood loss of 15% to 30% of blood volume or approximately 750 to 1500 mL. Tachycardia, tachypnea, and a decreased pulse pressure occur. The decreased pulse pressure is due to a rise in diastolic pressure due to an increase in circulating catecholamines. Notably, there is not a significant decrease in systolic blood pressure. Subtle central nervous system (CNS) changes such as anxiety may be apparent. Urine output is only minimally decreased. Some of these patients may require blood transfusion. Class III hemorrhage describes blood loss of 30% to 40% of blood volume or about 1500 to 2000 mL. These patients present with classic signs, including marked tachycardia, tachypnea, systolic hypotension, significant changes in mental status, and oliguria. In an otherwise uncomplicated patient, this is the least amount of blood loss that causes a decrease in systolic blood pressure. These patients almost always require transfusion of blood products. Class IV hemorrhage describes blood loss of over 40% of blood volume or over 2000 mL. This degree of blood loss is immediately life threatening. Marked tachycardia, significant and sustained hypotension, a very narrow pulse pressure, negligible urine output, markedly depressed mental status, and cold pale skin are characteristic. These patients require transfusion of blood products and immediate control of the bleeding source. Loss of more than half of the blood volume results in loss of consciousness and bradycardia.

Coagulopathy Associated With Massive Hemorrhage and Injury

Excessive blood loss of any etiology, prolonged shock, severe injuries, and traumatic brain injury with disruption of the blood-brain barrier have all been demonstrated to disrupt normal coagulation and result in a coagulopathy. This perturbation is manifested as abnormal clot formation or fibrinolysis or both. The coagulopathy leads to further bleeding, resulting in the "lethal triad" of hypothermia, acidosis, and coagulopathy. Depletion coagulopathy causes abnormalities in traditionally measured coagulation parameters such as the international normalized ratio (INR) and the activated partial thromboplastin time (aPTT) and is a predictor of mortality. Fibrinolytic coagulopathy does not cause abnormalities of INR and PTT and predicts infection, organ failure, and mortality.

Damage Control Resuscitation

Overview and general principles. Damage control resuscitation or hemostatic resuscitation is a useful adjunct in the prevention and reversal of the aforementioned coagulopathy associated with massive hemorrhage and injury. General principles include early hemorrhage control, permissive hypotension until hemorrhage is controlled, avoidance of crystalloids, and early use of blood components facilitated by implementation of institutionally based massive transfusion protocols (MTPs). Correction of hypothermia, acidosis, and hypocalcemia are important adjuncts.

Limitation of crystalloid use. Rapid and large-volume crystalloid infusion in exsanguinating patients can worsen bleeding by clot disruption, dilutional coagulopathy, thrombocytopenia, anemia, and acidosis. Crystalloid resuscitation in massively bleeding trauma patients has been associated with substantial increases in morbidity and ICU and hospital length of stay. Additionally, albumin and starch-based fluids should not be used as resuscitative adjuncts in actively bleeding patients.

Optimal transfusion practice. A variety of definitions apply to the term *massive transfusion,* one of the most common being transfusion of 10 units of packed red blood cells (PRBCs) in 24 hours. Patients who require massive transfusion benefit from early delivery of component therapy using standardized protocols. MTPs have been demonstrated to optimize this process and improve outcomes. Reduction in 24-hour and 30-day mortality, decreased intraoperative crystalloid administration, and reduced postoperative blood product use have been demonstrated when MTPs are implemented.

Determination of the optimal ratio of blood component delivery has been the subject of numerous investigations. It appears that high-ratio protocols are optimal, with data indicating that a 1:1:1 ratio of units of plasma:platelets:PRBCs is associated with improved hemostasis and a decreased mortality due to exsanguination at 24 hours. These high-ratio protocols apply only to patients who require massive transfusion. They do not improve survival in patients who are not massively bleeding; in fact, they may worsen outcomes in those patients.

Role of Procoagulants in the Exsanguinating Patient

Clotting factors. Fresh frozen plasma (FFP) contains all of the clotting factors. Individual recombinant clotting factors are also available for the management of a coagulopathy due to inadequate amounts of one or a few clotting factors. The most widely studied and utilized recombinant clotting factor since the turn of this century has been recombinant human coagulation factor VIIa (rFVIIa), approved in 1999 for the treatment of bleeding in patients with hemophilia and in patients who have inhibitors to factor VIII or factor IX. The clotting mechanism is initiated by activation of factors IX and X in the presence of tissue factor. Activated factor X, in conjunction with factor V, calcium, and phospholipids, converts prothrombin to thrombin, which converts fibrinogen to fibrin. Thrombin generation on the surface of activated platelets is also promoted. This process results in formation of a fibrin-platelet plug at the site of vascular injury.

Bleeding surgical and trauma patients are obviously different than those with hemophilia, since massive blood loss results in deficiency of all clotting factors, platelets, and RBCs. The use of rFVIIa was never approved for use in trauma patients, but its off-label use in this population was initially widespread. It was also used by the US military during the Iraq and Afghanistan conflicts. As rFVIIa was subjected to further investigation, it became apparent that this intervention failed to improve outcomes in trauma patients, and concern developed regarding the risk of thrombotic complications. At present, the consensus is that there are no proven clinically significant benefits of rFVIIa as a general hemostatic agent in patients who do not have hemophilia. Especially given its potential thrombotic risks, the use of rFVIIa as a general hemostatic agent in patients without hemophilia is not recommended. When damage control resuscitation using high-ratio blood component replacement is used, all of the clotting factors, platelets, and RBCs required for clot generation are administered, making use of individual recombinant factors unnecessary.

One special scenario in which low-volume rapid reversal of coagulopathy is essential is the management of elderly trauma patients who are anticoagulated with warfarin, particularly in the setting of traumatic brain injury. Rapid infusion of large volumes of FFP is often impossible owing to comorbidities predisposing to volume overload (e.g., congestive heart failure, renal failure). Prothrombin complex concentrates (PCCs) provide rapid and low-volume delivery of vitamin K–dependent clotting factors. These products contain factors II, IX, and X, with variable quantities of factor VII and the anticoagulant proteins C and S. The prothrombin complex concentrate that includes factor VII is four-factor PCC. In addition to use in traumatic brain injury, studies have demonstrated prothrombin complex concentrates can be effective in rapidly reversing coagulopathy to allow for surgery or to control postoperative bleeding in patients who have been taking warfarin. There are no data to support use of prothrombin complex concentrates in the absence of warfarin use, but these products are often used as salvage therapy for reversal of persistent coagulopathy that occurs despite appropriate use of blood component therapy.

Antifibrinolytic agents. Under normal circumstances, plasmin initiates clot resolution by degradation of fibrin. Trauma-associated coagulopathy is characterized by poor clot formation and rapid lysis of clots. Tranexamic acid is an antifibrinolytic drug that binds with plasminogen to prevent its activation to plasmin, thereby interfering with the process of clot lysis and slowing bleeding. Experts in trauma resuscitation have developed evidence-based guidelines for the use of tranexamic acid in adult trauma patients. Administration should be limited to patients with severe hemorrhagic shock (systolic blood pressure <75 mm Hg) with known predictors for fibrinolysis or with documented fibrinolysis on thromboelastography. It should be administered *only if* the time since injury is less than 3 hours. The recommended dose is 1 g IV over 10 minutes followed by 1 g by infusion over 8 hours.

The Anticoagulated Patient

A special subset of patients develops life-threatening hemorrhage while being anticoagulated for management of comorbid conditions. Patients taking antiplatelet drugs can also be included in this group. The fundamental principle of anticoagulation is inhibition of thrombin and/or platelet activation. Thrombin generates fibrin from fibrinogen and activates factor V, factor VII, and platelets. Activated platelets adhere to injured endothelium, express glycoprotein IIb/IIIa receptors, aggregate, and increase thrombin generation from prothrombin. Reversal of the effects of anticoagulants and antiplatelet drugs are adjunctive measures in the management of acute hemorrhage. The decision to reverse the therapeutic effects of these drugs in an individual patient is based on a risk-benefit analysis, weighing the risk of ongoing hemorrhage versus the risk of thrombosis.

For a detailed discussion of the currently available anticoagulant and antiplatelet medications, their mechanisms of action, and the availability of antidotes for their activity, see Chapter 23.

Platelet dysfunction and thrombocytopenia. Inhibition of platelet activation is crucial for the management of patients who have ischemic cardiovascular disease and atherosclerosis. Platelet inhibitors and antiplatelet drugs increase the risk of bleeding.

Aspirin is an irreversible platelet cyclooxygenase and thromboxane A_2 inhibitor and is also a relatively weak antiplatelet agent. More potent antiplatelet drugs include the glycoprotein

IIb/IIIa receptor antagonists (abciximab, tirofiban, and eptifibatide). Additional potent antiplatelet drugs include clopidogrel, prasugrel, and ticagrelor, which selectively and irreversibly bind to the P2Y12 receptor to inhibit the adenosine diphosphate–dependent mechanism of glycoprotein IIb/IIIa receptor expression and platelet activation.

Clopidogrel is the major antiplatelet drug in current use. Dual antiplatelet therapy (i.e., aspirin and clopidogrel) is standard treatment following revascularization by percutaneous coronary intervention (PCI) with stent placement. Dual therapy is recommended for up to 4 weeks after placement of bare-metal stents and for 6 to 12 months after placement of drug-eluting stents. *Methods for monitoring the effects of clopidogrel have not been established, and specific therapy in the event of associated bleeding is not available.* In patients who have coronary artery stents and require surgery, the operation should be deferred for more than 6 weeks after bare-metal stent placement and more than 6 months after drug-eluting stent placement if possible. In patients who require surgery within 6 weeks of bare-metal stent placement or within 6 months of drug-eluting stent placement, antiplatelet therapy should be continued perioperatively. The actively bleeding patient with recent placement of coronary stents comprises a third category. In these patients, the risks and benefits of stopping clopidogrel must be weighed against the risk of stent thrombosis and against the need for surgical intervention.

Platelet dysfunction without thrombocytopenia may occur in many clinical circumstances, including inherited and acquired coagulopathies. Desmopressin (DDAVP) is a synthetic analogue of the natural hormone arginine vasopressin. DDAVP injection has been approved for and is indicated in patients with hemophilia A with factor VIII coagulant activity levels above 5% and for patients with mild to moderate classic von Willebrand disease (type I) with factor VIII levels above 5%. In these patients, the bleeding time is shortened or corrected by release of endogenous factor VIII from storage pools. DDAVP has also been demonstrated to shorten or correct the bleeding time in uremia, but the mechanism of this action is unknown. The use of DDAVP in the actively hemorrhaging patient with platelet dysfunction is not well established.

Thrombocytopenia is the most common coagulation disorder in the ICU and is defined as a platelet count below 150,000/mm^3. The two most important etiologies of thrombocytopenia in this setting are sepsis and heparin-induced thrombocytopenia (HIT). However, other potential causes are many and are generally classified according to whether platelets are consumed, sequestered, or underproduced. HIT is a special circumstance, and platelet transfusion should be avoided in these patients because of the risk of exacerbation of the prothrombotic state. Likewise, platelets are not usually transfused if the thrombocytopenia is due to immune-mediated destruction, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, or uncomplicated cardiac bypass surgery.

The threshold for prophylactic transfusion of thrombocytopenic ICU patients is not clear. However, we do know that thrombocytopenia is associated with an increased risk of bleeding with surgery or invasive procedures only when the platelet count is below 50,000/mm^3. Spontaneous bleeding, especially intracerebral bleeding, usually does not occur until the platelet count is below 10,000/mm^3. Therefore, in the absence of active bleeding or the need for an invasive procedure, most patients with very low platelet counts and no associated risk factors for bleeding are transfused when the platelet count is below 10,000/mm^3. If they have additional risk factors for bleeding, the trigger is typically less than 20,000/mm^3. In the presence of an associated coagulopathy, active bleeding, or platelet dysfunction, a more liberal transfusion strategy is undertaken, but guidelines for platelet transfusion triggers are not well established.

In the massively hemorrhaging patient, platelet transfusions in conjunction with correction of plasma coagulation factor deficits are indicated when the platelet count is below 50,000/mm^3 or below 100,000/mm^3 in the presence of diffuse microvascular bleeding. If the patient meets criteria for activation of an MTP, a 1:1:1 ratio of units of plasma:platelets:PRBCs should be administered.

Acute Cardiopulmonary Instability

Acute cardiovascular or pulmonary decompensation in the immediate perioperative period is a significant cause of morbidity and mortality in the critically ill surgical patient. Rapid assessment, diagnosis, and treatment are key to limiting morbidity and preventing mortality. Pattern recognition and attention to detail allow precision in the management of these conditions.

Hemodynamic Compromise and Circulatory Collapse

Cardiac etiologies. Circulatory collapse attributable to cardiac dysfunction can involve the myocardium, the pericardium, the cardiac valves, and the outflow tract of the heart. Disease processes involving these components of the heart are reviewed in detail elsewhere in this textbook. However, principles pertaining to the acute deterioration typical of critically ill surgical patients are highlighted here.

Acute deterioration attributable to myocardial dysfunction is most often associated with an acute coronary syndrome (ACS), which includes a continuum of associated disorders such as ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation myocardial infarction (NSTEMI), and unstable angina pectoris (UA). The pathophysiology shared by these disorders is rupture of a previously quiescent atherosclerotic plaque, which triggers the release of vasoactive substances and activation of platelets and the coagulation cascade. All patients suspected of ACS should be treated with supplemental oxygen, sublingual nitroglycerine (unless systolic pressure is <90 mm Hg), and aspirin. Despite the common etiology of the subtypes of ACS, rapid recognition of the STEMI variant is crucial because these patients benefit from immediate reperfusion and should be treated with fibrinolytic therapy or urgent revascularization. Conversely, fibrinolytics have demonstrated no benefit and an increased risk of adverse events when used in patients with NSTEMI or unstable angina. Multiple clinical trials have demonstrated that the early administration of fibrinolytic agents in STEMI reduces infarct

size, preserves left ventricular function, and reduces short- and long-term mortality. Tissue plasminogen activator (tPA) is the fibrinolytic drug most commonly used. However, systemic fibrinolysis poses a special problem in the trauma and surgical patient population because trauma or major surgery within 2 weeks of fibrinolysis that could be a source of rebleeding is an absolute contraindication to fibrinolytic therapy in STEMI. In the surgical patient, the risk of thrombolysis may be prohibitive, and emergency coronary angiography with a PCI may be preferable. However, PCI mandates use of antiplatelet drugs and immediate adjunctive therapeutic anticoagulation, which can also be problematic in the trauma or surgical patient. A risk-benefit analysis of reperfusion by each method is imperative for each patient. If a patient is deemed to be a candidate for reperfusion, the time to revascularization is crucial. A medical contact-to-needle time for initiation of fibrinolytic therapy of under 30 minutes or a medical contact-to-balloon time for PCI of under 90 minutes are the currently accepted goals. In patients with diffuse and complex coronary lesions, coronary artery bypass grafting (CABG) may be preferred. The invasive nature of CABG must be weighed against the likelihood of a requirement for repeated interventions after initial PCI. PCI may be a reasonable alternative in patients with complex coronary lesions and severe coexisting diseases that substantially increase the risk of coronary bypass surgery.

Cardiogenic shock, resulting from either left ventricular pump failure or mechanical complications, is the next leading cause of in-hospital death after MI. Systolic dysfunction results in decreased cardiac output and decreased stroke volume. Systemic perfusion is decreased, which results in compensatory vasoconstriction and fluid retention, which can contribute to further myocardial dysfunction. Hypotension causes a decrease in coronary perfusion pressure and worsens myocardial ischemia. Diastolic dysfunction can also cause an increase in left ventricular end-diastolic pressure, pulmonary congestion, and hypoxemia, which can also worsen myocardial ischemia. Interruption of this cycle of ischemia and myocardial dysfunction is the basis for treatment of cardiogenic shock. Adequate oxygenation and ventilation are maintained with endotracheal intubation and mechanical ventilation if necessary. Electrolyte abnormalities are corrected, narcotics are administered, and dysrhythmias and heart block are corrected with antidysrhythmic drugs, cardioversion, or pacing. Preload should be optimized and is especially important in patients who have right ventricular infarction. If hypotension persists despite adequate volume resuscitation, vasopressors may be needed to maintain coronary perfusion pressure. Norepinephrine is superior to dopamine for management of hypotension in cardiogenic shock. Phenylephrine may be added if tachydysrhythmias are problematic. If tissue perfusion is inadequate despite achieving an adequate blood pressure, inotropic support and/or intraaortic balloon pump (IABP) counterpulsation are initiated. Dobutamine, a selective β_1-adrenergic receptor agonist, is the initial drug of choice in patients with systolic pressures above 80 mm Hg. Phosphodiesterase inhibitors (e.g., milrinone) are less dysrhythmogenic than catecholamines but may cause hypotension. Intraaortic balloon counterpulsation reduces systolic afterload, augments diastolic perfusion pressure, increases cardiac output, and improves coronary blood flow, all without increasing oxygen demand. However, IABP counterpulsation does not improve blood flow distal to a critical coronary stenosis and has not been demonstrated to improve mortality when used without reperfusion therapy or revascularization. Rather, use of an IABP can serve as a bridge to help stabilize patients prior to definitive therapeutic measures. Ventricular assist devices may also be used in appropriate clinical settings. Randomized trials have demonstrated that cardiogenic shock in the setting of acute MI is a class I indication for emergency revascularization, either by PCI or CABG. Systemic fibrinolysis is not a preferred option in this circumstance.

Additional complications of acute MI include postinfarction angina, ventricular free wall rupture, ventricular septal rupture, acute mitral regurgitation, and right ventricular infarction. A high index of suspicion and familiarity with the presentation of these entities allows for their prompt diagnosis and treatment.

Postinfarction angina is a syndrome of chest pain that may occur at rest or with minimal activity that occurs 24 hours or later after an acute MI. It may result from ischemia around the fresh infarction or at a distance and is generally associated with a poor long-term prognosis. It can be diagnosed clinically and evaluated by coronary angiography and is an indication for revascularization. PCI is useful for anatomically appropriate lesions. CABG is considered in patients with left main coronary artery disease, three-vessel coronary artery disease, and for lesions unsuitable for percutaneous interventions. IABP counterpulsation is often required as a bridge to revascularization if the angina cannot be controlled medically or if the patient is hemodynamically unstable.

Ventricular free wall rupture may occur during the first week after infarction. The typical patient is elderly, female, and hypertensive. Left ventricular pseudoaneurysm formation with leakage may be a sentinel event, presenting as chest pain, nausea, and anxiety, but frank rupture is catastrophic and presents with shock and electromechanical dissociation. Echocardiography will demonstrate a pericardial effusion. Postinfarction pericardial effusions larger than 10 mm in width on echo images taken in diastole are frequently associated with cardiac rupture. Pericardiocentesis may be required to relieve acute tamponade but is best performed in the OR immediately prior to thoracotomy and ventricular repair.

Ventricular septal rupture presents with severe heart failure or cardiogenic shock. Auscultation demonstrates a pansystolic murmur and a parasternal thrill. The hallmark on echocardiography is a left-to-right intracardiac shunt. Rapid institution of IABP counterpulsation and supportive pharmacologic therapy must be undertaken. Operative repair should occur within 48 hours of the rupture.

Acute mitral regurgitation is usually associated with an inferior wall MI and ischemia or infarction of the posterior papillary muscle, but anterior papillary muscle rupture is also possible. Papillary muscle rupture occurs in a bimodal distribution: either within 24 hours or as late as 3 to 7 days after an acute MI.

The presentation is catastrophic, with pulmonary edema, hypotension, and cardiogenic shock. The murmur may be limited to early systole, soft or even inaudible. Echocardiography is essential for diagnosis. Management may include afterload reduction, IABP counterpulsation, inotropic support, and vasopressor therapy as a bridge to surgical valve repair or replacement, which should occur as soon as possible.

Right ventricular infarction occurs in up to one-third of patients with inferior wall MI. The classic presentation is a clear chest x-ray and jugular venous distention in a patient with a known inferior wall MI. ST-segment elevation is present in the right precordial leads. Right atrial and right ventricular end-diastolic pressures are elevated, pulmonary artery occlusion pressure is normal to low, and cardiac output is low. Echocardiography demonstrates decreased right ventricular contractility. Right ventricular preload should be maintained with volume resuscitation. Some patients may require inotropic support or IABP counterpulsation. Reperfusion of the occluded coronary artery is also imperative.

Acute deterioration associated with pericardial pathology is usually caused by pericardial effusion and/or cardiac tamponade. A pericardial effusion may be characterized as a transudate, an exudate, a pyopericardium, or a hemopericardium. Large effusions are common with cancer. Loculated effusions tend to occur in the postsurgical patient, the trauma patient, and those with purulent pericarditis. Heart sounds are distant. Symptoms include orthopnea, cough, and dysphagia. Pericarditis is associated with typical chest pain, a pericardial friction rub, fever, and diffuse ST-segment elevation. Large effusions look like globular cardiomegaly on chest x-ray. (See Chapter 11 for details about pericardial diseases.) The size of an effusion can be graded by echocardiography, which can also detect signs of cardiac tamponade. One-third of patients with asymptomatic large pericardial effusions will go on to develop cardiac tamponade. Triggers for the development of tamponade include hypovolemia, tachydysrhythmias, and acute pericarditis. Pericardiocentesis is indicated for immediate management of tamponade. Patients with very large effusions, electrical alternans, or pulsus paradoxus should also undergo pericardiocentesis. Patients with penetrating cardiac wounds, postinfarction myocardial rupture, or dissecting aortic hematomas presenting as tamponade require emergency cardiac surgery.

Valvular heart disease can present in two ways in the critically ill patient: (1) acute valve dysfunction resulting in acute heart failure and (2) decompensation of chronic valve disease. Regurgitation is the most common type of acute valve dysfunction. Although stenosis is typically chronic and slowly progressive, acute decompensation may occur if there is a significant superimposed hemodynamic demand. For instance, previously asymptomatic mitral stenosis may present with pulmonary edema in the setting of systemic infection, and asymptomatic aortic stenosis may present with cardiogenic shock in the setting of acute gastrointestinal hemorrhage. Echocardiography is essential in the diagnosis of all these entities.

In addition to acute MI, common etiologies of acute mitral regurgitation include endocarditis and mitral valve prolapse. These patients can present with pulmonary edema, and the characteristic murmur may be soft or absent. Surgical repair should occur as soon as possible.

Causes of acute aortic regurgitation include endocarditis and aortic dissection. The diastolic murmur may be indistinct. Treatment is emergency surgery.

Rheumatic mitral stenosis usually occurs in young women and may present during pregnancy. Acute decompensation can often be treated conservatively. Percutaneous balloon mitral valvulotomy is the preferred intervention in this situation.

Aortic stenosis is common in the elderly patient population. Decompensation occurs with an increased hemodynamic demand. A systolic murmur is auscultated. Conservative management for decompensation is appropriate. Aortic valve replacement is performed for severe symptomatic disease.

Mechanical valves are subject to valve thrombosis, and management of this problem is controversial. Options include therapeutic anticoagulation, surgical intervention with valve replacement, and systemic thrombolytic therapy. Tissue valves degenerate within 10 to 15 years after implantation. Acute regurgitation associated with tissue valves is similar to native valve regurgitation and requires valve replacement.

Obstruction to cardiac outflow is most commonly encountered in patients with a pulmonary embolism, which is the most common preventable cause of hospital death. Acute pulmonary embolism can be divided into several overlapping syndromes: (1) transient dyspnea and tachypnea; (2) pulmonary infarction or congestive atelectasis manifested by pleuritic chest pain, cough, hemoptysis, pleural effusion, or pulmonary infiltrates; (3) right ventricular failure associated with severe dyspnea and tachypnea; (4) cardiovascular collapse with hypotension, syncope, and coma (massive pulmonary embolism); and (5) nonspecific symptoms, including confusion, coma, pyrexia, wheezing, recalcitrant heart failure, and dysrhythmias. Thrombolytic therapy is indicated for patients with cardiovascular collapse and for some who have clinical evidence of right ventricular failure or right ventricular hypokinesis on echocardiography. Thrombolytic therapy provides rapid lysis of a pulmonary embolism and rapid restoration of right ventricular function. However, many trauma and surgical patients are not candidates for systemic thrombolysis, but some may be candidates for catheter-directed thrombolytic therapy. Thoracotomy and surgical pulmonary embolectomy remains an option for life-threatening hemodynamic collapse due to a pulmonary embolism when thrombolysis and catheter-directed therapy are not feasible.

Peripheral etiologies. Peripheral etiologies of cardiovascular collapse in the critically ill patient include loss of vascular tone and massive hemorrhage. An understanding of the differential diagnosis and presentation of these entities leads to rapid identification of the culprit and targeted management.

Loss of vascular tone leading to cardiovascular collapse is most common in distributive shock. Etiologies include sepsis, severe trauma, anaphylaxis, specific drug intoxications, neurogenic shock, adrenal insufficiency, and severe pancreatitis. A special circumstance is intraoperative vasodilation associated with the use of volatile anesthetics. The systemic hemodynamic effects of volatile anesthetics are determined by myocardial

depression, direct arterial and venous vasodilation, and autonomic nervous system activity. All volatile anesthetics can cause a concentration-dependent decrease in arterial blood pressure that can be mitigated by surgical stimulation or by judicious administration of a vasoconstrictor such as phenylephrine.

Massive hemorrhage may occur in a number of different clinical circumstances. Etiologies of hemorrhage that are visible include penetrating trauma with blood loss emanating from the wounds, hemorrhage occurring intraoperatively, upper and lower gastrointestinal blood loss, and obstetric or gynecologic uterine hemorrhage. Etiologies of hemorrhage that are not readily apparent by direct observation include hemorrhage into the thoracic cavity, abdomen, or pelvis as a result of blunt or penetrating trauma; hemorrhage into the extremities as a result of long-bone fractures; spontaneous hemorrhage of solid organs or major blood vessels (e.g., ruptured or leaking aneurysms); and postoperative hemorrhage. A particularly high index of suspicion and clinical acumen is required to rapidly diagnose and treat clinically significant occult hemorrhage.

Acute Exacerbation of Respiratory Failure

Anatomic mechanical etiologies. The most common causes of pneumothorax in the ICU include invasive procedures (most often placement of subclavian and internal jugular central venous catheters) and barotrauma. Pneumothorax can also occur in any trauma patient as a result of either blunt or penetrating injury to the chest. Tension pneumothorax is perhaps the most dramatic example of acute life-threatening respiratory failure originating from an anatomic mechanical etiology. Tension physiology occurs when a one-way valve air leak tracks from a defect in the lung or through a defect in the chest wall into the pleural space. Air accumulates and is trapped in the ipsilateral thoracic cavity, eventually completely collapsing the affected lung. The mediastinum is displaced contralaterally, decreasing venous return and compressing the opposite lung. Malperfusion results from the lack of venous inflow, with a resultant decline in cardiac output. Obstructive shock ensues. This typically begins as respiratory distress and, if left untreated, progresses to hemodynamic collapse. Nonspecific signs and symptoms include chest pain, air hunger, respiratory distress, tachycardia, hypotension, neck vein distention, and cyanosis. Specific signs signifying this diagnosis include tracheal deviation away from the affected side, unilateral absence of breath sounds, and a distended hemithorax without respiratory movement. In the mechanically ventilated patient, increasing peak and plateau airway pressures, decreasing compliance, and auto-PEEP may be noted. Additionally, the patient may be difficult to bag ventilate, and difficulty delivering the prescribed mechanical tidal volume may occur.

Tension pneumothorax is diagnosed clinically, and treatment should not be delayed to wait for radiologic confirmation. Immediate decompression is required and may be initially managed by inserting a large-caliber needle into the second intercostal space in the midclavicular line of the affected hemithorax. This temporizes the situation to allow definitive treatment, which consists of insertion of a chest tube into the fifth intercostal space just anterior to the midaxillary line. Successful decompression results in rapid restoration of hemodynamics.

Laparoscopic operations are widely performed, even in critically ill patients. Carbon dioxide (CO_2) is insufflated into the peritoneal cavity. Particularly in a patient with already perturbed hemodynamics, this may interfere with cardiac, circulatory, and respiratory function. A carbon dioxide pneumoperitoneum may result in hypercapnia and acidosis, which in turn can lead to decreased cardiac contractility, a propensity for dysrhythmias, and vasodilation. From a respiratory standpoint, adverse effects include a decreased functional residual capacity, vital capacity, and compliance, as well as increased atelectasis and peak airway pressures. These effects may persist into the postoperative period, further complicating perioperative cardiopulmonary management.

Airway circuit mechanical etiologies. Capnometry is the measurement of expired CO_2 and is a useful diagnostic tool. Changes in the shape of the expired CO_2 waveform in an intubated patient can alert the intensivist or anesthesiologist to developing problems. The end-expiratory (end-tidal) CO_2 pressure ($PETCO_2$) underestimates $PaCO_2$ by 1 to 5 mm Hg under physiologic conditions because of normally occurring alveolar dead space. Monitoring of $PETCO_2$ during mechanical ventilation can be used to assess cardiovascular status, $PaCO_2$ trends, and adequacy of ventilation. Factors that increase alveolar dead space widen the $PETCO_2$-$PaCO_2$ gradient. Pulmonary embolism acutely increases alveolar dead space. Therefore, an abrupt decrease in $PETCO_2$ indicates a sudden decrease in cardiac output or pulmonary embolism. Disappearance of the capnograph waveform may indicate cardiovascular collapse or massive airway obstruction, but it is usually due to disconnection from the ventilator circuit. Capnometry is the confirmation method of choice to confirm proper placement of an endotracheal tube and has been used to assess efficacy of chest compression during cardiopulmonary resuscitation.

Primary pulmonary etiologies. Pulmonary pathology common in critically ill patients can pose special challenges in perioperative management. Asthma, emphysema, and bronchitis may complicate management in the intraoperative, immediately postoperative, and extended postoperative periods.

Bronchospasm is a potentially serious problem encountered in the intraoperative management of patients undergoing general anesthesia. Although volatile anesthetics are bronchodilators, bronchospasm can still occur and may have grave consequences. Transient increases in airway resistance frequently occur after endotracheal intubation and may be caused by an increase in bronchiolar smooth muscle tone. Even otherwise healthy patients undergoing stimulation of the pulmonary parenchyma or airways are at risk for bronchospasm. This occurrence can be reduced by the administration of bronchodilator therapy directly into the airway. Patients with either quiescent or active asthma are at even greater risk. Patients without recent symptoms of asthma have a low frequency of perioperative respiratory complications, but perioperative bronchospasm develops in over 5% of patients who carry a diagnosis of asthma. In asthmatics, prophylactic steroids and bronchodilators can reduce the bronchoconstriction associated with tracheal intubation, as does the use of

topical lidocaine with flexible fiberoptic intubation. A number of patients who incur bronchospasm intraoperatively will have an intractable course and suffer brain damage or death, and only half of these seriously affected patients will have a history of asthma or chronic obstructive pulmonary disease (COPD).

COPD comprises three disorders: emphysema, peripheral airway disease, and chronic bronchitis. Any individual patient may have one or any combination of these components. The predominant clinical feature of COPD is impairment of expiratory airflow. Flow limitation is especially prominent in emphysema. The primary problem here is loss of lung elastic recoil, which results in marked dyspnea on exertion. Mechanical compression of airways by overinflated alveoli is a primary cause of airflow obstruction in emphysema. Patients with severe airflow limitation are at risk of hemodynamic collapse with the institution of positive pressure ventilation, owing to dynamic pulmonary hyperinflation. In addition to flow limitation, baseline hypercarbia, hypoxemia, and right ventricular dysfunction may make weaning from mechanical ventilation in the immediate postoperative period challenging in patients with COPD. Finally, severe life-threatening COPD exacerbations can be encountered in SICU patients and are characterized by a pH less than 7.30 and a PaO_2 less than 60 mm Hg; these episodes require oxygen supplementation and pharmacologic and ventilatory treatment. Administering noninvasive pressure support ventilation (PSV) and continuous positive airway pressure (CPAP) during COPD exacerbations may reduce intubation rates, complications, in-hospital mortality, and hospital length of stay. If mechanical ventilation is used, minute ventilation should be targeted to the predecompensation CO_2 level to minimize alveolar hyperinflation and avoid rebound respiratory acidosis when extubation occurs.

Inhaled anesthetics decrease the rate of mucous clearance by decreasing ciliary beat frequency, disrupting metachronism, or altering the characteristics of mucus. Pulmonary surfactant decreases the work of breathing by reducing alveolar surface tension. Volatile anesthetics cause reductions in phosphatidylcholine, the main lipid component of surfactant. Altered mucociliary function in mechanically ventilated patients can contribute to postoperative hypoxemia and atelectasis. Patients at greatest risk have excessive or abnormal mucus or surfactant production or acute lung injury (ALI). Examples of high-risk patients include those with chronic bronchitis, cystic fibrosis, and those receiving chronic mechanical ventilation. Difficulty with retained secretions in patients with chronic bronchitis can be very challenging postoperatively.

Acute hypoxemic respiratory failure is a common clinical scenario in critically ill surgical patients. Low-tidal-volume ventilation, described previously in the context of sepsis-related ARDS, is the most widely used treatment strategy, but alternative methods of rescue ventilation are sometimes used to manage refractory cases.

Airway pressure release ventilation (APRV) is an example of a pressure-controlled mode that allows spontaneous respiration in addition to intermittent mandatory ventilation. The majority of the respiratory cycle occurs at a set higher pressure (P-high), with brief periods at a set lower pressure (P-low). Additional prescribed parameters include time at P-high (T-high), time at P-low (T-low), and FIO_2. Benefits include increased lung recruitment, improved ventilation/perfusion matching, lower sedation requirements, and a positive effect on hemodynamics. A recent systematic review and meta-analysis (Critical Care Medicine, 2019) identified an association with a mortality benefit and improved oxygenation when compared to conventional ventilation strategies. However, the cumulative number of assessed patients was low, necessitating larger multicenter studies to validate these findings. Indeed, subsequent to the pivotal randomized controlled ARDSNet trial (*New England Journal of Medicine*, 2000), most studies investigating alternative ventilatory strategies to mitigate hypoxemic respiratory failure have not demonstrated benefit.

Metabolic Derangements

An extensive discussion of disease-based metabolic derangements is covered elsewhere in this textbook. In this section, conditions of particular relevance to the management of the critically ill perioperative patient are reviewed.

Malnutrition

Optimization of nutrition therapy and mitigation of malnutrition are primary therapeutic goals and improve outcomes. Basal energy expenditure (BEE) in hospitalized patients is estimated using the Harris-Benedict equations:

$$\text{BEE (men)} = 66.47 + 13.75\,(\text{weight in kg}) + 5.0\,(\text{height in cm}) - 6.78\,(\text{age in years})$$

$$\text{BEE (women)} = 655 + 9.56\,(\text{weight in kg}) + 1.85\,(\text{height in cm}) - 4.68\,(\text{age in years})$$

Minimally stressed patients require 25 kcal/kg/day, which is about 1.1 times greater than the calculated resting energy expenditure. The provision of 30 kcal/kg/day is required for most postsurgical patients. Trauma and sepsis increase energy substrate demands even further, such that severely stressed patients require 30 to 35 kcal/kg/day, and burn patients require 35 to 40 kcal/kg/day, which is 2 times greater than the calculated resting energy expenditure. Substrate requirements for protein synthesis must also be met. Higher protein intake may benefit healing in selected hypermetabolic or critically ill patients. Provision of 1 g protein/kg/day is appropriate in minimally stressed patients. Provision of 2 g/kg/day in severely stressed patients and 2.5 g/kg/day in burn patients helps limit the use of their protein stores as an energy source.

Oral intake is not possible for many critically ill patients. Therefore nutrition therapy is necessary. In addition to meeting the aforementioned goals for caloric and protein intake, nutrition therapy modulates and restores physiologic immune responses to critical illness. When provided enterally, nutrition therapy also maintains the functional and anatomic integrity of the gut.

In general, enteral nutrition is preferred over parenteral nutrition and should be initiated early. Management strategies to optimize the success of enteral feeding include feeding distal to the stomach, directly into the small bowel (facilitated by placement of nasojejunal tubes) in patients at risk of gastric ileus or

aspiration; elevating the head of the bed to 30 to 45 degrees; and using directed feeding protocols. Small-volume (trophic or trickle) feeding may not be sufficient to maintain gut integrity and normal mucosal permeability. Rather, 50% to 60% of caloric requirements are needed to achieve these therapeutic end points. In patients who do not tolerate enteral nutrition at goal rates, individualized energy supplementation with supplemental parenteral nutrition has been demonstrated to reduce nosocomial infections. Full parenteral nutrition should be started early in severely malnourished patients and in patients with a nonfunctional gastrointestinal tract.

Overfeeding. Overfeeding usually occurs when caloric needs are overestimated. This can happen when actual body weight is used to calculate the basal energy expenditure in critically ill patients with significant fluid overload and/or significant obesity. Estimated dry weight or adjusted lean body weight should be used to calculate the BEE in these circumstances. Overfeeding can lead to increased oxygen consumption, increased CO_2 production, prolonged ventilatory requirements, fatty liver, suppression of leukocyte function, hyperglycemia, and increased susceptibility to infection.

Refeeding syndrome. Refeeding syndrome can occur with rapid and excessive initiation of enteral or parenteral feeding in patients who have severe malnutrition due to starvation, alcoholism, delayed nutritional support, anorexia nervosa, or massive weight loss. When feeding is initiated in these patients, a shift from fat to carbohydrate metabolism triggers insulin release, which causes cellular uptake of electrolytes, especially phosphorous, magnesium, potassium, and calcium. Adverse clinical consequences of these electrolyte abnormalities include cardiac dysrhythmias, confusion, respiratory failure, and even death. Prevention of refeeding syndrome includes (1) correction of underlying electrolyte and volume deficits, (2) administration of thiamine prior to the initiation of feeding, and (3) slow initiation of feeding with a gradual increase in nutritional support over the course of the first week.

Hyperglycemia. Blood glucose levels are normally tightly regulated within a narrow range of 60 to 140 mg/dL in both the fed and fasted states. Diabetic hyperglycemia is defined as a fasting blood glucose concentration of 126 mg/dL or higher and a fed blood glucose concentration of over 200 mg/dL. There are no clear guidelines for defining hyperglycemia in the critically ill patient.

Stress-induced hyperglycemia occurs in critically ill patients and results from the effects of complicated hormonal, cytokine, and nervous system signals on glucose metabolic pathways. This hyperglycemia is due to insulin resistance in the liver and skeletal muscle. Hepatic insulin resistance causes increased hepatic gluconeogenesis and glucose production. Decreased glycogen synthesis and a shift from insulin-dependent to non–insulin-dependent glucose uptake occurs in skeletal muscle. Additionally, increased levels of stress mediators such as glucagon, cortisol, and growth hormone increase hepatic gluconeogenesis, while increased levels of epinephrine and norepinephrine increase hepatic glycogenolysis. Interleukins (IL1 and IL6) and tumor necrosis factor (TNF) may enhance both of these hyperglycemic mechanisms. Finally, exercise-stimulated glucose uptake into skeletal muscle is eliminated when critically ill patients are immobilized.

Paradigm shifts. Until the beginning of this millennium, blood glucose levels of up to 220 mg/dL were routinely tolerated in critically ill patients. It was suggested that this stress response was beneficial for organs that rely solely on glucose for their energy supply, such as the brain and RBCs. Subsequently, stress hyperglycemia has been shown to be associated with adverse outcomes in critically ill patients. In patients without diabetes mellitus, hyperglycemia has an almost linear relationship with mortality risk. In patients with established diabetes, the relationship between hyperglycemia and mortality is significantly blunted. It has been difficult to establish how tightly blood glucose levels should be controlled in ICU patients.

Van den Berghe's landmark study in 2001 supported the use of intensive insulin therapy to target tight glycemic control in critically ill patients, with a goal blood glucose of 80 to 110 mg/dL. In 2009, the NICE-SUGAR trial demonstrated an increase in mortality and an increase in the incidence of hypoglycemia in critically ill patients managed with this intensive insulin regimen. This and similar studies have resulted in widespread adoption of higher blood glucose targets in the critically ill population. Many of the studies support a blood glucose range of 140 to 180 mg/dL. Recent literature has also indicated that glucose variability over time may be an even more important determinant of mortality than the absolute blood glucose level at any given time.

Sick Euthyroid Syndrome

Critical illness can cause many nonspecific alterations in thyroid hormone concentrations in patients who do not have intrinsic thyroid dysfunction. These alterations relate to the severity of the critical illness and are termed sick euthyroid syndrome.

The alterations in thyroid hormone concentrations in the critically ill represent a continuum of changes that depends on the severity of the illness and can be categorized into distinct stages. The stages reflect the severity of critical illness and are designated *mild, moderate, severe,* and *recovery.* The alterations in thyroid function are usually associated with alterations in other endocrine systems, such as decreases in serum gonadotropin and sex hormone concentrations and increases in adrenocorticotropic hormone (ACTH, or corticotropin) and cortisol levels. Sick euthyroid syndrome is then functionally part of a systemic reaction to illness involving the immune and endocrine systems.

Low T3 state. A substantial depression of serum triiodothyronine (T_3) levels is seen throughout all stages of the sick euthyroid syndrome and can occur as early as 24 hours after onset of illness. This is accompanied by a reciprocal increase in reverse T_3.

Low T4 state. As the severity and duration of the illness increases, serum total thyroxine (T_4) levels become abnormal. Their decline correlates with prognosis in the critically ill patient. Mortality increases as serum total T_4 levels decrease below 4 μg/dL and approaches 80% for levels below 2 μg/dL. Of note, free T_4 hormone levels are normal even when total T_4 levels are

decreased. This may be why these patients appear clinically euthyroid. This low T_4 state is unlikely to result from hormone deficiency; rather, it is a marker of multisystem failure in critically ill patients.

Recovery state. As acute illness resolves, so do the altered thyroid hormone concentrations. This stage is characterized by modest increases in serum thyroid-stimulating hormone (TSH) levels. The recovery stage may be prolonged, and it may take weeks to months following hospital discharge for thyroid hormone levels to return to normal.

Treatment. Thyroid hormone replacement therapy is not of benefit in the vast majority of sick euthyroid patients. In the absence of clinical evidence of hypothyroidism, there is no good evidence for thyroid hormone replacement in patients who have decreased thyroid hormone concentrations due to the sick euthyroid syndrome.

Utility of thyroid function tests in the critically ill patient. Because of the high prevalence of abnormal thyroid function tests and the low prevalence of actual thyroid dysfunction, routine screening of critically ill patients for thyroid dysfunction is not recommended. Thyroid function tests should only be obtained if there is a high clinical suspicion for intrinsic thyroid dysfunction. The best tests to order are free T_4 and TSH. Interpretation of results must occur in the context of the duration, severity, and stage of the critical illness.

A mildly elevated TSH and low free T_4 may be indicative of primary hypothyroidism early in an acute illness but not in the recovery stage. The clinical context is very relevant. A history of thyroid disease or use of medications that may affect thyroid function should be sought. An increased TSH and low free T_4 are more likely to be indicative of true hypothyroidism in a hypothermic, bradycardic patient but not in a normothermic patient with normal vital signs. If both TSH and free T_4 are normal, intrinsic thyroid dysfunction is not present.

Relative Adrenal Insufficiency

Adrenal insufficiency is the inability of the adrenal gland to produce enough adrenocortical steroid hormones to satisfy bodily needs. Primary adrenal insufficiency is usually caused by an autoimmune disorder that destroys more than 90% of the adrenal cortex. Secondary adrenal insufficiency is caused by low ACTH levels. Tertiary adrenal insufficiency is caused by long-term treatment with steroid hormones, which induces feedback inhibition of the hypothalamic-pituitary-adrenal axis.

Relative adrenal insufficiency in critically ill patients occurs when the baseline plasma cortisol level is less than 18 to 25 μg/mL. This insufficiency may be due to sepsis, impaired pituitary ACTH release, decreased adrenal responsiveness to ACTH, a reduction in cortisol synthesis, impaired cortisol transport, or an impaired response to cortisol at the tissue level. Septic shock is the most common cause of relative adrenal insufficiency. Septic shock refractory to volume resuscitation and vasopressor therapy is an indication for steroid replacement. The steroids can be tapered when vasopressors are no longer required. Steroid therapy in septic patients without refractory shock is not recommended.

Acute Renal Dysfunction

Acute renal dysfunction, also called acute kidney injury (AKI) or acute renal failure (ARF), is common and occurs in up to one-third of ICU patients. In the majority of critically ill patients, its etiology is multifactorial and attributable to hypotension, sepsis, and nephrotoxic medications. The associated mortality can be as high as 50% and generally is part of multiple organ failure. The mortality of acute renal dysfunction increases as the number of organs that fail increases. Mortality is 53% with two organ failures, 80% with three organ failures, and 100% with five organ failures. However, acute renal dysfunction even by itself is associated with increased morbidity and mortality. The risk of developing acute renal dysfunction increases with age, baseline chronic kidney disease, oliguria, and sepsis.

Acute renal failure has traditionally been defined as an abrupt decrease in glomerular filtration rate (GFR) with a resultant retention of urea and other nitrogenous waste products along with dysregulation of body fluids and electrolytes. However, this definition is qualitative, not quantitative, and is of limited clinical utility. Until 2004, there was no quantitative definition or characterization of ARF. With the establishment of standardized criteria, the ability to effectively characterize ARF has enhanced precise communication from a clinical standpoint and has improved the rigor of research initiatives.

RIFLE criteria. In 2004, the Acute Dialysis Quality Initiative (ADQI) group established the RIFLE criteria to define ARF in critically ill patients: R = risk, I = injury, F = failure, L = loss, E = end stage. The first three stages (R, I, F) reflect progressively severe increases in serum creatinine, decreases in GFR, and the severity of oliguria within a 7-day period. The last two stages (L, E) reflect longer-term renal function outcomes; L describes complete loss of kidney function requiring renal replacement therapy for longer than 4 weeks, and E describes end-stage kidney disease requiring dialysis for longer than 3 months.

AKIN criteria. In 2007, the Acute Kidney Injury Network (AKIN) proposed the term *acute kidney injury* to represent the entire spectrum of ARF. The AKIN criteria are based on the acute changes in serum creatinine or urine output comprising stages 1, 2, or 3 AKI. These criteria simplify the RIFLE definitions by describing only three stages evaluated over a 48-hour period. Measurement of GFR was eliminated, and an increase in serum creatinine of as little as 0.3 mg/dL was incorporated into stage 1 AKI.

KDIGO criteria. In 2013, the AKIN criteria were further modified by the Kidney Disease: Improving Global Outcomes (KDIGO) group. This work represented the first-ever international multidisciplinary clinical practice guidelines for AKI and focused on definitions, risk assessment, evaluation, and treatment. AKI is defined as any of the following (with three stages of severity [1, 2, 3]):

- An increase in serum creatinine by 0.3 mg/dL or more within 48 hours, *or*
- An increase in serum creatinine by 1.5 or more times baseline within the prior 7 days, *or*
- Urine output less than 0.5 mL/kg/h for 6 hours

Cirrhosis

Cirrhosis is characterized by fibrous infiltration throughout the liver, a consequence of sustained wound healing in response to chronic liver injury. It leads to end-stage liver disease (ESLD). Complications of ESLD include hyperbilirubinemia, malnutrition, decreased hepatic synthetic function, coagulopathy, portal hypertension, hepatic encephalopathy, and extreme fatigue. Patients with these complications are frequently managed in the ICU because of the critical nature of these issues. The Child-Pugh score is useful in predicting the surgical risk of intraabdominal surgery in cirrhotic patients. Variables used to calculate this score include the bilirubin level, albumin level, INR, and the presence of encephalopathy and/or ascites. Class A cirrhosis carries an overall surgical mortality of 10%; class B, 30%; and class C, 75% to 80%. Perioperative mortality and morbidity correlates well with the Child-Pugh score. The Model for End-Stage Liver Disease (MELD) score is a linear regression model based on the INR, bilirubin level, and creatinine level. The MELD score has been the sole method of liver transplant allocation in the United States since 2002. A minimum MELD score of 18 is necessary to have a survival benefit with liver transplantation. MELD is also useful for predicting mortality in patients undergoing nontransplant surgical procedures. Patients with a MELD below 10 can safely undergo elective surgery; those with a MELD between 10 and 15 may undergo surgery with caution; those with a MELD above 15 should not undergo elective surgery. Familiarity with the Child-Pugh and MELD classifications is important for the surgical intensivist because patients with ESLD are likely to be managed in the SICU following nontransplant surgical procedures and after liver transplantation.

Fulminant Hepatic Failure

Fulminant hepatic failure (FHF), otherwise known as acute liver failure, is uncommon. It is defined as the presence of hepatic encephalopathy and coagulopathy (INR >5.0) within 26 weeks of the first appearance of symptoms in patients with no history of underlying liver disease. Loss of hepatocyte function initiates multisystem organ dysfunction and terminates in death. Complications include worsening encephalopathy, cerebral edema, sepsis, ARDS, hypoglycemia, coagulopathy, gastrointestinal hemorrhage, pancreatitis, and ARF. Acetaminophen toxicity, idiosyncratic drug reactions, and hepatotropic viruses are the most common causes of acute hepatic failure in the United States. Acute hepatic failure accounts for 5% to 6% of liver transplantations. A liver transplant is the only definitive treatment option for these patients, who are unlikely to recover spontaneously. Without liver transplantation, the mortality rate for fulminant hepatic failure is 50% to 80%. Grade III or IV hepatic encephalopathy is an indication for endotracheal intubation and diagnostic and therapeutic modalities to treat intracranial hypertension, which is the major cause for early mortality in acute hepatic failure. This intracranial hypertension is due to cerebral hyperemia, osmotic factors, and derangements of the blood-brain barrier. Continuous monitoring of intracranial pressure (ICP) is initiated when grade III encephalopathy occurs. Elevated ICP is managed with hyperventilation, mannitol, mild hypothermia, and therapeutic sedation. CVVH is the preferred method if renal replacement therapy is required. It avoids the hemodynamic fluctuations that may be particularly problematic in this situation.

Neurologic Disorders

The purpose of this section is to highlight those neurologic entities of particular importance in the management of the critically ill perioperative patient.

Pain, Agitation, and Delirium

Pain, agitation, and delirium are pervasive conditions in the critically ill patient population and have the potential to adversely affect outcomes if not managed properly. The principles outlined here pertain to adult ICU patients.

Pain and analgesia. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." The ability to reliably assess pain is key to optimal management of pain. Critically ill patients may be unable to communicate effectively. Therefore it is necessary to use alternative assessment methods to detect, quantify, and manage their pain. These patients may experience pain at rest; pain as a sequela of surgery, trauma, burns, or cancer; and pain related to ICU procedures. Unrelieved pain has significant and long-lasting psychological consequences, including chronic pain, posttraumatic stress disorder (PTSD), and low health-related quality of life. The physiologic consequences of pain include increased levels of catecholamines, which cause arteriolar vasoconstriction and impaired tissue perfusion and oxygen delivery. Catabolic hypermetabolism causes hyperglycemia, lipolysis, and muscle wasting. Wound healing is also impaired, increasing the risk of wound infection.

The Behavioral Pain Scale (BPS) and the Critical Care Pain Observation Tool (CPOT) are the most reliable behavioral pain scales available for use in medical, postoperative, and trauma patients (adult ICU patients) who are unable to self-report pain and in whom motor function is intact. *Vital signs should not be used as a sole determinant of pain assessment.*

IV opioids are the first-line drugs to treat nonneuropathic pain in critically ill patients. Nonopioid analgesics should be considered only to decrease the dose of opioids used and to decrease opioid-related side effects. Gabapentin or carbamazepine should be added to IV opioids for management of neuropathic pain. Thoracic epidural anesthesia/analgesia should be considered for postoperative analgesia in selected patients.

Agitation and sedation. Agitation and anxiety are common in critically ill patients and lead to adverse clinical outcomes. The first step in management is identification and treatment of the underlying causes of agitation, including pain, delirium, hypoxemia, hypoglycemia, hypotension, and withdrawal syndromes. Maintenance of patient comfort, pain control, reorientation, and environmental hygiene to maintain normal sleep patterns should be optimized before sedatives are prescribed.

Prolonged deep sedation has negative consequences. Therefore sedative medications should be titrated to maintain light rather than deep sedation in ICU patients. Sedation scales, sedation protocols designed to minimize sedative use, and use of nonbenzodiazepine medications are associated with improved outcomes, including fewer days of mechanical ventilation, fewer days in the ICU and fewer days in the hospital, less delirium, and less long-term cognitive dysfunction.

The Richmond Agitation-Sedation Scale (RASS) and the Sedation-Agitation Scale (SAS) are the most reliable sedation assessment tools for adult ICU patients. However, these are subjective tests. Objective measures of brain function include auditory evoked potentials, bispectral index, Narcotrend Index, patient state index, and state entropy. These parameters can be used as adjuncts to subjective sedation assessments in patients receiving neuromuscular blockade. Electroencephalogram (EEG) monitoring should be used to monitor brain electrical activity in patients who have known or suspected seizures or to titrate electrosuppressive medications to achieve burst suppression in patients who have intracranial hypertension.

When a sedative is required, dexmedetomidine or propofol are generally preferred. Dexmedetomidine has no active metabolites, and side effects include bradycardia, hypotension, hypertension with the loading dose, and loss of airway reflexes. Propofol also has no active metabolites, and side effects include hypotension, respiratory depression, hypertriglyceridemia, pancreatitis, and propofol infusion syndrome. The latter is rare but lethal and is associated with infusion of propofol at 4 mg/kg/h or greater for 48 hours or longer. The syndrome is characterized by acute refractory bradycardia that may lead to asystole. Metabolic acidosis, rhabdomyolysis, hyperlipidemia, and an enlarged or fatty liver may also be present. Hyperkalemia and a cardiomyopathy with acute cardiac failure may also occur. In addition to the high propofol dosage, risk factors for propofol infusion syndrome include poor oxygen delivery, sepsis, and severe cerebral injury.

Delirium. Delirium is characterized by acute onset of cerebral dysfunction resulting in (1) an altered level of consciousness (reduced awareness of the environment) with a reduced ability to focus, sustain, or shift attention and (2) either a change in cognition (i.e., memory deficits, disorientation, or language disturbance) or the development of a perceptual disturbance (i.e., hallucinations or delusions). The underlying pathophysiology is poorly understood.

Patients can be agitated (hyperactive delirium), calm, or lethargic (hypoactive delirium). Hyperactive delirium is more easily diagnosed and is associated with hallucinations and delusions. Hypoactive delirium is associated with confusion and sedation and is frequently misdiagnosed or even entirely overlooked. Delirium may be a disease-induced syndrome (e.g., a manifestation of organ dysfunction in severe sepsis), iatrogenic (e.g., from exposure to sedative or opioid medications), or environmentally induced (e.g., from prolonged use of physical restraints or immobilization).

Several risk factors are associated with the development of delirium in the ICU: preexisting dementia, history of hypertension, history of alcoholism, and a high severity of illness at the time of ICU admission. Coma is an independent risk factor. Opioids and benzodiazepines may be associated with the development of delirium in adult ICU patients.

Delirium is very common; 80% of mechanically ventilated patients may be affected. It is also an independent predictor of negative outcomes in ICU patients, including increased mortality, hospital length of stay, cost, and long-term cognitive impairment.

Routine monitoring for delirium should be undertaken in all ICU patients. The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most reliable delirium monitoring tools for adult ICU patients.

In mechanically ventilated patients who require sedation, dexmedetomidine infusion may be associated with a lower prevalence of delirium compared to a benzodiazepine infusion. Early mobilization may reduce the incidence and duration of delirium. There are no drugs that can prevent delirium. There is also no evidence that haloperidol reduces the overall duration of delirium in ICU patients. Nonetheless, use of haloperidol is widespread for episodic acute management of the potentially dangerous behaviors associated with agitated delirium. Given the lack of definitive drug treatment options, the key to management of delirium is mitigation of risk factors and prevention.

Global strategies to manage pain, agitation, and delirium in all ICU patients should include (1) daily sedation interruption or a light level of sedation in mechanically ventilated patients, (2) analgesia-first sedation in mechanically ventilated patients, (3) promoting normal sleep cycles by optimizing the environment, and (4) an interdisciplinary team approach incorporating provider education, protocols, order sets, and checklists to facilitate optimal management of pain, agitation, and delirium.

Metabolic Encephalopathy

Coma is uninterrupted loss of the capacity for arousal, which is due to an acute or subacute brain insult causing either diffuse or bilateral cerebral dysfunction, failure of the brainstem-thalamic ascending reticular activating system, or both. The eyes are closed, sleep/wake cycles are absent, and stimulation elicits only reflex responses at best. Nonstructural disorders such as metabolic or toxic pathology induce coma by depressing the brainstem and cerebral arousal mechanisms and are common in critically ill patients. The anatomic target of metabolic brain disease has not been precisely defined. Onset of coma can be abrupt or may evolve more slowly after a period of inattention or confusion.

The primary abnormalities in metabolic encephalopathy are altered arousal and cognitive function. Additional symptoms revolve around abnormalities of the sleep/wake cycle, autonomic dysfunction, and abnormal breathing patterns. A primary distinguishing feature of diffuse metabolic encephalopathy is preservation of the pupillary light response. Exceptions to this rule include an overdose of anticholinergic drugs, near-fatal anoxia, and malingering. Elderly patients with serious systemic illnesses or who have undergone complicated surgery are particularly prone to metabolic encephalopathy.

Metabolic encephalopathy manifests as multilevel CNS dysfunction. Misperception, disorientation, hallucinations, concentration and memory deficits, and hypervigilance may progress to coma. Motor abnormalities are typically bilateral and symmetric. Examples include tremor, asterixis, and multifocal myoclonus. Hypoactivity or hyperactivity may be present, depending on the etiology of the encephalopathy. Seizures may occur after substance withdrawal and with hypoglycemia, hepatic failure, uremia, abnormal calcium levels, or toxin ingestion. Hypothermia or hyperthermia may occur as a result of autonomic dysfunction.

Etiologies of metabolic encephalopathy include toxin ingestion, substance withdrawal, hypoglycemia, hypoxemia, hepatic dysfunction, uremia, electrolyte imbalances, pancreatic inflammation, and infection. Initial therapy of all patients with metabolic encephalopathy includes maintenance of adequate oxygenation and ventilation, maintenance of circulation and perfusion, empirical administration of glucose and thiamine, seizure control if indicated, careful and mild sedation if indicated in agitated patients, specific antidotes for reversal of the effects of ingested substances, and maintenance of normothermia. Once these supportive measures are established, efforts can be focused on a search for and treatment of the specific underlying etiology.

Critical Illness Polyneuropathy

Critical illness polyneuropathy is a diffuse sensorimotor peripheral neuropathy that develops in the setting of multiple organ failure and sepsis. This entity is probably the most common neuromuscular cause of prolonged ventilator dependency in patients without prior neuromuscular disease. Symptoms include extremity muscle weakness and wasting, distal sensory loss, and paresthesias. Deep tendon reflexes are usually diminished. Electrodiagnostic studies are important to establish a definitive diagnosis because the clinical findings may not be readily discernible in the critically ill patient. The pathophysiology is unknown. However, it has been suggested that increased microvascular permeability may result in endoneural edema and axonal hypoxia and degeneration. It is important to distinguish this disease entity from Guillain-Barré syndrome.

The severity of critical illness polyneuropathy is correlated with ICU length of stay, the number of invasive procedures, hyperglycemia, hypoalbuminemia, and the severity of multiple organ failure. Overall prognosis is dependent on recovery from the underlying critical illness. Most survivors recover from the neuropathy in several months. Even though ventilator dependence may be prolonged, critical illness polyneuropathy does not worsen long-term prognosis. However, the prognosis can be adversely affected when compression neuropathies complicate this disorder.

Acute Quadriplegic Myopathy

Acute quadriplegic myopathy, otherwise known as acute myopathy of intensive care, develops in critically ill patients without preexisting neuromuscular disease. It usually occurs in the setting of severe pulmonary disease for which neuromuscular blockade has been used to facilitate mechanical ventilation, and high-dose corticosteroids have been administered at the same time. Typically, it occurs in those in whom nondepolarizing neuromuscular blockade was used for more than 2 days. This disorder is characterized by an acute necrotizing myopathy. Diffuse flaccid quadriparesis with involvement of respiratory muscles and muscle wasting occurs after several days of induced paralysis. Sensation is intact, but deep tendon reflexes are diminished. Creatine kinase levels are usually elevated. The paralysis is severe and may prolong the period of mechanical ventilation, but the prognosis for recovery from the myopathy is good. Functional recovery occurs over weeks to months. In general, high-dose corticosteroids should be avoided when neuromuscular blockade is required.

Prolonged Effects of Neuromuscular Blockade

Prolonged neuromuscular blockade may occur with most depolarizing or nondepolarizing neuromuscular blockers, especially in the setting of hepatic or renal insufficiency. Acidosis and hypermagnesemia are also predisposing factors. This phenomenon occurs with vecuronium, which is metabolized by the liver. Atracurium and cisatracurium rarely cause this problem because they do not require organ metabolism for their clearance. If a peripheral nerve stimulator is used to monitor muscle twitch responses to a train-of-four stimulus during neuromuscular blockade, drug dosing can be titrated to preserve one or two twitches. This will reduce the overall amount of neuromuscular blocker used and thus prevent overdosing and this prolonged paralytic effect.

GENERAL PRINCIPLES OF PERIOPERATIVE MANAGEMENT IN THE CRITICALLY ILL PATIENT

Although intensive care is complex and multifaceted, several general principles apply to perioperative management of the critically ill surgical patient. Implementation of these principles is important when care of the patient is transitioned from the SICU to the OR and back again. A shared understanding of these concepts is key to the communication between the surgeons and anesthesiologists caring for this patient population.

Intravenous Fluid Management

Parenteral Solutions

IV fluids are used for resuscitation and maintenance of critically ill patients. Maintenance fluid therapy replaces fluids normally lost over the course of a day. Resuscitative fluid therapy replaces preexisting deficits and ongoing fluid losses. Maintenance and resuscitative fluid therapy can occur simultaneously, but different fluids may be used for these two needs. Parenteral solutions are either crystalloids or colloids. Fluid selection is based on maintenance requirements, fluid deficits, ongoing fluid losses, and clinical context.

Lactated Ringer (LR) solution is a crystalloid that has a composition similar to plasma. It is usually used as a resuscitative fluid to replace loss of fluid that has a similar composition to plasma. LR has a relatively low sodium content (130 mEq/L) and is therefore mildly hypotonic. Hyponatremia can occur with excessive or prolonged use. This is problematic in patients who have traumatic brain injury because they require a higher

plasma osmolality. The lactate in LR solution is sodium lactate, which dissociates when infused. The lactate anions are metabolized to bicarbonate and do not contribute to acidosis.

Normal saline solution is another resuscitative crystalloid and contains 154 mEq/L of both sodium and chloride. Normal saline is excellent for the treatment of hyponatremic hypochloremic metabolic alkalosis. However, in other clinical circumstances the excessive chloride load can lead to hyperchloremic metabolic acidosis, which can worsen a preexisting acidosis.

Hypertonic saline solutions are administered to replace sodium deficits in symptomatic hyponatremia. The most widely used formulations are 3% NaCl and 1.5% NaCl. The former is infused through a central venous catheter, but the latter may be administered peripherally. Hypertonic saline solutions have also been used in the resuscitation of hypovolemia in trauma and burn patients. Intravascular volume is increased more quickly, and the total resuscitation volume may be decreased compared to standard crystalloids. However, significant acid-base and electrolyte abnormalities often occur.

Naturally occurring colloids include albumin (5% and 25% are available in the United States) and FFP. Albumin solutions are typically prepared in normal saline; therefore large-volume resuscitation might cause hyperchloremic metabolic acidosis. In 2004, the SAFE (Saline versus Albumin Fluid Evaluation) trial demonstrated that albumin is as safe as saline in the vast majority of patients.

Hydroxyethyl starch preparations are the most common synthetic colloids. Starches were used much more frequently in the past, but now their use has fallen out of favor.

Maintenance Fluid Therapy

Weight-based formulas are used to calculate maintenance fluid requirements and take into account both sensible and insensible losses. A commonly used formula is the 4-2-1 rule:

- First 10 kg of body weight: 4 mL/kg/h
- Second 10 kg of body weight: 2 mL/kg/h
- Each additional 10 kg of body weight: 1 mL/kg/h

For example, the hourly maintenance fluid requirement for a 70-kg patient using this formula is 110 mL/h. For patients who have clinically severe obesity, the adjusted body weight rather than the actual body weight is used to calculate the maintenance fluid rate:

$$\text{Adjusted body weight} = \text{ideal body weight (IBW)} + 1/3\,(\text{actual body weight} - \text{IBW})$$

Maintenance fluids are hypotonic and usually contain 5% dextrose. The prototypical maintenance fluid for adults is D_5-1/2 normal saline + 20 mEq KCl/L. Dextrose is an aid in gluconeogenesis, and sodium and potassium are provided in a quantity based on daily requirements. However, potassium should be excluded from solutions provided to patients who have renal impairment or anuria.

Resuscitative Fluid Therapy: Crystalloid Versus Colloid

Resuscitative fluid therapy replaces preexisting deficits and ongoing fluid losses. Crystalloid solutions are used most commonly. In particular, a dextrose-free isotonic (or nearly isotonic) salt solution, such as LR solution, is used in surgical patients.

The capillary endothelium is permeable to isotonic and hypotonic salt solutions, and crystalloid distributes between the intravascular and interstitial spaces in proportion to the relative volumes of these spaces. The intravascular space comprises 25% of the extracellular fluid, and the interstitial space comprises 75% of the extracellular fluid (a 1:3 ratio). Therefore, for each liter of crystalloid infused intravenously, 250 mL remains in the intravascular space and 750 mL diffuses into the interstitial space.

Another disadvantage of crystalloid solutions is their pro-inflammatory effect. From a historical perspective, these disadvantages of crystalloid therapy have been the basis of the crystalloid-versus-colloid debate.

Under normal physiologic conditions, the average leakage rate of infused albumin and other iso-oncotic solutions into the interstitial space is approximately 25% to 35%. For each liter of 5% albumin infused intravenously, roughly 750 mL remain in the intravascular space and 250 mL diffuse into the interstitial space. This relationship is opposite to that of crystalloid isotonic salt solutions. At least in theory, the ratio of intravascular filling between colloid and crystalloid solutions is 3:1. However, this effect of albumin has been overly simplified. Even under physiologic conditions, leakage of albumin is highly variable and dependent on the unique characteristics of various capillary beds. Furthermore, surgical patients, particularly those who are critically ill, have significant perturbations of microvascular permeability. In a severely inflamed capillary bed, up to half of infused albumin may diffuse into the interstitial space. Albumin appears to be safe in most patient populations but may not provide a survival advantage over isotonic salt solutions. The major exception is patients with traumatic brain injury, who have an increased risk of death after administration of albumin.

The most recent Cochrane review of the colloid-versus-crystalloid debate was published in 2018 and demonstrated that there is no evidence to indicate that resuscitation with colloids, compared to resuscitation with crystalloids, reduces the risk of death in patients with trauma, burns, or following surgery. Since colloids are not associated with improved survival and are more expensive than crystalloids, continued use of colloids in clinical practice may not be justified in most circumstances.

Interruption of Enteral Nutrition Preoperatively

The primary objective of preoperative fasting is to reduce the risk of pulmonary aspiration. In 2011, the American Society of Anesthesiology published practice guidelines pertaining to preoperative fasting in healthy patients undergoing elective procedures. Fasting for 2 hours after ingestion of clear liquids was recommended, as was fasting for 6 hours after a light meal and 8 hours after a fatty meal.

Critically ill patients frequently undergo surgery or interventions that traditionally mandate nil per os (NPO) status. However, it is not clear what this means in those patients whose enteric intake bypasses the stomach (e.g., patients fed via a nasojejunal tube or a feeding jejunostomy). Given the very significant degree of malnutrition present in critically ill

surgical patients, stopping nutritional support prior to surgery or procedures is not inconsequential. In addition, many of these procedures are scheduled on an add-on basis without a specific start time. If tube feedings are discontinued at midnight prior to the planned operation and the case does not start until evening, nutritional support will have been interrupted in excess of 18 hours prior to the beginning of surgery.

At present, there are no widely accepted guidelines pertaining to discontinuation of tube feedings in the critically ill patient population. Some institutions have developed internal guidelines, whereas other hospitals leave the decision of when to stop tube feeding preoperatively to the anesthesiologist managing the patient in the OR.

In this patient population, the risk for aspiration can be assessed by evaluating the following clinical parameters:

- Surgery: intraabdominal versus extraabdominal
- Preoperative airway status: intubated versus not intubated
- Tube feeding route: gastric versus postpyloric
- If feeding by a postpyloric route: gastric drainage versus no gastric drainage

Using this assessment, a patient considered at high risk of aspiration will be one about to undergo an intraabdominal operation who is not yet intubated and who is receiving intragastric feedings. Conversely, a patient at low risk will be one about to undergo an extraabdominal operation who is already intubated and is receiving jejunal feedings with concomitant nasogastric tube suction drainage. Additional clinical considerations may include the potential for a difficult airway in a patient who is not already intubated and patient factors that increase the risk for aspiration, such as gastrointestinal motility disorders and diabetes mellitus.

A risk-benefit analysis should be undertaken with respect to the timing of preoperative cessation of tube feedings. The risk of aspiration versus the impact of withholding nutritional support for a period of time must be considered.

Administration of Blood Products

Transfusion of blood products is an integral component of the management of severely injured or hemorrhaging patients. The process whereby blood products are obtained varies depending on the clinical urgency of the situation.

Emergency Transfusion

In many situations the need for blood products is urgent, before completion of compatibility testing can occur. Anesthesiologists and surgeons who work in high-volume trauma centers and high-acuity SICUs must make decisions regarding how much and exactly how the crossmatch process can be attenuated in emergencies. If time permits, the best option when using uncrossmatched blood is to obtain an ABO-Rh typing and an immediate-phase crossmatch. This will provide type-specific partially crossmatched blood and takes 1 to 5 minutes. Serious hemolytic reactions that result from errors in ABO typing are eliminated. The next best option is type-specific uncrossmatched blood; the ABO-Rh type is determined. For patients who have never been exposed to foreign RBCs, most ABO type-specific transfusions occur without significant issues. Complications resulting from incompatibility are more likely to occur in patients who have been previously transfused or who have been pregnant.

Type O Rh-negative PRBCs are designated as universal donor blood. Type O blood lacks the A and B antigens and is not hemolyzed by anti-A or anti-B antibodies in recipient blood. This blood is used in emergency situations when typing and crossmatching are not available in the timeframe required for lifesaving intervention. In hospitals that have an MTP, type O Rh-negative RBCs are used in addition to thawed plasma and platelet concentrates.

Reconstitution of PRBCs

PRBCs are transfused in many clinical situations with varying degrees of urgency. Administration is facilitated by reconstituting the PRBCs with crystalloid or colloid. However, crystalloids containing calcium, such as LR solution, should not be used because clotting may occur. This is important to note, since LR solution is frequently being used in the management of surgical and trauma patients. In addition, administration of very hypotonic fluids may cause hemolysis of the transfused PRBCs. Solutions recommended for the reconstitution of PRBCs include D_5-1/2 normal saline, D_5-normal saline, normal saline, and Normosol-R.

Mitigation of Surgical Site Infections

Surgical site infections (SSIs) are infections of the tissues, organs, and spaces exposed by surgeons during an operation. Classification includes superficial incisional (skin and subcutaneous tissues), deep incisional, and organ/organ space infections. Surgical wounds are further classified based on the magnitude of the bacterial load present at surgery: class I (clean), class ID (clean with device implantation), class II (clean/contaminated), class III (contaminated), and class IV (dirty). Hospitals in the United States are required to conduct surveillance for development of SSIs for a period of 30 days after surgery. Adherence to preventive measures has become a surrogate measure of quality. SSIs are clearly associated with morbidity, mortality, substantial healthcare costs, and patient inconvenience and dissatisfaction.

Risk Factors

The development of SSIs is primarily related to (1) host factors, (2) duration of the procedure, and (3) degree of contamination. Patient risk factors include advanced age, immunosuppression, obesity, diabetes mellitus, chronic inflammation, malnutrition, smoking, renal failure, peripheral vascular disease, anemia, radiation, chronic skin disease, microbial carrier status, and recent surgery. This list indicates that critically ill patients are at especially high risk for development of SSIs. In addition to prolonged procedures, risk factors related to the surgery itself include open compared to laparoscopic surgery, poor skin preparation, contaminated instruments, inadequate antibiotic prophylaxis, local tissue necrosis, blood transfusion, hypoxemia, and hypothermia. Finally, in addition to the bacterial burden, specific microbial risk factors include prolonged hospitalization resulting in colonization with nosocomial organisms, toxin secretion, and resistance to clearance.

Preventive Measures

The incidence of SSIs can be reduced if preventive measures are implemented. These measures require a collaborative approach, including the anesthesiologist, the surgeon, and the OR nursing team. Appropriate patient preparation includes hair removal at the operative site, using clippers rather than razors. Skin preparation of the operative site with an appropriate antiseptic must be performed. Maintenance of perioperative normoglycemia and normothermia and avoidance of hypoxemia are also important. For class III and IV wounds, the skin should not be closed. Rather, the superficial aspects of the wound should be packed open and allowed to heal by secondary intention. Appropriate perioperative antibiotic administration must also be undertaken.

General Principles of Prophylactic Perioperative Antibiotic Administration

Guidelines for the prevention of surgical site infection were published by the Centers for Disease Control and Prevention in 2017. These guidelines include recommendations for prophylactic perioperative antibiotic administration. Effective implementation in the OR requires clear communication between all members of the anesthesiology, surgery, and nursing teams. An ideal antimicrobial agent for surgical prophylaxis should (1) prevent an SSI, (2) prevent SSI-related morbidity and mortality, (3) reduce the duration and cost of health care, (4) produce no adverse effects, and (5) have no adverse consequences for the normal microbial flora of the patient or hospital. Therefore the ideal antibiotic should be (1) active against the pathogens most likely to contaminate the surgical site, (2) dosed to ensure adequate serum and tissue concentrations during the period of potential contamination, (3) safe, and (4) administered for the shortest effective period to minimize adverse effects, resistance, and cost.

Surgical wounds of class II, II, III, and IV require antibiotic prophylaxis. Specific drugs are selected based on their activity against microbes likely to be present at the surgical site. It appears that the optimal timing for administration of preoperative doses of prophylactic antibiotics is within the 60 minutes prior to surgical incision. Weight-based dosing in obese patients is advised. Intraoperative redosing to ensure continued adequate serum and tissue concentrations of the antibiotic is advised if the duration of the operation exceeds two half-lives of the drug or if there is excessive blood loss. The redosing interval should be measured from the time of administration of the preoperative dose, not from the time of skin incision. Redosing may not be necessary if patient factors result in prolongation of the drug's half-life (e.g., renal insufficiency). In the recent past, recommendations for the duration of prophylactic antibiotic therapy included one preoperative dose, appropriate intraoperative redosing if indicated, and continuation for no longer than 24 hours postoperatively. However, the newer guidelines recommend that additional doses should not be administered after the incision is closed in the OR. Additionally, continuing antibiotics is not indicated based on the presence of indwelling drains or intravascular catheters.

Ongoing Antimicrobial Management of Established Infections in the OR

Critically ill surgical patients already in the SICU but proceeding to the OR for various indications are frequently under treatment for established infections. Scheduled dosing of prescribed antimicrobial therapy should continue intraoperatively.

Venous Thromboembolism Prophylaxis

The American College of Chest Physicians published Guidelines for Antithrombotic Therapy and Prevention of Thrombosis in 2012. In 2016, they published additional Guidelines for Antithrombotic Therapy for Venous Thromboembolic Disease. These guidelines provide evidence-based recommendations for management of anticoagulant therapy, including anticoagulation for venous thromboembolism (VTE) prophylaxis in critically ill patients, a subset of patients at significant risk for the development of VTE.

Critically Ill Nonsurgical Patients

General recommendations for VTE prophylaxis in critically ill nonsurgical patients include drug administration with low-molecular-weight heparin (LMWH) or low-dose unfractionated heparin. If these patients are actively bleeding or at high risk for significant bleeding, mechanical prophylaxis with intermittent pneumatic compression is recommended until the bleeding risk is decreased, at which time anticoagulant drug therapy can be added to the mechanical thromboprophylaxis.

Critically Ill Surgical Patients

Critically ill surgical patients are at high risk for VTE. Various risk assessment models can place patients into risk categories based on the type of surgery performed and particular patient characteristics. Many SICU patients fall into the high-risk and very-high-risk categories. These high-risk patients can be further subdivided into nonorthopedic surgical patients and orthopedic surgical patients.

Nonorthopedic surgical patients. Nonorthopedic surgical patients include those undergoing general and abdominal-pelvic operations, such as gastrointestinal, urologic, gynecologic, bariatric, vascular, plastic, or reconstructive procedures. For patients at high risk for VTE but not at high risk for major bleeding complications, LMWH or low-dose unfractionated heparin and mechanical prophylaxis are recommended. Patients having cancer surgery should have extended-duration prophylaxis (4 weeks) with LMWH. For patients at high risk for bleeding complications or those in whom the consequences of bleeding are particularly dangerous, mechanical prophylaxis is recommended. When the risk of bleeding diminishes, pharmacologic prophylaxis should be initiated. If LMWH and low-dose unfractionated heparin are contraindicated, low-dose aspirin, fondaparinux, or mechanical prophylaxis is recommended.

Cardiac surgery patients with an uncomplicated postoperative course should receive only mechanical prophylaxis. If the hospital course is prolonged by nonhemorrhagic surgical complications, pharmacologic thromboprophylaxis with low-dose unfractionated heparin or LMWH can be added.

For thoracic surgery patients at high risk for VTE who are not at high risk of bleeding, low-dose heparin or LMWH plus mechanical prophylaxis are recommended. If these patients are at high risk of bleeding, mechanical prophylaxis is recommended until the risk of bleeding diminishes and pharmacologic prophylaxis can be initiated.

For patients undergoing craniotomy, only mechanical prophylaxis is recommended. However, patients at very high risk for VTE (e.g., those undergoing craniotomy for malignancy) can have pharmacologic prophylaxis added once hemostasis is established and the risk of bleeding has decreased.

For patients undergoing spinal surgery, mechanical prophylaxis is recommended. For those at high risk for VTE (e.g., those with malignancy or those undergoing a combined anterior-posterior approach), the addition of pharmacologic prophylaxis is recommended once adequate hemostasis has been achieved and the risk of bleeding has decreased.

For major trauma patients at high risk for VTE (including those with acute spinal cord injury and traumatic brain injury), mechanical prophylaxis can be added to pharmacologic prophylaxis if not contraindicated by lower extremity trauma. If LMWH or low-dose unfractionated heparin is contraindicated, mechanical prophylaxis can be used if not contraindicated by lower extremity injury. Pharmacologic prophylaxis can be added when the risk of bleeding diminishes or the contraindication to heparin resolves.

In many instances, the decision-making process for initiation of pharmacologic VTE prophylaxis in critically ill surgical patients is complex and requires specific collaboration and communication between the operative surgeon and the surgical intensivist. A particularly complex subset is the multiply injured trauma patient. Ongoing collaboration must involve the surgical intensivist, the trauma surgeon, and consulting surgeons. For example, in traumatic brain injury, the decision to initiate pharmacologic VTE prophylaxis occurs when all agree that the risk of neurologic compromise due to further intracranial hemorrhage has been minimized. Typically, this occurs when sequential computed tomography (CT) imaging of the head is stable, usually in the timeframe of 24 to 72 hours after injury; low-dose unfractionated heparin is preferred over LMWH in this situation. Of course, this decision is further complicated if there are other sources of hemorrhage in the multisystem trauma patient that remain an issue.

Orthopedic surgical patients. Patients undergoing major orthopedic surgery, including total hip arthroplasty, total knee arthroplasty, and hip fracture surgery, are sometimes managed in the SICU postoperatively because of their complex comorbidities and adverse intraoperative events. Therefore it is important for the surgical intensivist to understand VTE prophylaxis paradigms in this patient population.

For patients undergoing total hip or total knee arthroplasty, one of the following is recommended for a minimum of 10 to 14 days: LMWH, low-dose unfractionated heparin, fondaparinux, apixaban, dabigatran, rivaroxaban, warfarin, aspirin, or mechanical prophylaxis. In patients undergoing hip fracture surgery, the newer novel oral anticoagulant drugs such as apixaban, dabigatran, and rivaroxaban are not routinely used. For all these patients, LMWH prophylaxis should begin 12 or more hours preoperatively or 12 or more hours postoperatively.

It is also important to note that thromboprophylaxis must be extended well into the posthospital phase of recovery—for up to 35 days from the day of surgery. Dual mechanical and drug prophylaxis is recommended throughout the duration of hospitalization. For patients who decline or are uncooperative with injections or use of pneumatic devices, apixaban or dabigatran are recommended. Patients undergoing these major orthopedic operations who have an increased risk of bleeding should receive mechanical prophylaxis.

In none of the previous categories of patients is routine deep vein thrombosis ultrasound surveillance recommended, nor is the use of inferior vena cava filters recommended for primary VTE prevention.

Glycemic Management

Perioperative Impact of Diabetes Mellitus

Diabetes mellitus afflicts many critically ill patients. Because this disease affects multiple organ systems, its perioperative impact can be significant. Diabetes affects oxygen transport because glucose binds covalently to hemoglobin, thereby altering the allosteric interactions between β chains. This may decrease oxygen saturation and RBC oxygen transport. Autonomic dysfunction is mediated by lack of appropriate vasoconstriction, which predisposes to hypothermia and orthostatic hypotension. Additionally, the changes in heart rate that occur with administration of atropine and β blockers are blunted in patients who have autonomic dysfunction. Diabetics are at increased risk of coronary artery disease and are more likely to have silent myocardial ischemia than their nondiabetic counterparts. Lifesaving surgery may be mandated before the various risk factors of diabetes mellitus have been optimized. Because diabetes adversely affects gastrointestinal motility, including gastric emptying, diabetics should be managed as if they have a full stomach. Preoperative treatment with drugs that inhibit gastric acid secretion and neutralize gastric acid is needed as is a rapid-sequence induction.

Perioperative and Intraoperative Glycemic Control Regimens

Several factors impact perioperative and intraoperative glycemic management. The differentiation between type 1 and type 2 diabetes is especially important because type 1 patients are at risk for ketonemia if insulin is withheld. This risk is increased with surgical stress and with critical illness. Preexisting long-term glucose control also affects management and is best assessed by measurement of glycosylated hemoglobin (hemoglobin A_{1c}), which is a measure of glucose control over the prior 2 to 3 months. An elevated hemoglobin A_{1c} correlates with complication rates in diabetics, and the quantity of insulin normally required by a diabetic is important in the determination of how blood glucose should be managed intraoperatively.

There are many different protocols for preoperative and intraoperative insulin management, but there is a paucity of

prospective studies comparing regimens. This is particularly true for management of critically ill patients, for which there is no consensus about the method of insulin therapy or the exact range of blood glucose that is considered optimal. However, several general concepts are useful. First, effective perioperative glucose management incorporates careful monitoring. The blood glucose monitoring equipment must be readily available, accurate, and efficient. Continuous glucose monitoring devices and other advances for use in the acute care setting are under development. Second, protocols and standards for utilization must be individualized and validated for use in the ICU and OR in which the protocols will be used. What works in one hospital may not work in another because of variability in equipment, training of providers, and the level of expertise and experience in those rendering care.

Steroid Management

Indications for Administration of Stress Steroid Dosing

Perioperative stress is related to the extent of the operation and the depth of anesthesia. One can postulate that the presence of critical illness also impacts the degree of physiologic stress. Additionally, deep general anesthesia or regional anesthesia delays the glucocorticoid surge in response to stress. Some patients who have suppressed adrenal function due to administration of exogenous steroids will have perioperative cardiovascular issues if they do not receive perioperative supplemental steroids. This is because glucocorticoids mediate catecholamine-induced increases in cardiac contractility and maintenance of vascular tone. However, it must be kept in mind that when these patients develop hypotension perioperatively, glucocorticoid or mineralocorticoid deficiency is not usually the etiology. Alternative explanations should be sought, especially in the critically ill patient, in whom other etiologies of hypotension are much more common. Nonetheless, when acute adrenal insufficiency occurs, it is life threatening.

It is not unusual to lack laboratory data defining the adequacy of the pituitary-adrenal axis preoperatively, especially in patients undergoing emergency surgery. Steroid supplementation for any patient who has received steroids within the past year should be considered. This includes topical steroids but not inhaled steroids. Many different dosages and tapering regimens are used. Often a patient is administered the estimated maximum quantity of glucocorticoid the body usually manufactures in response to maximal stress. Depending on the overall condition of the patient and the burden of critical illness, the dose can be decreased gradually until the usual maintenance dose of glucocorticoids is achieved or the steroids have been completely stopped.

Risks associated with stress steroid dosing. Rare complications associated with perioperative glucocorticoid supplementation include aggravation of hypertension, fluid retention, stress ulcers, and psychosis. More common complications include abnormal wound healing and an increased rate of infection. The effect on wound healing specifically attributed to short-term perioperative supplementation is probably very small. The increased risk of infection in patients taking long-term steroids is documented, but it is unclear whether perioperative steroid supplementation increases this risk.

Thermal Regulation

Body temperature is controlled by a negative feedback system in the hypothalamus. Eighty percent of the thermal input is derived from core body temperature, which is measured using distal esophageal, nasopharyngeal, or tympanic membrane thermometers. The hypothalamus coordinates increases in heat production (nonshivering thermogenesis and shivering), increases in heat loss (sweating), and decreases in heat loss (vasoconstriction) to maintain normothermia.

Hypothermia

Mild hypothermia is common during surgery and anesthesia, including both general and neuraxial anesthesia. General anesthetics decrease the threshold for vasoconstriction and shivering by 2°C to 3°C. The major initial cause of hypothermia in the OR is core-to-peripheral redistribution of body heat. Neuraxial anesthesia impairs both central and peripheral thermoregulation. Cool OR environments also contribute to hypothermia. Large, randomized trials have proven that even mild hypothermia (35°–35.5°C) causes an increase in adverse outcomes, including cardiac complications, wound infections, coagulopathy, need for transfusion, prolonged recovery times, and increased hospital length of stay. Hypothermia may decrease the triggering of malignant hyperthermia and reduce its severity.

The effects of hypothermia are especially pronounced in critically ill surgical patients who are undergoing emergent surgery for control of massive hemorrhage. Hypothermia is one component of the lethal triad of hypothermia, coagulopathy, and acidosis that if left untreated leads to death. Core temperature should be monitored in any critically ill patient undergoing surgery, with a goal temperature of 36°C to 37°C. Active cutaneous warming is key; forced-air warming offers the best combination of efficacy, safety, and price. Infused fluids and blood products should be warmed in patients undergoing large-volume resuscitation. Additional measures ensure that irrigation of the Foley catheter, nasogastric tube, or any body cavity is performed with warmed fluid. Active airway heating and humidification can also be performed via the endotracheal tube.

Hyperthermia

Etiologies of increased core temperature result from augmented thermogenesis (i.e., malignant hyperthermia), excessive heating (i.e., passive hyperthermia), or an increase in the thermoregulatory target (i.e., fever). The particular cause should be sought and treated.

Malignant hyperthermia. Malignant hyperthermia (MH) is an anesthetic-related disorder of increased skeletal muscle metabolism. Anesthetic drugs known to trigger MH include ether, halothane, enflurane, isoflurane, desflurane, sevoflurane, and depolarizing muscle relaxants (succinylcholine). MH is inherited in an autosomal dominant pattern. The abnormal function of the skeletal muscle ryanodine receptor is associated with abnormal intracellular calcium metabolism. Tachycardia, an increased $PETCO_2$, muscle rigidity, and an increased body temperature above 38.8°C (with no other apparent cause) are associated with this increased metabolism. Central thermoregulation remains intact during an MH crisis, but efferent heat

loss mechanisms are compromised by the increased peripheral vasoconstriction resulting from the extremely high catecholamine concentrations. Dantrolene normalizes myoplasmic calcium concentrations, restores normal muscle metabolism, and reverses the signs of metabolic stimulation. Affected patients are typically managed in the SICU postoperatively.

SPECIAL SCENARIOS IN THE MANAGEMENT OF THE CRITICALLY ILL SURGICAL PATIENT

Transporting the Critically Ill Patient to and From the Operating Room

Transport of critically ill and mechanically ventilated patients from the ICU to other locations in the hospital is a common phenomenon. Typical destinations include diagnostic radiology, interventional radiology, and the OR. Critically ill patients who require transport out of the ICU for diagnostics or therapeutics have higher severity-of-illness scores on admission than do those who do not require transport. Children and trauma patients require more frequent trips for diagnostics than other patients.

These trips can be life threatening. Physiologic stress is common, and almost all transported patients experience temporary changes in vital signs that may require intervention. Unplanned events are common, and all are potentially life threatening. Included is equipment failure. Complex and numerous pieces of equipment must accompany the patient. Common equipment-related adverse events include electrocardiogram (ECG) lead disconnection and monitor power failure. More serious events directly related to the patient include changes in cardiorespiratory physiology (such as gas exchange deterioration), need for intubation or reintubation, heart rate and blood pressure variability (hypotension and dysrhythmias), elevated intracranial pressure, anoxic brain injury, and death.

General Principles

Specific guidelines for in-hospital transport have been published by the American Society for Critical Care Medicine. The first rule of transport is that the patient must be stabilized prior to transport. A requirement for sedation during the trip must be anticipated. Equipment and medication checklists must be confirmed prior to the trip. The receiving location must confirm that they have the equipment and staff needed to appropriately care for the patient on arrival. Adequate medical supervision for the trip must be immediately available. The frequency of unplanned events is decreased if the accompanying physician has a high level of experience. Equipment for the trip includes a portable resuscitation kit that contains everything on a crash cart, including emergency cardiovascular drugs. The airway compartment includes everything required for intubation or reintubation. An oxygen cylinder with low-pressure alarms, a flowmeter, and oxygen tubing are essential. *The critically ill patient in transit should be monitored just as closely as was necessary in the ICU immediately prior to transport.*

Maintenance of Therapies

Whatever specific therapies the patient is being treated with must continue en route and at the destination. The most important example is mechanical ventilation. A mechanical ventilator rather than manual ventilation devices is preferred for transport. The manual devices are associated with more variability in CO_2 and pH, often caused by unintentional hyperventilation. These devices are also associated with more deterioration in PaO_2.

In patients whose hemodynamics are dependent on ventricular assist devices and IABP counterpulsation, personnel experienced in the operation of these devices must be present during the transport and at the destination. Medication infusions are maintained during transport and continued at the destination. If possible, blood product transfusions are completed prior to transport; however, if a patient must be moved to a location such as the OR or interventional radiology for definitive therapy, transfusion may be ongoing during transport.

In addition to intravascular catheters, great care should be taken to maintain the integrity and functionality of other indwelling devices. These include chest tubes, gastric decompression tubes, feeding tubes, surgical drains, and Foley and other types of urinary drainage catheters.

Contraindications to Transport

Transport out of the ICU is contraindicated when there is an inability to provide adequate oxygenation and ventilation during transport or at the receiving location. It is also contraindicated when there is an inability to adequately monitor cardiovascular hemodynamics during transport or at the destination. Transport out of the ICU is also contraindicated if the patient is hemodynamically unstable, unless the destination will provide the means to achieve restoration of hemodynamic integrity.

A risk-benefit analysis of all transports should be undertaken prior to embarking on movement of a critically ill patient to an alternate location. In recent years, fortunately, bedside alternatives for many diagnostic and therapeutic procedures have been developed.

Specific Operations in Critically Ill Patients

Patients come to the SICU after surgery. Some elective surgery mandates intensive monitoring even in a stable patient. However, many emergent operations result in an unstable patient whose physiology must be repaired. Although circumstances requiring intensive care can occur after any operation, two surgical scenarios of particular interest to the surgical intensivist deserve specific review: abdominal compartment syndrome and damage control in the critically injured trauma patient. Common operative procedures that facilitate management of the critically ill patient will also be discussed: tracheostomy and enteral feeding access.

Abdominal Compartment Syndrome

Definitions. Abdominal compartment syndrome is a recently recognized pathologic entity, physiologically characterized in the laboratory in 1985 and clinically defined in 1989. Abdominal compartment syndrome is distinct from intraabdominal hypertension. Intraabdominal pressure (IAP) can be measured by

determining bladder pressure as transmitted through a Foley catheter. Normal IAP is 2 to 5 mm Hg, but it can be as high as 12 mm Hg in obese or pregnant adults. IAP is higher in critically ill patients, typically 5 to 7 mm Hg.

Intraabdominal hypertension is defined as an intraabdominal pressure of 12 mm Hg or higher and can be graded: Grade I is 12 to 15 mm Hg; grade II, 16 to 20 mm Hg; grade III, 21 to 25 mm Hg; and grade IV, over 25 mm Hg. Abdominal compartment syndrome is defined as a sustained IAP above 20 mm Hg associated with new-onset organ dysfunction or failure. Abdominal perfusion pressure is measured as the difference between MAP and IAP. An abdominal perfusion pressure of at least 60 mm Hg is required to maintain adequate perfusion to the viscera contained in the abdomen. End-organ dysfunction occurs if the perfusion pressure goes below this critical level.

Abdominal compartment syndrome can be further characterized as primary, secondary, and tertiary. Primary abdominal compartment syndrome is caused by abdominopelvic pathology that creates a space-occupying or expanding lesion, such as a ruptured abdominal aortic aneurysm, abdominal trauma, or retroperitoneal hemorrhage. Secondary abdominal compartment syndrome (extraabdominal compartment syndrome) is caused by massive bowel edema due to extraabdominal conditions requiring massive fluid resuscitation in the presence of capillary leak, such as sepsis and burns. Tertiary abdominal compartment syndrome (recurrent abdominal compartment syndrome) occurs after resolution of an earlier episode of primary or secondary abdominal compartment syndrome.

Significance: Progressive organ failure. The common characteristic of all types of abdominal compartment syndrome is progressive organ failure, including failure of the kidneys, splanchnic bed, lungs, heart, and brain. If abdominal compartment syndrome is not recognized and treated expeditiously, hemodynamic collapse and death ensue.

Treatment. Nonoperative management of abdominal compartment syndrome includes sedation and paralysis to relax the abdominal wall, evacuation of intraluminal gastrointestinal contents, evacuation of large abdominal fluid collections, optimization of abdominal perfusion pressure with vasopressor support if necessary, and correction of a positive fluid balance. If these maneuvers are unsuccessful in correcting organ dysfunction, definitive management includes a decompressive laparotomy and temporary abdominal closure until the underlying disease process is reversed.

Damage Control in the Trauma Patient

Damage control surgery is applied to trauma patients who have devastating cervical, truncal, or extremity injuries and intraoperative physiologic compromise termed the "lethal triad": hypothermia, coagulopathy, and acidosis. Definitive repair of all injuries and closure of the incision is impossible in some patients, too time consuming in others, and may cause a postoperative compartment syndrome (e.g., abdominal compartment syndrome) following trauma laparotomy. Surgical management of these severely injured patients is staged.

The initial operation: A band-aid for anatomy to facilitate repair of physiology. The initial operation is limited to control of hemorrhage and gross contamination. Hemorrhage is controlled via rapid repair, ligation or shunting of major vascular injuries, and packing of organs or compartments. Major injuries to the gastrointestinal tract are resected and left in discontinuity, without anastomosis. A quick temporary closure is used to cover the surgical incision. The anesthesiology team provides ongoing resuscitation following a massive transfusion protocol while the surgeons are operating. Ideally this operation is completed within 2 hours, and the patient is then transported to the SICU.

The SICU resuscitation: Abrogation of the lethal triad. On arrival to the SICU, the patient is aggressively rewarmed, and resuscitation is ongoing with infusion of blood, blood products, vasopressors, and inotropes if indicated to manage hemorrhagic and traumatic shock. As coagulopathy is corrected and nonsurgical bleeding ceases, perfusion is restored and acid-base balance normalizes. Supportive management can limit some organ failure, such as ALI and AKI. This SICU phase is variable in length but may require 48 to 72 hours.

The definitive operation: Restoration of anatomy. Ideally, the patient is taken back to the OR when hypotension, coagulopathy, acidosis, and hypothermia have resolved and when the postresuscitation diuretic phase has begun. Definitive repairs are performed, missed injuries are sought and managed, gastrointestinal continuity is restored (either with anastomoses or ostomies), and formal closure of the incision is undertaken if possible.

After Damage Control: Subsequent Operative Interventions

Saving a life comes at a price. Some of the patients who survive injury and the damage control required to repair it must undergo multiple subsequent interventions and operations. Particularly after damage control for abdominal trauma, definitive closure of the surgical incision is not always feasible at the time of the first repeat laparotomy. This results in an open abdomen, which mandates subsequent repeat laparotomies. If primary closure of the abdominal wall is not ultimately possible, common management includes insertion of absorbable mesh and eventual application of a skin graft. This will result in loss of abdominal domain and a large ventral incisional hernia.

After the patient has sufficiently recovered from the acute illness, a major definitive restorative operation can be undertaken, including repair of fistulas, closure of ostomies, and the hernia repair, typically with abdominal wall reconstruction. Because of the magnitude of these operations, some patients require monitoring in the SICU in the immediate postoperative period. The time frame from initial injury to these operations is typically 6 to 12 months.

Common Operations to Facilitate Management of the Critically Ill Patient

Tracheostomy. Tracheostomy is indicated in critically ill patients who require prolonged intubation, typically longer than 2 weeks. Additional indications include access for frequent pulmonary suctioning, the presence of neurologic deficits that compromise protective airway reflexes, and facial trauma or operations that anatomically compromise the upper airway. The procedure can be performed either via a percutaneous or open technique. When the indication for tracheostomy has resolved,

decannulation is undertaken, and the opening spontaneously closes, usually over a 2-week period.

Enteral feeding access. If nasoenteric feeding is anticipated for longer than 30 days, long-term percutaneous or surgical feeding access should be considered. The most common indications for prolonged enteral feeding in the critically ill patient are prolonged mechanical ventilation, impaired swallowing, oropharyngeal or esophageal obstruction, and major facial trauma.

Long-term gastric feeding access can be obtained via a percutaneous, laparoscopic, or open surgical technique. Percutaneous endoscopic gastrostomy (PEG) is one of the most frequently used methods to achieve durable feeding access. Long-term jejunal feeding access is usually obtained via a laparoscopic or open surgical approach. However, direct percutaneous endoscopic jejunostomy (DPEJ) is available in some institutions. This is more technically challenging than PEG placement. A PEG can also be converted to jejunal access (PEG-jejunal tube) via a two-stage procedure in which a PEG is placed first. This is followed by passing the jejunal feeding tube through the PEG under fluoroscopic guidance. Jejunal access is desired in patients who are at high risk of aspiration or are otherwise intolerant of gastric feeding.

Acute Management of the Critically Ill Burn Patient

Patients who suffer substantial acute thermal injuries present unique challenges for the surgical intensivist. Perhaps more than for any other category of critical illness, initial care of the substantially burned patient mandates a collaborative, multidisciplinary, and interprofessional approach, with input from the intensivist, burn surgeon, anesthesiologist, and expert nursing staff in the ICU and OR.

Resuscitation is the first priority. In addition to the obvious local injury at the site of the burn, severe thermal injuries involving 20% or more total body surface area (TBSA) result in burn shock. This phenomenon is characterized by acute systemic responses, including increased capillary permeability, increased microvasculature hydrostatic pressure, protein and fluid shift into the interstitial space, increased systemic vascular resistance, reduced cardiac output, and intravascular hypovolemia. This pathophysiologic phenomenon is most pronounced in the first 24 hours following burn injury. Therefore fluid resuscitation is the cornerstone of the initial management of these patients.

Volume administration guidelines and choice of fluid composition are variable between burn centers; however, a few general principles are widely applicable. Volume requirements are estimated utilizing the total burn size (proportion of TBSA) and the patient's weight. A variety of formulas can be used to estimate crystalloid requirements, typically 2 to 4 mL/kg body weight/%TBSA during the first 24 hours. The most widely utilized crystalloid burn resuscitation fluid remains LR solution. During large-volume resuscitations, the adjunctive addition of colloids (such as albumin) may successfully reduce the total volume requirement. The most common method of colloid implementation is to administer albumin as an adjunct to crystalloid during the second half of the first 24 hours of resuscitation.

The goal is to utilize the least quantity of fluid necessary to maintain organ and tissue perfusion. This mandates that the volume infused be continuously titrated to avoid under- and overresuscitation. Increased requirements occur in patients with full thickness injuries, inhalation injury, and a delay in initiation of resuscitation. In spite of the availability of sophisticated monitoring technology, the most widely used end point of resuscitation remains urine output. Fluid resuscitation is titrated to maintain a urine output of 0.5 to 1.0 mL/kg/h.

Underresuscitation results in decreased perfusion, acute renal failure progressing to multiple organ dysfunction, hemodynamic collapse, and ultimately death. In the decades since the establishment of weight- and injury-size-based resuscitation formulas, underresuscitation has become uncommon. Rather, overresuscitation has become more problematic and potentially results in adverse consequences such as excessive peripheral edema, elevated compartment pressures with resultant compartment syndromes (abdominal, torso, extremity, and ocular), ARDS, multiple organ dysfunction related to organ edema, and delayed wound healing.

Once acute resuscitation has been accomplished, early excision of full thickness and deep partial thickness burns, as well as wound coverage or grafting, becomes the next priority. The burn surgeon, anesthesiology team, and OR nursing team work together to achieve this goal. Excision 24 to 48 hours after injury is associated with improved outcomes. Specifically, blood loss, infection, length of hospital stay, and mortality are decreased, and graft take is increased. The specific techniques of burn excision, wound coverage, and grafting are beyond the scope of this chapter.

In addition to oversight of the acute resuscitation and preparing the patient for initial operative interventions, priorities for the intensivist include aggressive surveillance for and treatment of infection, optimization of nutritional support, and oversight of rehabilitation in the ICU to mitigate the consequences of prolonged immobilization and contracture formation.

KEY POINTS

- Communication and teamwork between anesthesiologists and surgeons are the basis of optimal care delivery to critically ill patients who require surgical intervention.
- Shock is an abnormality of the circulatory system that causes inadequate organ perfusion and tissue oxygenation. Subsets of shock based on differential hemodynamic profiles include hypovolemic, cardiogenic, obstructive, and distributive.
- Sepsis and severe trauma are two of the most common diagnoses encountered in the SICU. Systemic inflammation is a common denominator in these two conditions. Septic shock and traumatic shock result when the immune response to either of these insults is dysregulated, resulting in an amplified systemic inflammatory response and multiple organ failure.

- The Surviving Sepsis Campaign guidelines provide evidence-based recommendations for the management of patients with sepsis and septic shock. These recommendations include low-tidal-volume mechanical ventilation for management of sepsis-induced acute respiratory distress syndrome, implementation of ventilator weaning protocols, and protocols for management of blood glucose, targeting a goal of 180 mg/dL or lower.
- The systemic inflammatory response, CARS, and PICS represent a continuum of immunologically and genomically mediated consequences of the pathophysiologic response to sepsis and severe injury.
- Ideal management of massive hemorrhage includes prompt control of the bleeding source and damage control resuscitation, including implementation of an institutionally specific massive transfusion protocol. Class III hemorrhage—loss of 30% to 40% of total blood volume—results in hemorrhagic shock and is the least amount of blood loss that consistently causes a decrease in systolic blood pressure. In the exsanguinating patient, administration of crystalloid should be minimized, and blood component therapy in a 1:1:1 ratio of units of fresh frozen plasma, platelets, and PRBCs has been demonstrated to improve hemostasis and decrease mortality due to exsanguination at 24 hours.
- Prothrombin complex concentrates provide for rapid low-volume reversal of warfarin-induced coagulopathy in elderly patients who have traumatic brain injury.
- Tranexamic acid in the management of hemorrhagic shock is of most benefit in patients who present with severe shock (systolic blood pressure <75 mm Hg) within 3 hours of the time of injury.
- The trigger for platelet transfusion in patients undergoing surgery or invasive procedures is below 50,000/mm^3. The trigger for empirical platelet transfusion in patients without additional risk factors for bleeding is below 10,000/mm^3, and for patients with additional risk factors for bleeding it is below 20,000/mm^3.
- In the massively hemorrhaging patient, platelet transfusions in conjunction with correcting plasma coagulation factor deficits are indicated when the platelet count is below 50,000/mm^3 or below 100,000/mm^3 in the presence of diffuse microvascular bleeding.
- Circulatory collapse attributable to cardiac dysfunction can involve the myocardium, pericardium, cardiac valves, and outflow tract of the heart.
- Rapid recognition of an ST-segment elevation myocardial infarction is crucial because these patients benefit from immediate reperfusion and, in the appropriate clinical circumstances, should be treated with fibrinolytic therapy or urgent revascularization either by percutaneous coronary intervention or coronary artery bypass surgery.
- Massive pulmonary embolism in the critically ill patient can be managed with systemic thrombolysis, catheter-directed thrombolysis, or surgical pulmonary embolectomy.
- Tension pneumothorax is a clinical, not radiographic, diagnosis and must be treated with immediate decompression of the involved hemithorax.
- A sudden decrease in $PETCO_2$ is usually a result of a circuit disconnection, airway obstruction, an abrupt decrease in cardiac output, or pulmonary embolism.
- Low-tidal-volume ventilation is the most commonly used strategy to manage acute hypoxemic respiratory failure. Rescue modes of ventilation, such as APRV, are sometimes used to manage refractory cases.
- The optimal target for glycemic management in the critically ill patient population remains elusive and has undergone a significant paradigm shift in the past 2 decades. At present, the literature supports a target blood glucose range of 140 to 180 mg/dL.
- In the absence of clinical evidence of hypothyroidism, thyroid hormone replacement in patients who have low measured thyroid hormone concentrations due to the sick euthyroid syndrome is not indicated.
- If intrinsic thyroid dysfunction is suspected in the critically ill patient, the best tests to obtain are a free T_4 and TSH.
- In the setting of relative adrenal insufficiency, septic shock refractory to volume resuscitation and vasopressor therapy is an indication for steroid replacement. A typical regimen is hydrocortisone 50 mg IV every 6 hours. Steroid therapy for sepsis in the absence of refractory shock is not recommended.
- Acute kidney injury is a significant cause of morbidity and mortality in the critically ill patient population. The Kidney Disease: Improving Global Outcomes group developed criteria that categorize patients according to the degree of AKI based on the absolute change in serum creatinine during a particular time interval and the reduction in urine volume.
- Child-Pugh and MELD scores are used to predict surgical mortality in patients with cirrhosis and end-stage liver disease undergoing nontransplant surgical procedures.
- Delirium is a poorly understood form of cerebral dysfunction that afflicts many ICU patients and is an independent predictor of negative outcomes. Features include inattention, reduced awareness of the environment, and either a change in cognition or the development of perceptual disturbances. The key to management of delirium is mitigation of its risk factors and prevention.
- Global strategies to manage pain, agitation, and delirium in the ICU include minimizing sedation and optimizing normal sleep/wake cycles.
- Critical illness polyneuropathy develops in patients who have multiple organ failure and sepsis and is likely the most common neuromuscular cause of prolonged ventilator dependency in patients without prior neuromuscular disease.
- Acute quadriplegic myopathy (acute myopathy of intensive care) most frequently occurs in the setting of severe pulmonary disease in which neuromuscular blockade is used to facilitate mechanical ventilation and high-dose corticosteroids are administered at the same time.
- There is no evidence to indicate that resuscitation with colloids, compared to resuscitation with crystalloids, reduces the risk of death in patients with trauma, burns, or following surgery.

- Lactated Ringer solution and significantly hypotonic crystalloid solutions should not be used to reconstitute PRBCs.
- Appropriate perioperative antibiotic prophylaxis should be administered within 60 minutes of incision time, should be dose adjusted in obese patients, should be redosed intraoperatively during long procedures or if the blood loss exceeds 1500 mL, and should not be continued after the surgical incision is closed in the OR.
- Perioperative stress-dose steroid supplementation should be considered for any patient who has received corticosteroids within the past year.
- Hypothermia in the critically ill perioperative patient is associated with adverse outcomes and should be corrected.
- Malignant hyperthermia is inherited in an autosomal dominant pattern and is treated with dantrolene. Clinical manifestations in the anesthetized patient include tachycardia, an increased $PETCO_2$, muscle rigidity, and a body temperature above 38.8°C (without another explanation).
- Abdominal compartment syndrome defines a sustained intraabdominal pressure above 20 mm Hg and is associated with new-onset organ dysfunction or failure. If medical management is unsuccessful, decompressive laparotomy with a temporary abdominal closure provides definitive management.
- Damage control surgery is applied to trauma patients who have devastating cervical, truncal, or extremity injuries and intraoperative physiologic compromise termed the "lethal triad": hypothermia, acidosis, and coagulopathy.
- Tracheostomy and enteral feeding access are elective operative procedures performed in critically ill patients that facilitate optimal management.
- Burn shock is an acute systemic response to severe thermal injury involving 20% or more of the total body surface area. Intravascular hypovolemia is the end result. Therefore fluid resuscitation is the cornerstone of the initial resuscitation of severely burned patients.

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5

Ischemic Heart Disease

Shamsuddin Akhtar

OUTLINE

The prevalence of ischemic heart disease and atherosclerotic vascular disease in the United States increases significantly with age (Fig. 5.1). By some estimates, 30% of patients who undergo surgery annually in the United States have ischemic heart disease. Angina pectoris, acute myocardial infarction (AMI), and sudden death are often the first manifestations of ischemic heart disease, and cardiac dysrhythmias are probably the major cause of sudden death in these patients. Genetic factors, a high-fat and energy-rich diet, smoking, and sedentary lifestyle are associated with the emergence of ischemic heart disease Additional risk factors include hypercholesterolemia, systemic hypertension, cigarette smoking, diabetes mellitus, obesity, and a family history of premature development of ischemic heart disease (Table 5.1). Psychological factors such as type A personality and stress have also been implicated. Patients with ischemic heart disease can have chronic stable angina or an acute coronary syndrome (ACS) at presentation. The latter includes ST-segment elevation myocardial infarction (STEMI) and unstable angina/non–ST-segment elevation myocardial infarction (UA/NSTEMI).

STABLE ANGINA PECTORIS

The coronary artery circulation normally supplies sufficient blood flow to meet the demands of the myocardium in response to widely varying workloads. An imbalance between coronary

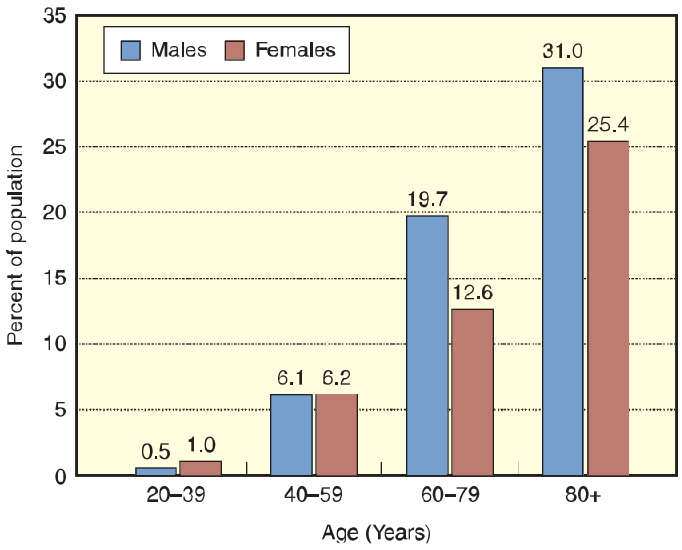

Fig. 5.1 Prevalence of coronary heart disease by age and gender in the United States (2013-2016). (Data from National Center for Health Statistics and National Heart, Lung, and Blood Institute.)

TABLE 5.1 Risk Factors for Development of Ischemic Heart Disease

Male gender
Increasing age
Hypercholesterolemia
Hypertension
Cigarette smoking
Diabetes mellitus
Obesity
Sedentary lifestyle
Genetic factors/family history

blood flow (supply) and myocardial oxygen consumption (demand) can precipitate ischemia, which frequently manifests as chest pain (i.e., angina pectoris). Stable angina typically develops in the setting of partial occlusion or significant (70%) chronic narrowing of a segment of coronary artery. When the imbalance becomes extreme, congestive heart failure, electrical instability with cardiac dysrhythmias, and MI may result. Angina pectoris reflects intracardiac release of adenosine, bradykinin, and other substances during ischemia. These substances stimulate cardiac nociceptive and mechanosensitive receptors whose afferent neurons converge with the upper five thoracic sympathetic ganglia and somatic nerve fibers in the spinal cord and ultimately produce thalamic and cortical stimulation that results in the typical chest pain of angina pectoris. These substances also slow atrioventricular conduction and decrease cardiac contractility, which improves the balance between myocardial oxygen supply and demand. Atherosclerosis is the most common cause of impaired coronary blood flow resulting in angina pectoris, but it may also occur in the absence of coronary obstruction as a result of myocardial hypertrophy, severe aortic stenosis, or aortic regurgitation. It may also occur with paroxysmal tachydysrhythmias, marked anemia, or hyperthyroidism. Syndrome X is a rare cause of angina, and in this situation the chest pain is thought to be due to microvascular dysfunction of the coronary circulation.

Diagnosis

Angina pectoris is typically described as retrosternal chest discomfort, pain, pressure, or heaviness that may radiate to any dermatome from C8 to T4. This chest discomfort often radiates to the neck, left shoulder, left arm, or jaw and occasionally to the back or down both arms (especially the ulnar surfaces of forearm and hand). Angina may also be perceived as epigastric discomfort resembling indigestion. Some patients describe angina as shortness of breath, mistaking a sense of chest constriction as dyspnea. The need to take a deep breath rather than breathe rapidly often identifies shortness of breath as an anginal equivalent. Angina pectoris usually lasts several minutes and is crescendo-decrescendo in nature. A sharp pain that lasts only a few seconds or a dull ache that lasts for hours is rarely caused by myocardial ischemia. Physical exertion, emotional tension, and cold weather may induce angina. Rest and/or nitroglycerin relieve it. Chronic stable angina refers to chest pain or discomfort that does not change appreciably in frequency or severity over 2 months or longer. Unstable angina, by contrast, is defined as angina at rest, angina of new onset, or an increase in the severity or frequency of previously stable angina without an increase in levels of cardiac biomarkers. Sharp retrosternal pain exacerbated by deep breathing, coughing, or change in body position suggests pericarditis. There are many causes of noncardiac chest pain (Table 5.2). Noncardiac chest pain is often exacerbated by chest wall movement and is associated with tenderness over the involved area, which is often a costochondral

TABLE 5.2 Common Causes of Acute Chest Pain

System	Condition
Cardiac	Angina
	Rest or unstable angina
	Acute myocardial infarction
	Pericarditis
Vascular	Aortic dissection
	Pulmonary embolism
	Pulmonary hypertension
Pulmonary	Pleuritis and/or pneumonia
	Tracheobronchitis
	Spontaneous pneumothorax
Gastrointestinal	Esophageal reflux
	Peptic ulcer
	Gallbladder disease
	Pancreatitis
Musculoskeletal	Costochondritis
	Cervical disk disease
	Trauma or strain
Infectious	Herpes zoster
Psychological	Panic disorder

junction. Esophageal spasm can produce severe substernal pressure that may be confused with angina pectoris and may also be relieved by administration of nitroglycerin.

Electrocardiography

The resting electrocardiogram (ECG) may be normal in patients with angina, or it may show nonspecific ST–T-wave changes or abnormalities related to an old MI. During myocardial ischemia, the standard 12-lead ECG demonstrates ST-segment depression (characteristic of subendocardial ischemia) that coincides in time with the anginal chest pain. This may be accompanied by transient symmetric T-wave inversion. Patients with chronically inverted T waves resulting from previous MI may show a return of the T waves to the normal upright position (i.e., pseudonormalization of the T wave) during myocardial ischemia. These ECG changes are seen in about half of patients. Dynamic ST-segment changes and T-wave changes that accompany episodes of angina pectoris and disappear thereafter are more specific. Variant angina—that is, angina that results from coronary vasospasm rather than occlusive coronary artery disease—is diagnosed by ST-segment elevation during an episode of angina pectoris.

Exercise ECG is useful for detecting signs of myocardial ischemia and establishing their relationship to chest pain. The test also provides information about exercise capacity. Exercise testing is often combined with imaging studies (nuclear, echocardiographic, or magnetic resonance imaging [MRI]) to demonstrate areas of ischemic myocardium. Exercise testing is not always feasible, however, because of the inability of a patient to exercise owing to peripheral vascular or musculoskeletal disease, deconditioning, dyspnea on exertion, prior stroke, or the presence of chest pain at rest or with minimal activity. The presence of conditions that interfere with interpretation of the exercise ECG (e.g., paced rhythm, left ventricular hypertrophy, digitalis administration, or a preexcitation syndrome) also limit the utility of exercise stress testing. The risk of MI related to exercise testing is about 2/10,000 tests and death is 1/10,000. Contraindications to exercise stress testing include rest angina with 48 hours, unstable rhythm, severe aortic stenosis, severe hypertension, acute myocarditis, uncontrolled heart failure, severe pulmonary hypertension, and active infective endocarditis.

The exercise ECG is most likely to indicate myocardial ischemia when there is at least 1 mm of horizontal or downsloping ST-segment depression during or within 4 minutes after exercise. The greater the degree of ST-segment depression, the greater the likelihood of significant coronary artery disease. When the ST-segment abnormality is associated with angina pectoris and occurs during the early stages of exercise and persists for several minutes after exercise, significant coronary artery disease is likely. Exercise ECG is less accurate but more cost effective than imaging tests for detecting ischemic heart disease. A negative stress test result does not exclude the presence of coronary artery disease, but it makes the likelihood of three-vessel or left main coronary disease extremely low. Exercise ECG is less sensitive (overall sensitivity ~75%) and specific in detecting ischemic heart disease than nuclear cardiology techniques.

Nuclear Cardiology Techniques

Nuclear stress imaging is useful for assessing coronary perfusion. It has greater sensitivity for detection of ischemic heart disease than exercise testing alone. It can define vascular regions in which stress-induced coronary blood flow is limited and can estimate left ventricular systolic size and function. Tracers such as thallium and technetium can be detected over the myocardium by single-photon emission computed tomography (SPECT) techniques. Recent data also suggest positron emission tomography (PET) imaging (with exercise or pharmacologic stress) using N-13 ammonia or rubidium-82 nuclide as another technique for assessing perfusion. A significant coronary obstructive lesion causes a reduction in blood flow, and thus less tracer activity is present in that area. Exercise increases the difference in tracer activity between normal and underperfused regions because coronary blood flow increases markedly with exercise *except* in those regions distal to a coronary artery obstruction. Imaging is carried out in two phases: The first is immediately after cessation of exercise to detect regional ischemia, and the second is hours later to detect reversible ischemia. Areas of persistently absent uptake signify an old MI. The size of the perfusion abnormality is the most important indicator of the significance of the coronary artery disease detected.

Alternative methods of exercise testing are available when exercise ECG is not possible or interpretation of ST-segment changes would be difficult. Administration of atropine, infusion of dobutamine, or institution of artificial cardiac pacing produces a rapid heart rate to create cardiac stress. Alternatively, cardiac stress can be produced by administering a coronary vasodilator such as adenosine or dipyridamole. These drugs dilate normal coronary arteries but evoke minimal or no change in the diameter of atherosclerotic coronary arteries. After cardiac stress is induced by these interventions, radionuclide tracer scanning is performed to assess myocardial perfusion.

Echocardiography

Echocardiographic regional wall motion analysis can be performed immediately after stressing the heart either pharmacologically or with exercise. Stress echocardiography is more sensitive than exercise electrocardiography in the diagnosis of ischemic heart disease. New ventricular wall motion abnormalities induced by stress correspond to sites of myocardial ischemia, thereby localizing obstructive coronary lesions. In contrast, exercise ECG can indicate only the presence of ischemic heart disease but does not reliably predict the location of the obstructive coronary lesion. One can also visualize global wall motion under baseline conditions and under cardiac stress. Valvular function can be assessed as well. Limitations imposed by poor visualization have been improved by newer contrast-assisted technologies.

Stress Cardiac MRI

Pharmacologic stress imaging with cardiac MRI compares favorably with other methods and is being used clinically. Cardiac magnetic resonance stress testing with dobutamine infusion

can be used to assess wall motion abnormalities accompanying ischemia, as well as myocardial perfusion.

Electron Beam CT

Calcium deposition occurs in atherosclerotic blood vessels. Coronary artery calcification can be detected by electron beam CT (EBCT) and multidetector CT (MDCT). Although the sensitivity, specificity, and negative predictive values are high (¯90%), its routine use has not been clarified.

CT Angiography

The heart and coronary arteries can be visualized with contrast medium and multislice CT scanning. This modality is most useful in ruling out coronary artery disease in patients with a low likelihood for significant coronary artery disease. The role of CT angiography in routine clinical practice has yet to be defined.

Coronary Angiography

Coronary angiography provides the best information about the condition of the coronary arteries. It is indicated in patients with known or possible angina pectoris who have survived sudden cardiac death, those who continue to have angina pectoris despite maximal medical therapy, those who are being considered for coronary revascularization, those who develop a recurrence of symptoms after coronary revascularization, those with chest pain of uncertain cause, and those with a cardiomyopathy of unknown cause. It can also be used for the definitive diagnosis of coronary disease for occupational reasons (e.g., in airline pilots). Coronary angiography is also useful for establishing the diagnosis of nonatherosclerotic coronary artery disease, such as coronary artery spasm, Kawasaki disease, radiation-induced vasculopathy, and primary coronary artery dissection. A narrowing of coronary luminal diameter by 50% is considered hemodynamically and clinically significant. Intravascular ultrasound is an invasive diagnostic method to determine the extent of intraluminal disease when the angiogram is equivocal. It can also help assess the results of angioplasty or stenting.

The important prognostic determinants in patients with coronary artery disease are the anatomic extent of the atherosclerotic disease, the state of left ventricular function (ejection fraction), and the stability of the coronary plaque. Left main coronary artery disease is the most dangerous anatomic lesion and is associated with an unfavorable prognosis when managed with medical therapy alone. A stenosis of greater than 50% of the left main coronary artery is associated with an annual mortality rate of 15%.

Unfortunately, coronary angiography cannot predict which plaques are most likely to rupture and initiate acute coronary syndromes. Vulnerable plaques (i.e., those most likely to rupture and form an occlusive thrombus) have a thin fibrous cap and a large lipid core containing a large number of macrophages. The presence of vulnerable plaque predicts a greater risk of MI regardless of the degree of coronary artery stenosis. Indeed, AMI most often results from rupture of a plaque that had produced less than 50% stenosis of a coronary artery. Currently there is no satisfactory test to measure the stability of plaques.

Treatment

Comprehensive management of ischemic heart disease has five aspects: (1) identification and treatment of diseases that can precipitate or worsen myocardial ischemia, (2) reduction of risk factors for progression of coronary artery disease, (3) lifestyle modification, (4) pharmacologic management of angina, and (5) revascularization by coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) with or without placement of intracoronary stents. The goal of treatment of patients with chronic stable angina is to achieve complete or almost complete elimination of anginal chest pain and a return to normal activities with minimal side effects.

Treatment of Associated Diseases

Conditions that increase oxygen demand or decrease oxygen delivery may contribute to an exacerbation of previously stable angina. These conditions include fever, infection, anemia, tachycardia, thyrotoxicosis, heart failure, and cocaine use. Treatment of these conditions is critical to the management of stable ischemic heart disease.

Reduction of Risk Factors and Lifestyle Modification

The progression of atherosclerosis may be slowed by cessation of smoking, maintenance of an ideal body weight by consumption of a low-fat, low-cholesterol diet, regular aerobic exercise, and treatment of hypertension. Hypercholesterolemia is an important modifiable risk factor and should be controlled by diet and/or drugs such as statins. Drug treatment is strongly recommended in patients with clinical atherosclerosis or when the low-density lipoprotein (LDL) cholesterol level exceeds 160 mg/dL (goal is ∟50% reduction or ∟70 mg/dL). Hypertension increases the risk of coronary events as a result of direct vascular injury, left ventricular hypertrophy, and increased myocardial oxygen demand. Lowering the blood pressure from hypertensive levels to normal levels decreases the risk of MI, congestive heart failure, and stroke. In combination with lifestyle modifications, an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), ¯ blockers, and calcium channel blockers are especially useful in managing hypertension in patients with angina pectoris.

Medical Treatment of Myocardial Ischemia

Pharmacotherapy for ischemic heart disease is designed to reduce the frequency of anginal episodes, MI, and coronary death. Antiplatelet drugs, nitrates, ¡ blockers, ranolazine, calcium channel blockers, and ACE inhibitors are used in the medical treatment of angina pectoris.

Antiplatelet drugs are widely used in the management of ischemic heart disease: aspirin, thienopyridines (clopidogrel and prasugrel), reversible platelet inhibitors (cangrelor and ticagrelor), and platelet glycoprotein IIb/IIIa inhibitors (eptifibatide, tirofiban, and abciximab). (See Chapter 23 for a detailed discussion of platelet inhibition.)

Aspirin inhibits the enzyme cyclooxygenase-1 (COX-1). This results in inhibition of thromboxane A_2, which plays an important role in platelet aggregation. This inhibition is irreversible, lasts for the duration of platelet life span (≈7 days), and

can be produced by low dosages of aspirin. Daily aspirin therapy (75–325 mg/d) decreases the risk of cardiac events in patients with stable or unstable angina pectoris and is recommended for all patients with ischemic heart disease. Clopidogrel inhibits the adenosine diphosphate (ADP) receptor $P2Y_{12}$ and inhibits platelet aggregation in response to ADP release from activated platelets. Clopidogrel-induced inhibition of ADP receptors is irreversible and also lasts for the duration of the platelet's life span. Seven days after cessation of this drug, 80% of platelets will have recovered normal aggregation function. Clopidogrel is a prodrug that is metabolized into an active compound in the liver. Owing to genetic differences in the enzymes that metabolize clopidogrel to the active drug, significant variability in its activity has been observed. By some estimates, 10% to 20% of patients taking clopidogrel demonstrate resistance or hyperresponsiveness. Furthermore, some drugs (e.g., proton pump inhibitors) can affect the enzyme that metabolizes clopidogrel to its active compound and thereby can reduce the effectiveness of clopidogrel. Clopidogrel can be used in patients who have a contraindication to or are intolerant of aspirin. Prasugrel also inhibits the ADP $P2Y_{12}$ receptor irreversibly. However, the pharmacokinetics of prasugrel are more predictable. It is rapidly absorbed, has a faster onset of action, and demonstrates less individual variability in platelet responses compared with clopidogrel. It also is more potent than clopidogrel, and a higher risk of bleeding has been associated with its use. Ticagrelor and its equipotent metabolite reversibly interact with the platelet $P2Y_{12}$ ADP receptor, thereby preventing signal transduction and platelet activation and aggregation. Though ticagrelor and prasugrel have been shown to be more effective after ACS or stent placement, they are associated with an increased risk of bleeding. Platelet glycoprotein IIb/IIIa receptor antagonists (abciximab, eptifibatide, tirofiban) inhibit platelet activation, adhesion, and aggregation. Limited-term administration of antiplatelet drugs is particularly useful after placement of an intracoronary stent.

Organic nitrates decrease the frequency, duration, and severity of angina pectoris and increase the amount of exercise required to produce ST-segment depression. The antianginal effects of nitrates are greater when these drugs are used in combination with blockers or calcium channel blockers. Nitrates dilate coronary arteries and collateral blood vessels and thereby improve coronary blood flow. The venodilating effect of nitrates decreases venous return and hence left ventricular preload, left ventricular end-diastolic volume, and pressure, thereby reducing myocardial wall tension and myocardial oxygen consumption. Nitrates also decrease peripheral vascular resistance, which reduces left ventricular afterload and myocardial oxygen consumption. They also have potential antithrombotic effects. Nitrates are contraindicated in the presence of hypertrophic cardiomyopathy or severe aortic stenosis and should not be used within 24 hours of sildenafil, tadalafil, or vardenafil use because this combination may produce severe hypotension. Administration of sublingual nitroglycerin by tablet or spray produces prompt relief of angina pectoris. The most common side effect of nitrate treatment is headache. Hypotension may occur after nitrate administration in hypovolemic patients. For long-term therapy, long-acting nitrate preparations (e.g., isosorbide tablets and nitroglycerin ointment or patches) are equally effective. The therapeutic value of organic nitrates can be compromised by the development of tolerance. To avoid nitrate tolerance, a daily 8- to 12-hour interval free of nitrate exposure is recommended.

 blockers are the only drugs that have been shown to prolong life in patients with coronary artery disease. They have antiischemic, antihypertensive, and antidysrhythmic properties. Long-term administration of blockers decreases the risk of death and myocardial reinfarction in patients who have had an MI, presumably by decreasing myocardial oxygen demand. This benefit is present even in patients in whom blockers were traditionally thought to be contraindicated, such as those with congestive heart failure, pulmonary disease, or advanced age. Drug-induced blockade of β_1-adrenergic receptors by atenolol, metoprolol, acebutolol, or bisoprolol results in heart rate slowing and decreased myocardial contractility that are greater during activity than at rest. The result is a decrease in myocardial oxygen demand with a subsequent decrease in ischemic events during exertion. The decrease in heart rate also increases the length of diastole and thus coronary perfusion time. Nonspecific-adrenergic blockers (propranolol, nadolol) can increase the risk of bronchospasm in patients with reactive airway disease. Despite differences between β_1 and β_2 effects, all blockers seem to be equally effective in the treatment of angina pectoris. The most common side effects of blocker therapy are fatigue and insomnia. Heart failure may be intensified. blockers are contraindicated in the presence of severe bradycardia, sick sinus syndrome, severe reactive airway disease, second- or third-degree atrioventricular heart block, and uncontrolled congestive heart failure. Diabetes mellitus is not a contraindication to blocker therapy, although these drugs may mask signs of hypoglycemia. Abrupt withdrawal of blockers after prolonged administration can worsen ischemia in patients with chronic stable angina.

Long-acting calcium channel blockers are comparable to blockers in relieving anginal pain. However, short-acting calcium channel blockers such as verapamil and nifedipine are not. Diltiazem can be combined with blockers in patients with normal left ventricular function and no conduction defects. Calcium channel blockers are uniquely effective in decreasing the frequency and severity of angina pectoris due to coronary artery spasm (Prinzmetal or variant angina). They are not as effective as blockers in decreasing the incidence of myocardial reinfarction. The effectiveness of calcium channel blockers is due to their ability to decrease vascular smooth muscle tone, dilate coronary arteries, decrease myocardial contractility and myocardial oxygen consumption, and decrease systemic blood pressure. Many calcium channel blockers such as amlodipine, nicardipine, isradipine, felodipine, and long-acting nifedipine are potent vasodilators and are useful in treating both hypertension and angina. Amlodipine and blockers have complimentary actions. Common side effects of calcium channel blocker therapy include hypotension, peripheral edema, and headache. Calcium channel blockers are contraindicated in patients with severe congestive heart failure or severe aortic stenosis. They

must be used cautiously if given in combination with _ blockers because both classes of drugs have significant depressant effects on heart rate and myocardial contractility.

Ranolazine is a cardioselective antiischemic agent. It interacts with sodium and potassium channels and inhibits late inward sodium current in cardiac myocytes. *It is indicated for chronic angina only, when standard medical therapy has failed to control angina, and should not be used for the management of acute episodes of angina pectoris.* It is excreted by the kidney and can cause significant QTc prolongation and should be avoided in patients with kidney and/or liver disease.

Excessive angiotensin II plays a significant role in the pathophysiology of cardiac disorders. It can lead to development of myocardial hypertrophy, interstitial myocardial fibrosis, increased coronary vasoconstriction, and endothelial dysfunction. Angiotensin II also promotes inflammatory responses and atheroma formation. ACE inhibitors are important not only in the treatment of heart failure but also in the treatment of hypertension and in cardiovascular protection. ACE inhibitors are recommended for patients with coronary artery disease, especially those with hypertension, left ventricular dysfunction, or diabetes mellitus. ARBs offer similar benefits. Contraindications to ACE inhibitor use include documented intolerance or allergy, hyperkalemia, bilateral renal artery stenosis, and renal failure.

Revascularization

Revascularization by CABG or PCI with or without placement of intracoronary stents is indicated when optimal medical therapy fails to control angina pectoris. Revascularization is also indicated for specific anatomic lesions, in particular left main coronary artery stenosis of more than 50% or 70% or greater stenosis in an epicardial coronary artery. Revascularization is also indicated in patients with significant coronary artery disease with evidence of impaired left ventricular contractility (ejection fraction ∃40%). However, the presence of hypokinetic or akinetic areas in the left ventricle connotes a poor prognosis. Extensive myocardial fibrosis from a prior MI is unlikely to be improved by revascularization. However, some patients with ischemic heart disease have chronically impaired myocardial function (hibernating myocardium) that demonstrates improvement in contractility after surgical revascularization. In patients with stable angina pectoris and significant one- or two-vessel coronary artery disease, a PCI, with or without stent placement, or surgical CABG may be used for revascularization. CABG is preferred over PCI in patients with significant left main coronary artery disease, those with three-vessel coronary artery disease, and patients with diabetes mellitus who have two- or three-vessel coronary artery disease. Operative mortality rates for CABG surgery currently range from 1.5% to 2% in younger patients but increase to 4% to 8% in older individuals (∃80 years) and in those who have had prior CABG.

ACUTE CORONARY SYNDROME

ACS represents an acute or worsening imbalance of myocardial oxygen supply to demand. It typically occurs as a result of focal disruption of an atheromatous plaque that triggers the coagulation cascade, with subsequent generation of thrombin and partial or complete occlusion of the coronary artery by a thrombus. Rarely it may result from prolonged coronary vasospasm, embolic occlusion, vasculitis, or aortic root/coronary artery dissection. Imbalance of myocardial oxygen supply and demand leads to ischemic chest pain. ACS can be classified into three categories based on the findings of a 12-lead ECG and the levels of cardiac-specific biomarkers (troponins). Patients with ST elevation at presentation are considered to have STEMI. Patients who have ST-segment depression or nonspecific changes on the ECG are categorized based on the levels of cardiac-specific troponins or myocardial creatine kinase (CK)-MB. Elevation of cardiac-specific biomarker levels in this situation indicates NSTEMI. If levels of cardiac-specific biomarkers are normal, unstable angina is present (Fig. 5.2). STEMI and UA/NSTEMI syndromes are managed differently and have different prognoses. Many more patients have UA/NSTEMI than have STEMI at presentation.

ST-Segment Elevation Myocardial Infarction

Mortality rates from STEMI have declined steadily because of early therapeutic interventions such as angioplasty, thrombolysis and aspirin, heparin, and statin therapy. However, the mortality rate of acute STEMI remains significant. In-hospital mortality rate after admission for AMI has declined from 10% to 5% over the past decade. One-year mortality rate is about

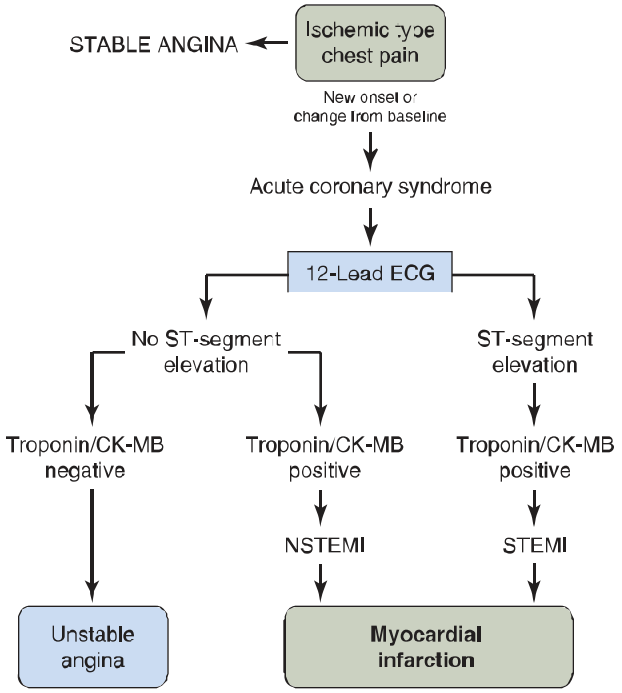

Fig. 5.2 Terminology of acute coronary syndrome. *CK-MB*, Creatine kinase, myocardial-bound isoenzyme; *ECG*, electrocardiogram; *NSTEMI*, non–ST-segment elevation myocardial infarction; *STEMI*, ST-segment elevation myocardial infarction. (Adapted from Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol.* 2000;36:959–969.)

15%. Advanced age (≥ 75 years) consistently emerges as one of the principal determinants of early mortality in patients with STEMI. Coronary angiography has documented that the majority of STEMIs are caused by thrombotic occlusion of a coronary artery. In rare cases STEMI may be due to coronary occlusion caused by coronary emboli, congenital abnormalities, coronary spasm, or inflammatory diseases.

The long-term prognosis after an acute STEMI is determined principally by the severity of residual left ventricular dysfunction, the presence and degree of residual ischemia, and the presence of malignant ventricular dysrhythmias. Most deaths that occur during the first year after hospital discharge take place within the first 3 months. Ventricular function can be substantially improved during the first few weeks after an AMI, particularly in patients in whom early reperfusion is achieved. Therefore measurement of ventricular function 2 to 3 months after an MI is a more accurate predictor of long-term prognosis than measurement of ventricular function during the acute phase of the infarction.

TABLE 5.3 Criteria for Diagnosis of Acute Myocardial Infarction

The term *myocardial infarction* should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers, preferably troponin (with at least one value above the 99th percentile of the upper reference limit) **AND** evidence of myocardial ischemia indicated by at least one of the following:
- Symptoms of ischemia
- ECG changes indicative of new ischemia (new ST-T changes, new left bundle branch block)
- Development of pathologic Q waves on the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

From Thygesen K, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J.* 2019;40(3):237–269.

Pathophysiology

Atherosclerosis is recognized as an inflammatory disease. The presence of inflammatory cells in atherosclerotic plaques suggests that inflammation is important in the cascade of events leading to plaque rupture. Indeed, serum markers of inflammation such as C-reactive protein and fibrinogen are increased in those at greatest risk of developing coronary artery disease.

STEMI occurs when coronary blood flow decreases abruptly. This decrease in blood flow is attributable to acute thrombus formation at a site where an atherosclerotic plaque fissures, ruptures, or ulcerates. This creates a local environment that favors thrombogenesis. Typically, vulnerable plaques (i.e., those with rich lipid cores and thin fibrous caps) are most prone to rupture. A platelet monolayer forms at the site of ruptured plaque, and various chemical mediators such as collagen, ADP, epinephrine, and serotonin stimulate platelet aggregation. The potent vasoconstrictor thromboxane A_2 is released, which further compromises coronary blood flow. Glycoprotein IIb/IIIa receptors on the platelets are activated, which enhances the ability of platelets to interact with adhesive proteins and other platelets and causes growth and stabilization of the thrombus. Further activation of coagulation leads to strengthening of the clot by fibrin deposition. This makes the clot more resistant to thrombolysis. It is rather paradoxical that plaques that rupture and lead to acute coronary occlusion are rarely of a size that causes significant coronary obstruction. By contrast, flow-restrictive plaques that produce chronic stable angina and stimulate development of collateral circulation are less likely to rupture.

Diagnosis

Criteria for the definition of an AMI have been revised (Table 5.3). Now this diagnosis requires detection of a rise and/or fall in cardiac biomarkers (preferably troponin with at least one value above the 99th percentile of the upper reference limit) and evidence of myocardial ischemia by one of the following: (1) symptoms of ischemia; (2) ECG changes indicative of new ischemia, such as new ST-T changes or new left bundle branch block (LBBB); (3) development of pathologic Q waves on the ECG; (4) imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality; or (5) identification of an intracoronary thrombus by angiography or autopsy. Contemporary studies using MRI suggest that the development of a Q wave on the ECG is more dependent on the volume of the infarcted tissue than the transmurality of the infarction.

Almost two-thirds of patients describe new-onset angina pectoris or a change in their anginal pattern during the 30 days preceding an AMI. The pain is often more severe than the previous angina pectoris and does not resolve with rest. It may radiate as high as the occipital area but not below the umbilicus. Other potential causes of severe chest pain (pulmonary embolism, aortic dissection, spontaneous pneumothorax, pericarditis, cholecystitis) should be considered. About a quarter of patients, especially the elderly and those with diabetes, have no or only mild pain at the time of AMI. Sometimes STEMI may masquerade as acute heart failure, syncope, stroke, or shock, with the patient's ECG showing ST-segment elevation or a new LBBB.

On physical examination, patients typically appear anxious, pale, and diaphoretic. Sinus tachycardia is usually present. Hypotension caused by left or right ventricular dysfunction or cardiac dysrhythmias may be present. Rales signal congestive heart failure due to left ventricular dysfunction. A cardiac murmur may indicate ischemic mitral regurgitation.

Laboratory studies. Troponin is a cardiac-specific protein and biochemical marker for AMI. An increase in the circulating concentration of troponin occurs early after myocardial injury. Levels of cardiac troponins (troponin T or I) increase within 3 hours after myocardial injury and remain elevated for 7 to 10 days. Elevated troponins and the ECG are powerful predictors of adverse cardiac events in patients with anginal pain. Troponin is more specific than CK-MB for determining myocardial injury. The currently accepted definition of AMI recommends assessing the magnitude of the infarction by measuring how much the

cardiac biomarker level is elevated above the normal reference range (Fig. 5.3).

Imaging studies. Patients with typical ECG evidence of AMI do not require evaluation with echocardiography. However, echocardiography is useful in patients with LBBB or an abnormal ECG in whom the diagnosis of AMI is uncertain and in patients with suspected aortic dissection. Echocardiography will demonstrate regional wall motion abnormalities in most patients with AMI. The time required to perform myocardial perfusion imaging and the inability to differentiate between new and old MI limits the utility of radionuclide imaging in the early diagnosis of AMI.

Treatment

Early treatment of AMI reduces morbidity and mortality. Initial steps include administering oxygen to all patients. Pain relief, usually provided by intravenous (IV) morphine and/or sublingual nitroglycerin, is necessary to reduce catecholamine release and the resultant increase in myocardial oxygen requirements. All patients with suspected or definite AMI should receive aspirin. Patients with allergy to aspirin should receive a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor). The combination of aspirin and $P2Y_{12}$ inhibitors improves outcomes. Alternatively, platelet glycoprotein IIb/IIIa inhibitors can be used even if urgent CABG is likely. Unfractionated heparin is frequently used in combination with antiplatelet drugs, especially if thrombolytic therapy or PCI is planned. ¯ blockers relieve ischemic chest pain, infarct size, and life-threatening dysrhythmias. ⊥ blockers are administered to patients in hemodynamically stable condition who are not in heart failure, not in a low cardiac output state, and not at risk of cardiogenic shock. ⊥ blockers are not given to those with heart block. *The primary goal in management of STEMI is to reestablish blood flow in the obstructed coronary artery as soon as possible.* This can be achieved by thrombolytic therapy or PCI. The time from the onset of symptoms to reperfusion strongly influences the outcome of an acute STEMI. Glucocorticoids and other nonsteroidal antiinflammatory drugs (NSAIDs) should be avoided (except for aspirin) in patients with STEMI.

Reperfusion therapy. Thrombolytic therapy with tissue plasminogen activator (tPA), streptokinase, reteplase, or tenecteplase should be initiated within 30 to 60 minutes of hospital arrival and within 12 hours of symptom onset. Thrombolytic therapy restores normal antegrade blood flow in the occluded coronary artery. Dissolution of the clot by thrombolytic therapy becomes much more difficult if therapy is delayed. The most feared complication of thrombolytic therapy is intracranial hemorrhage. This is most likely in elderly patients (⊥75 years) and in those with uncontrolled hypertension. Patients who have gastrointestinal bleeding or have recently undergone surgery are also at increased risk of bleeding complications with thrombolysis. Contraindications to fibrinolytic therapy include uncontrolled hypertension (systolic ¯ 180 mm Hg and/or diastolic ¯ 110 mm Hg), hemorrhagic strokes within the previous year, known intracranial neoplasm, recent head trauma, active or recent internal bleeding (within 3 weeks), or suspected aortic dissection.

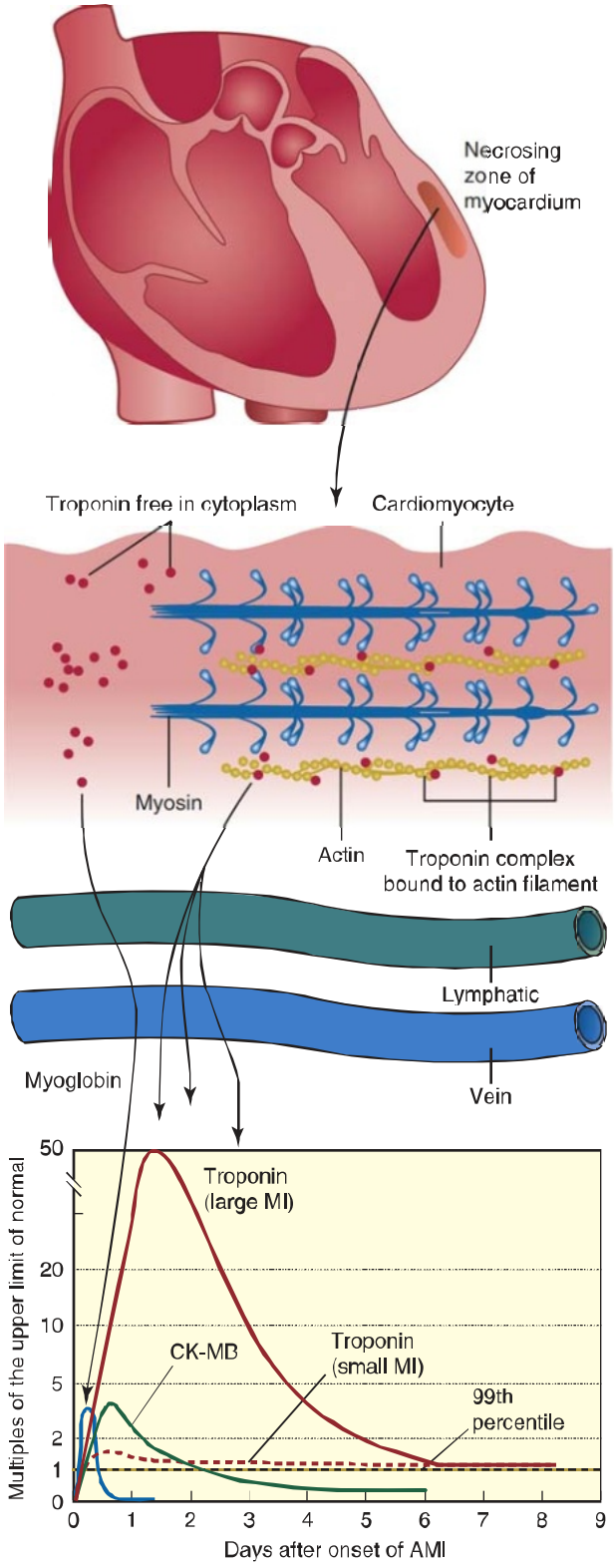

Fig. 5.3 Rate and extent of rise of cardiac troponin and myocardial creatine kinase (CK-MB) levels after a typical acute myocardial infarction (AMI). Cardiac microinfarctions can raise troponin levels without increasing CK-MB levels. (From Antman EM. ST-segment myocardial infarction: pathology, pathophysiology, and clinical features. In: Bonow RO, Mann DL, Zipes DP, et al, eds, *Braunwald's Heart Disease*. Philadelphia, PA: Saunders; 2012 [fig. 54–14].)

Percutaneous coronary intervention. PCI may be preferable to thrombolytic therapy for restoring flow to an occluded coronary artery if appropriate resources are available. Ideally, angioplasty should be performed within 90 minutes of arrival at the healthcare facility and within 12 hours of symptom onset. It is the treatment of choice in patients with a contraindication to thrombolytic therapy, in those with severe heart failure and/or pulmonary edema, when symptoms have been present for at least 2 to 3 hours, or when the clot becomes more mature and less likely to be lysed by fibrinolytic drugs. The combined use of intracoronary stents and antiplatelet drugs during emergency PCI provides the maximum chance of achieving normal antegrade coronary blood flow and decreases the need for a subsequent revascularization procedure. In some patients an integrated reperfusion strategy is adopted where fibrinolytic therapy is followed later by coronary angiography if there is evidence of persistent ischemia (rescue PCI) or inducible ischemia (urgent PCI).

Coronary artery bypass graft surgery. CABG can restore blood flow in an occluded coronary artery, but reperfusion is achieved faster with thrombolytic therapy or coronary angioplasty. Emergency CABG is reserved for patients in whom angiography reveals coronary anatomy that precludes PCI, patients with a failed angioplasty, and those with evidence of infarction-related ventricular septal rupture or mitral regurgitation. Patients with ST-segment elevation who develop cardiogenic shock, LBBB, or a posterior wall MI within 36 hours of an acute STEMI are also candidates for early revascularization. Mortality from CABG is significant during the first 3 to 7 days after AMI.

Adjunctive medical therapy

Antithrombotic agents. IV heparin therapy is commonly administered after thrombolytic therapy to decrease the risk of thrombus regeneration. A disadvantage of unfractionated heparin is the variability in the dose response due to its binding with plasma proteins other than antithrombin. Low-molecular-weight heparin (LMWH) provides a more predictable pharmacologic effect, a long plasma half-life, and a more practical means of administration (subcutaneous), without the need to monitor the activated partial thromboplastin time. Thus LMWH is an excellent alternative to unfractionated heparin. Direct thrombin inhibitors such as bivalirudin can be used in patients with a history of heparin-induced thrombocytopenia.

⊥ blockers. Administration of ⊥ blockers is associated with a significant decrease in early (in-hospital) and long-term mortality and myocardial reinfarction. Early administration of ⊥ blockers can decrease infarct size by decreasing heart rate, blood pressure, and myocardial contractility and improving the myocardial oxygen supply-demand relationship. In the absence of specific contraindications, it is recommended that patients receive ⊥ blockers as early as possible after AMI. ⊥ blocker therapy should be continued indefinitely.

Inhibition of the renin-angiotensin-aldosterone system. ACE inhibitors decrease the mortality rate after STEMI, and the mortality benefits are additive to those achieved with aspirin and ⊥ blockers. All patients with a large anterior wall MI, clinical evidence of left ventricular failure, an ejection fraction less than 40%, or diabetes should be treated with ACE inhibitors or angiotensin II receptor blockers. Barring significant renal dysfunction or hyperkalemia, aldosterone blockade should also be considered in this patient population.

Other agents. Calcium channel blockers should not be administered routinely but should be reserved for patients with persistent myocardial ischemia despite optimal use of aspirin, ⊥ blockers, nitrates, and heparin. Glycemic control is part of the standard care of diabetic patients with AMI. Aggressive statin therapy to achieve LDL levels less than 70 mg/dL is considered standard of care in patients who have sustained AMI. Routine administration of magnesium is not recommended, but magnesium therapy is indicated in patients with torsade de pointes ventricular tachycardia. Statins have strong immune-modulating effects and should be started as soon as possible after MI, especially in patients on long-term statin therapy.

Non–ST-Segment Elevation ACS (UA/NSTEMI)

UA/NSTEMI results from a reduction in myocardial oxygen supply. Typically, five pathophysiologic processes may contribute to the development of UA/NSTEMI: (1) rupture or erosion of a coronary plaque that leads to nonocclusive thrombosis; (2) dynamic obstruction due to vasoconstriction (Prinzmetal-variant angina, cold, cocaine use); (3) worsening coronary luminal narrowing due to progressive atherosclerosis, in-stent restenosis, or narrowing of CABGs; (4) inflammation (vasculitis); or (5) myocardial ischemia due to increased oxygen demand (sepsis, fever, tachycardia, anemia, thyrotoxicosis). Embolization of platelets and clot fragments into the coronary microvasculature leads to microcirculatory ischemia and infarction that can result in elevation of cardiac biomarker levels without elevation of the ST segments.

Diagnosis

UA/NSTEMI has three principal presentations: angina at rest (typically lasting □ 10 minutes unless interrupted by antianginal medication), chronic angina pectoris that becomes more frequent and more easily provoked, and new-onset angina that is severe, prolonged, or disabling. UA/NSTEMI can also present with hemodynamic instability or congestive heart failure. Signs of congestive heart failure (S_3 gallop, jugular venous distention, rales, peripheral edema) or ischemia-induced papillary muscle dysfunction causing acute mitral regurgitation may be evident. Fifty percent of patients with UA/NSTEMI have significant ECG abnormalities, including transient ST-segment elevation, ST depression, and/or T-wave inversion. Significant ST-segment depression in two or more contiguous leads and/or deep symmetric T-wave inversion (⊥ 0.3 mV), especially in the setting of chest pain, is highly consistent with a diagnosis of myocardial ischemia and UA/NSTEMI. Elevated levels of cardiac biomarkers or a new regional wall motion abnormality on echocardiogram establish the diagnosis of AMI. Approximately two-thirds of patients who would have been classified as having unstable angina have now been found to show evidence of myocardial necrosis based on sensitive cardiac enzyme assays. They should be classified as having NSTEMI.

Treatment

Management of UA/NSTEMI consists of an acute phase, which is directed at decreasing myocardial oxygen demand and stabilizing culprit lesion(s), and a longer-term phase, which involves therapies directed at prevention of disease progression and future plaque erosion and rupture.

Bed rest, supplemental oxygen, analgesia, and ¬ blocker therapy are indicated in the acute phase. Sublingual or IV nitroglycerin may improve myocardial oxygen supply. Calcium channel blockers can also be used if ischemia persists despite the use of _ blockers and nitrates. Antithrombotic therapy consisting of antiplatelet and anticoagulant drugs represent a second cornerstone of therapy. Aspirin, clopidogrel, prasugrel, or ticagrelor and heparin therapy (unfractionated heparin or LMWH) are strongly recommended to decrease further thrombus formation. Fondaparinux, a specific factor Xa inhibitor, can also be used as an anticoagulant. Glycoprotein IIb/IIIa agents may be used as an alternative or in addition to other antiplatelet drugs in certain clinical situations. Thrombolytic therapy is not indicated in UA/NSTEMI and has been shown to increase mortality. Older age (¬65 years), positive finding for cardiac biomarkers, rales, hypotension, tachycardia, and decreased left ventricular function (ejection fraction ı 40%) are associated with increased mortality. Patients at high risk include the elderly, those with ischemic symptoms in the preceding 48 hours, those with prolonged chest pain (120 minutes), those with heart failure or hemodynamic instability, those with sustained ventricular dysrhythmias, those who had a PCI within the past 6 months or had prior CABG surgery, those with elevated troponin levels, and those with angina at low-level activity. These patients should be considered for early invasive evaluation, which includes coronary angiography and revascularization by PCI or CABG if needed. Patients with mild to moderate renal insufficiency (creatinine clearance ¯30 mL/min) may also benefit from early invasive treatment. Patients at lower risk can be treated medically and undergo stress testing at a later time. Coronary angiography often follows the demonstration of significant ischemia on stress testing.

COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

Postinfarction Ischemia

Myocardial ischemia occurs in about one-third of patients after MI. It is more common after STEMI compared to NSTEMI. It is typically managed with ⌐ blockers, nitrovasodilators, antiplatelet agents, and anticoagulants. If medical management does not control the symptoms, patients may require early catheterization and revascularization by PCI or surgery.

Cardiac Dysrhythmias

Cardiac dysrhythmias, especially ventricular dysrhythmias, are a common cause of death during the early period following AMI.

Ventricular fibrillation occurs in 3% to 5% of patients with AMI, usually during the first 4 hours after the event. Rapid defibrillation with 200 to 300 J of energy is necessary when ventricular fibrillation occurs. Amiodarone is regarded as one of the most effective antidysrhythmic drugs available for control of ventricular tachydysrhythmias, especially after AMI. Administration of ⊥ blockers may decrease the early occurrence of ventricular fibrillation. Hypokalemia and hypomagnesemia are risk factors for ventricular fibrillation and should be treated. Ventricular fibrillation is often fatal when it occurs in patients with hypotension and/or congestive heart failure.

Ventricular tachycardia is common in AMI. Short periods of nonsustained ventricular tachycardia do not appear to predispose a patient to sustained ventricular tachycardia or ventricular fibrillation. Sustained or hemodynamically significant ventricular tachycardia must be treated promptly with electrical cardioversion. Asymptomatic ventricular tachycardia can be treated with IV amiodarone or lidocaine. Implantation of a cardioverter-defibrillator may be indicated in patients who experience recurrent ventricular tachycardia or ventricular fibrillation despite adequate revascularization.

Atrial fibrillation and atrial flutter are the most common atrial dysrhythmias seen with AMI. They occur in about 20% of patients. Precipitating factors include hypoxia, acidosis, heart failure, pericarditis, and sinus node ischemia. Atrial fibrillation may also result from atrial ischemia or from an acute increase in left atrial pressure as a result of left ventricular dysfunction. When atrial fibrillation is hemodynamically significant, cardioversion is necessary. If atrial fibrillation is well tolerated, ¯ blockers or calcium channel blockers can be used to control the ventricular response.

Sinus bradycardia is common after AMI, particularly in patients with inferior wall MI. This may reflect increased parasympathetic nervous system activity or acute ischemia of the sinus node or atrioventricular node. Treatment with atropine and/or a temporary cardiac pacemaker is needed only when there is hemodynamic compromise from the bradycardia. First-degree block (prolonged PR interval) is common and does not require treatment. Second- or third-degree atrioventricular heart block occurs in about 20% of patients with inferior wall MI and requires treatment if accompanied by severe bradycardia. Complete heart block occurs in about 5% of patients with acute inferior infarction and often requires temporary or permanent cardiac pacing.

Pericarditis

Acute pericarditis is a common complication that occurs a few days after MI in 10% to 15% of patients. It may cause chest pain that can be confused with continuing or recurrent angina. However, in contrast to the pain of myocardial ischemia, the pain of pericarditis is pleuritic, gets worse with inspiration or lying down, and may be relieved by changes in posture. It typically presents 2 to 7 days after MI. A pericardial friction rub can be heard but is often transient and positional. Diffuse ST-segment and T-wave changes may be present on the ECG. In the absence of a significant pericardial effusion, treatment of pericarditis is aimed at relieving the chest pain. Aspirin is recommended initially. Although indomethacin and corticosteroids can relieve the symptoms of pericarditis dramatically, they should be avoided because they impair infarct healing and predispose to myocardial

rupture. It is recommended that steroid therapy be deferred for at least 4 weeks after AMI. Dressler syndrome (post-MI syndrome) is a delayed form of pericarditis developing several weeks to months after AMI. It is thought to be immune mediated and is typically managed with NSAIDs or corticosteroids.

Mitral Regurgitation

Mitral regurgitation due to ischemic injury to a papillary muscle and/or the ventricular muscle to which the papillary muscles attach can occur 3 to 7 days after AMI. Severe mitral regurgitation is rare and usually results from rupture of a papillary muscle. Severe mitral regurgitation is 10 times more likely to occur after an inferior wall MI than after an anterior wall MI. Severe acute mitral regurgitation typically results in pulmonary edema and cardiogenic shock. Total papillary muscle rupture usually leads to death within 24 hours. Prompt surgical repair is required. Treatments that decrease left ventricular afterload and improve coronary perfusion, such as intraaortic balloon counterpulsation, can decrease the regurgitant volume and increase forward flow and cardiac output until surgery can be accomplished.

Ventricular Septal Rupture

Ventricular septal rupture (VSR) is a rare event (0.2%) and is more likely after an anterior wall MI. The characteristic holosystolic murmur of ventricular septal rupture may be difficult to distinguish from the murmur of severe mitral regurgitation. The diagnosis is made by echocardiography. Current guidelines recommend immediate surgical closure of VSR, irrespective of the patient's hemodynamic status, to avoid further hemodynamic deterioration. Intraaortic balloon counterpulsation (IABP) support is recommended as a bridge to surgery. If the defect is left untreated, mortality approaches more than 80%.

Myocardial Dysfunction

AMI is often complicated by some degree of left ventricular dysfunction. Dyspnea, orthopnea, rales, and arterial hypoxemia indicate this left ventricular dysfunction. The management of congestive heart failure in association with AMI is similar to that of acute heart failure secondary to other forms of heart disease. It is typically managed with supplemental oxygen, diuretics, morphine, nitrovasodilators (nitroglycerin in IV, sublingual, or transdermal forms), afterload reduction, and potential inotropic support. Nitroglycerin helps reduce preload and pulmonary congestion and improves left ventricular function. If blood pressure is acceptable, inotropes are typically avoided since they can increase myocardial oxygen demand.

Cardiogenic Shock

The term *cardiogenic shock* is restricted to an advanced form of acute heart failure in which the cardiac output is insufficient to maintain adequate perfusion of the brain, kidneys, and other vital organs. Hypotension and oliguria persist after relief of anginal pain, abatement of excess sympathetic nervous system activity, correction of hypovolemia, and treatment of dysrhythmias. Systolic blood pressure is low, and there may be associated pulmonary edema and arterial hypoxemia. Cardiogenic shock is usually a manifestation of infarction of more than 40% of the left ventricular myocardium. Though the incidence of cardiogenic shock after AMI has decreased from 20% to 7%, in-hospital mortality of cardiogenic shock is between 40% and 60%.

Important in the management of cardiogenic shock is the diagnosis and prompt treatment of potentially reversible mechanical complications of MI. These include (1) rupture of the left ventricular free wall, septum, or papillary muscles; (2) cardiac tamponade; and (3) acute, severe mitral regurgitation. Echocardiography is extremely helpful in diagnosing and quantifying these pathologic conditions. Treatment of cardiogenic shock depends on blood pressure and peripheral perfusion. Norepinephrine, vasopressin, dopamine, or dobutamine may be administered in an attempt to improve blood pressure and cardiac output. If the blood pressure is adequate, nitroglycerin can be used to decrease left ventricular preload and afterload. Concomitant pulmonary edema may require the use of morphine, diuretics, and mechanical ventilation. Circulatory assist devices can help sustain viable myocardium and support cardiac output until revascularization can be performed. Left ventricular assist devices (LVADs) improve cardiac output much more than IABP does. IABP is no longer recommended for the management of cardiogenic shock with left ventricular failure. Mechanical circulatory support devices to support the left, right, or both ventricles can be placed percutaneously or surgically. Rapid revascularization of the infarct-related artery is the only evidence-based treatment strategy for mortality reduction in cardiogenic shock in the setting of AMI.

Myocardial Rupture

Myocardial rupture occurs rarely and usually causes acute cardiac tamponade and death. This typically occurs within the first week after an MI and presents with sudden hemodynamic collapse or sudden death. In only an extremely small percentage of cases is it possible to have time for medical stabilization and definitive surgical repair.

Right Ventricular Infarction

Right ventricular infarction occurs in about one-third of patients with acute inferior wall MI. Isolated right ventricular infarction is very unusual. The right ventricle has a more favorable oxygen supply/demand ratio than the left ventricle. This is because of its smaller muscle mass and low intracavitary pressures during systole, which allows coronary blood flow during both systole and diastole. The clinical triad of hypotension, increased jugular venous pressure, and clear lung fields in a patient with an inferior wall MI is virtually pathognomonic for right ventricular infarction. Kussmaul sign (distention of the internal jugular vein on inspiration) is often seen. Right ventricular dilation, right ventricular asynergy, and abnormal motion of the interventricular septum can be seen on echocardiography.

Recognition of right ventricular infarction is important because some pharmacologic treatments for left ventricular failure may worsen right ventricular failure. In particular, administration of vasodilators and diuretics is very dangerous. Initial therapy for right ventricular failure consists of IV fluid administration. If hypotension persists, inotropic support, with

or without mechanical circulatory support, may be necessary. Cardiogenic shock, although uncommon, is the most serious complication of right ventricular infarction. Improvement in right ventricular function generally occurs over time, which suggests reversal of "ischemic stunning" of the right ventricular myocardium. About one-third of patients with right ventricular infarction develop atrial fibrillation. Heart block may occur in as many as 50% of these patients. Both of these situations may produce severe hemodynamic compromise. Third-degree atrioventricular heart block should be treated promptly with temporary atrioventricular pacing, in recognition of the value of atrioventricular synchrony in maintaining ventricular filling in the ischemic, and therefore noncompliant, right ventricle.

Mural Thrombus and Stroke

Infarction of the anterior wall and apex of the left ventricle results in thrombus formation at the location of the infarction in as many as one-third of patients. The risk of systemic embolization and the possibility of an ischemic stroke are then very significant in these patients. Echocardiography is used to detect a left ventricular thrombus. The presence of such a thrombus is an indication for immediate anticoagulation with heparin followed by 3 months of anticoagulation with warfarin.

Thrombolytic therapy is associated with hemorrhagic stroke in 0.3% to 1% of patients. The stroke is usually evident within the first 24 hours after the thrombolytic treatment and is associated with high mortality.

PERIOPERATIVE IMPLICATIONS OF PERCUTANEOUS CORONARY INTERVENTION

Percutaneous transluminal coronary angioplasty (PTCA) was introduced as an alternative to CABG to mechanically open a coronary artery stenosis. It was effective, but restenosis at the angioplasty site occurred in 15% to 60% of patients within a few months. To solve the problem of abrupt coronary closure after angioplasty, bare-metal stents were introduced. However, coronary restenosis due to neointimal hyperplasia was observed in 10% to 30% of patients with bare-metal stents. Stents coated with drugs (drug-eluting stents) were then introduced to reduce neointimal hyperplasia. The drugs in these stents do this by preventing cell division. First-generation stents released sirolimus or paclitaxel and had stainless steel platforms, whereas second-generation stents release everolimus, biolimus, or zotarolimus and feature cobalt-chrome or platinum-chrome platforms with thinner strut thickness and more biocompatible, durable polymer coatings. These second-generation stents have almost completely replaced the older coated stents. The two principal issues related to PCI with stent placement now are thrombosis and an increased risk of bleeding due to dual antiplatelet therapy.

Percutaneous Coronary Intervention and Thrombosis

Mechanically opening a coronary artery by angioplasty causes vessel injury, especially destruction of the endothelium. This makes the area prone to thrombosis. It takes about 2 to 3 weeks for the vessel to reendothelialize after balloon angioplasty. After bare-metal stent placement, reendothelialization can take up to 12 weeks, and a drug-eluting stent may not be completely endothelialized even after a full year. Thus thrombosis after angioplasty and stent placement is a major concern.

Stent thrombosis is categorized by the time interval between its occurrence and the date of the PCI: acute (within 24 hours), subacute (between 2 and 30 days), late (between 30 days and 1 year), and very late (after 1 year). Early stent thrombosis is usually mechanical in origin and due to coronary artery dissection or underexpansion of the stent. In contrast, late stent thrombosis is typically related to stent malposition, abnormal reendothelialization, or hypersensitivity to the stent. Use of second-generation stents is associated with less late and very late stent thrombosis. Platelets play an important role in the pathophysiology of stent thrombosis, and use of antiplatelet drugs is critical until the stent becomes less prone to thrombosis. Platelets can be activated by many triggers, and there is significant redundancy and crosstalk between these pathways. Thus multiple pathways must be blocked to achieve clinically effective platelet inhibition.

Discontinuation of antiplatelet therapy increases the risk of stent thrombosis. Dual antiplatelet therapy (aspirin with a $P2Y_{12}$ inhibitor) is better in preventing stent thrombosis compared to aspirin alone. $P2Y_{12}$ inhibitor discontinuation is the most significant independent predictor of stent thrombosis. The probability of a thrombotic event is increased more than three- to ninefold after discontinuation of these drugs. Current recommendations for dual antiplatelet therapy are as follows: It is needed for at least 2 weeks after balloon angioplasty without stenting, for at least 6 weeks after bare-metal stent placement, and for at least 1 year after drug-eluting stent placement. Some observational studies suggest that earlier discontinuation of dual antiplatelet therapy might be safe after implantation of either zotarolimus or everolimus drug-eluting stents.

Other factors can predispose to stent thrombosis, and these may be important in the perioperative period. Patients at risk for stent thrombosis include those with ACS, a low ejection fraction, diabetes, renal impairment, advanced age, prior brachytherapy, and cancer. Factors related to coronary anatomy (stent length, placement of multiple stents, bifurcated lesions) may also predispose to stent thrombosis. Both elective surgery and emergency surgery increase the risk of stent thrombosis because of the prothrombotic state present during the perioperative period.

Surgery and Risk of Stent Thrombosis

Surgery and Bare-Metal Stents

The frequency of major adverse cardiac events (MACE; death, MI, stent thrombosis, or the need for repeat revascularization) was about 10% when noncardiac surgery was performed within 4 weeks of PCI. This risk decreased to about 4% when surgery was performed between 31 and 90 days after PCI and to about 3% when surgery was performed more than 90 days after PCI. The

risk of death, MI, stent thrombosis, and urgent revascularization is increased by 5% to 30% if surgery is performed within the first 6 weeks after bare-metal stent placement.

Surgery and Drug-Eluting Stents

The absolute risk of thrombosis during noncardiac surgery 6 weeks after drug-eluting stent implantation is low but higher than in the absence of surgery. This is attributed to the delayed endothelialization seen with drug-eluting stents. The incidence of MACE is quite significant if dual antiplatelet therapy is discontinued and noncardiac surgery is performed within 1 year of drug-eluting stent placement. This is particularly true for the first-generation stents.

The risk of adverse events is higher in patients who undergo emergency surgery. In patients with bare-metal stents, emergency surgery increases the adverse event rate threefold compared to elective surgery. For patients with drug-eluting stents, there is a 3.5-fold increase in adverse events.

Risk of Bleeding Related to Antiplatelet Drugs

It is predictable that patients who are taking antiplatelet drugs will have a higher chance of bleeding, which can be of major concern in the perioperative period. It has been shown that continuing aspirin therapy increases the risk of bleeding by a factor of 1.5, but the severity of adverse events is not increased. The addition of clopidogrel to aspirin increases the relative risk of bleeding by 50%. So far, no increase in mortality has been noted except with intracranial surgery. In patients who have received coronary stents and must undergo surgical procedures that mandate discontinuation of $P2Y_{12}$ platelet receptor–inhibitor therapy, it is recommended that aspirin be continued if possible and that the $P2Y_{12}$ platelet receptor–inhibitor be discontinued preoperatively and restarted as soon as possible after surgery.

Bleeding Versus Stent Thrombosis in the Perioperative Period

Discontinuing antiplatelet therapy causes a significant increase in coronary, cerebrovascular, and peripheral vascular events. However, in the perioperative patient the risk of bleeding has to be weighed against the risk of thrombosis. In many situations the risk of coronary thrombosis is high, and the consequences of coronary thrombosis could be catastrophic; on the other hand, although the risk of bleeding is increased, bleeding could be manageable and may not contribute to significant morbidity and mortality. In such cases it may be prudent to continue antiplatelet therapy. However, some individuals are more prone to bleeding or need to undergo procedures in which bleeding can have severe consequences. These include neurosurgery, spinal cord decompression, aortic aneurysm surgery, and prostatectomy, among others. In such cases the risk of bleeding may outweigh the risk of thrombosis, so antiplatelet therapy should be stopped before these operations (at least 5 days before surgery for clopidogrel or ticagrelor and 7 days for prasugrel) and resumed as soon as feasible postoperatively. Some patients come for surgery receiving antiplatelet therapy for secondary prevention of cardiovascular events. These patients have no stents, so the risk of bleeding will outweigh the risk of cardiovascular events. In this situation the antiplatelet drugs can be temporarily withheld for high-risk surgery.

Perioperative Management of Patients With Stents

Five factors should be considered when caring for a patient with a coronary stent: (1) timing of the operation after PCI, also called the PCI-to-surgery interval; (2) continuation of dual antiplatelet therapy; (3) perioperative monitoring strategies; (4) anesthetic technique; and (5) immediate availability of an interventional cardiologist.

PCI-to-Surgery Interval

The risk of stent thrombosis is significant in the first month after stent placement and progressively decreases as the time from PCI to surgery increases. The longer one waits after stent placement, the better it is. For patients with bare-metal stents, waiting at least 30 days (preferably 90 days) before elective surgery is recommended. In patients with drug-eluting stents, waiting at least 1 year before elective noncardiac surgery is recommended (Table 5.4).

Continuation of Dual Antiplatelet Therapy

Dual antiplatelet therapy should be continued for at least 6 weeks after bare-metal stent placement and 1 year after drug-eluting stent placement. If dual antiplatelet therapy must be stopped, at least the aspirin portion of the therapy should be continued. Aspirin should be stopped before elective surgery only when absolutely indicated. Although less than 6 weeks after bare-metal stent placement and less than 1 year after drug-eluting stent placement is considered a highly vulnerable period for stent thrombosis, stent thrombosis can occur at any time. Intraoperative and postoperative monitoring should be based on the risk of the particular surgery, overall patient condition, and the interval between PCI and surgery. Patients who are in the vulnerable period should be monitored very closely, especially if antiplatelet therapy was discontinued for the surgery. In a bleeding patient, platelets can be administered to counteract the effects of antiplatelet drugs, but the effectiveness of the platelet infusions will depend on the timing of the last dose of antiplatelet drug. For example, platelet transfusions can be administered as soon as

TABLE 5.4 Recommended Time Intervals to Wait for Elective Noncardiac Surgery After Coronary Revascularization

Procedure	Time to Wait for Elective Surgery
Angioplasty without stenting	2–4 weeks
Bare-metal stent placement	At least 30 days; 12 weeks preferable
Coronary artery bypass grafting	At least 3 weeks; 12 weeks preferable
Drug-eluting stent placement	At least 3 months; at least 12 months after acute coronary syndrome

4 hours after discontinuation of clopidogrel, but they will be most effective 24 hours after the last dose of clopidogrel.

Perioperative Monitoring Strategies

Practitioners should have a high index of suspicion for cardiac events and concentrate on monitoring for myocardial ischemia and infarction. Intraoperative continuous ECG monitoring with ST-segment analysis is very helpful in monitoring for myocardial ischemia. Any angina in a patient with a stent should initiate an evaluation to rule out AMI, and an urgent cardiology evaluation should be sought.

Anesthetic Technique

Use of neuraxial anesthetic techniques in patients who are receiving dual antiplatelet therapy is controversial. However, both the American Society of Regional Anesthesia and Pain Medicine (ASRA) and the European Society of Anaesthesiology have adopted a conservative approach in this matter. Use of neuraxial blockade is not encouraged in patients who are receiving dual antiplatelet therapy. The risk of developing a spinal hematoma exists not only at the time of placement of the catheter but also at the time of its removal. The most up-to-date recommendations regarding waiting times before placement or removal of an epidural catheter and administration of antiplatelet agents are available online at www.asra.com.

Immediate Availability of an Interventional Cardiologist

Although many MIs in the perioperative period are silent, *any* angina in a patient with a stent should prompt evaluation to rule out AMI. There should be immediate access to interventional cardiology services. Once the diagnosis of AMI or acute stent thrombosis is made or considered, triage to interventional cardiology within 90 minutes is strongly recommended. Mortality increases substantially if reperfusion is delayed. Ambulatory surgical facilities, endoscopy suites, and other non–hospital-based operating locations without these resources on site must develop a relationship with interventional cardiologists that can facilitate rapid transfer if needed.

PERIOPERATIVE MYOCARDIAL INFARCTION

The incidence of perioperative cardiac injury is a cumulative result of the patient's preoperative medical condition, the specific surgical procedure, the expertise of the surgeon, the diagnostic criteria used to define MI, and the overall medical care at a particular institution. The risk of perioperative death due to cardiac causes is less than 1% in patients who do not have ischemic heart disease. Myocardial injury, defined as an elevated troponin level above the 99th percentile, occurs in up to 20% of patients after noncardiac surgery. The incidence of perioperative MI (PMI) in patients who undergo elective high-risk vascular surgery is 5% to 15%. This risk is even higher for emergency surgery. Patients who undergo urgent hip surgery have an incidence of PMI of 5% to 7%, whereas fewer than 3% of patients who undergo elective total hip or knee arthroplasty have a PMI. Early mortality after a PMI ranges from 3.5% to 25% and is higher in patients with marked troponin elevations compared to patients with minor troponin elevation.

Pathophysiology

Myocardial ischemia occurs whenever myocardial oxygen supply does not match myocardial oxygen demand. PMI is one of the most important predictors of short- and long-term morbidity and mortality associated with noncardiac surgery. Unfortunately, the exact mechanism for PMI remains uncertain and a subject of debate and controversy. The interaction between morphologic and functional factors is unpredictable. Some older pathologic and angiographic studies suggested that the etiology of PMI resembles that in the nonsurgical setting (i.e., plaque rupture was the cause of PMI in 50% of the cases). Endothelial injury at the site of a plaque rupture triggers the cascade of platelet aggregation and release of mediators. Aggregation of platelets and activation of other inflammatory and noninflammatory mediators potentiates thrombus formation and leads to dynamic vasoconstriction distal to the thrombus. The combined effects of dynamic and physical blood vessel narrowing cause ischemia and/or infarction. In the postoperative period, changes in blood viscosity, catecholamine concentrations, cortisol levels, endogenous tPA concentrations, and plasminogen activator inhibitor levels create a prothrombotic state. Changes in heart rate and blood pressure as a result of the stress response can increase the propensity for a plaque to fissure and develop endothelial damage. In combination, these factors can precipitate thrombus formation in an atherosclerotic coronary artery and lead to the development of STEMI. However, newer analysis suggests that myocardial oxygen supply-demand imbalance predominates as the cause of cardiac injury during the first 3 to 4 postoperative days. Patients suffer demand ischemia.

The high incidence of histologically confirmed perioperative transmural MIs seems to be contradictory to the ECG finding of almost exclusively non–Q-wave MIs. On the other hand, the presence of subendocardial myocardial injury is consistent with a myocardial oxygen supply-demand mismatch being the main trigger of myocardial injury. However, myocardial oxygen supply-demand mismatch and plaque rupture are not mutually exclusive mechanisms, and MIs may develop by different mechanisms at different locations in the same patient.

Most PMIs occur soon after surgery (1–4 days), and 90% occur within 7 days. Most are asymptomatic, of the non–Q-wave type (60–100%), and are commonly preceded by ST-segment depression rather than ST-segment elevation. Long-duration ST-segment changes (a single episode lasting ⊥20–30 minutes or a cumulative duration ⎯ 1–2 hours, either intraoperatively or postoperatively) seem to be more important than just the presence of postoperative ST-segment depression in the evolution of adverse cardiac outcomes (Fig. 5.4).

Diagnosis

In the perioperative period, ischemic episodes often are not associated with chest pain. In addition, many postoperative ECGs are not diagnostic. Nonspecific ECG changes, new-onset dysrhythmias, and noncardiac hemodynamic instability can further obscure the clinical picture of ACS in the perioperative period. Therefore the diagnosis of PMI may be quite difficult.

An acute increase in troponin levels does indicate MI in the perioperative setting. The increase in cardiac troponin levels is a

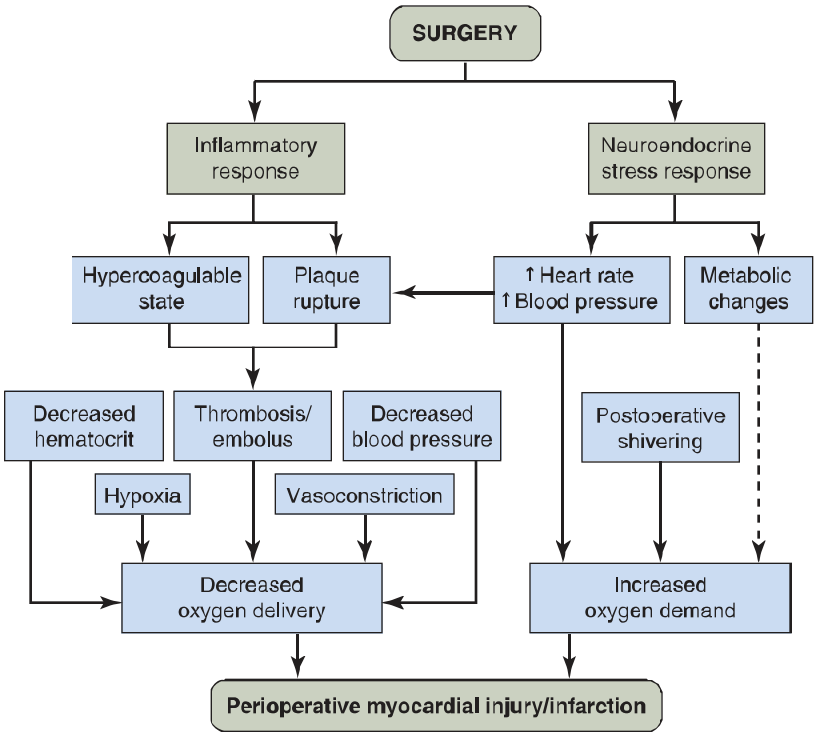

Fig. 5.4 Factors that can contribute to perioperative myocardial infarction. ↑, Increased.

marker of myocardial injury, and there is a good correlation between the duration of myocardial ischemia and the increase in the level of cardiac-specific troponin. There is also a significant association between increased troponin levels and short- and long-term morbidity and mortality in surgical patients. This association exists for cardiac death, MI, myocardial ischemia, congestive heart failure, cardiac dysrhythmias, and stroke. Even relatively minor cardiovascular complications such as uncontrolled hypertension, palpitations, increased fatigue, and shortness of breath can be correlated with increased levels of cardiac-specific troponins. An increase in troponin level postoperatively, even in the absence of clear cardiovascular signs and symptoms, is an important finding that requires careful attention and management. A new wall motion abnormality on echocardiography associated with a rise in troponin confirms the diagnosis of PMI.

PREOPERATIVE ASSESSMENT OF PATIENTS WITH KNOWN OR SUSPECTED ISCHEMIC HEART DISEASE

History

Preoperative history taking is meant to elicit the severity, progression, and functional limitations imposed by ischemic heart disease. It should focus on determining the presence of clinical risk factors in a particular patient (Table 5.5). Myocardial ischemia, left ventricular dysfunction, and cardiac dysrhythmias are usually responsible for the signs and symptoms of ischemic heart disease. Symptoms such as angina and dyspnea may be absent at rest, which emphasizes the importance of evaluating the patient's response to various physical activities such as walking or climbing stairs. Poor functional capacity is associated with increased risk of perioperative complications. Patients unable to perform workloads of 4 metabolic equivalents of the task (METs) or greater, such as climbing two or more flights of stairs or walking up a hill, have a twofold increased risk of perioperative cardiovascular complications. If a patient can climb two to three flights of stairs without symptoms it is likely that cardiac reserve is adequate. Dyspnea after the onset of angina pectoris suggests the presence of acute left ventricular dysfunction caused by myocardial ischemia.

TABLE 5.5 Clinical Predictors of Increased Perioperative Cardiovascular Risk

Unstable coronary syndromes
Acute or recent MI with evidence of important ischemic risk based on clinical symptoms or noninvasive study
Unstable or severe angina
Decompensated heart failure
Significant dysrhythmias
High-grade atrioventricular block
Symptomatic ventricular dysrhythmias in the presence of underlying heart disease
Supraventricular dysrhythmias with uncontrolled ventricular rate
Severe valvular heart disease
Mild angina pectoris
Previous MI based on history or Q waves on ECG
Compensated or previous heart failure
Diabetes mellitus (particularly insulin dependent)
Renal insufficiency
Age
Pulmonary hypertension

In some patients, myocardial ischemia does not evoke chest pain or discomfort. *This silent myocardial ischemia usually occurs at a heart rate and blood pressure substantially lower than that present during exercise-induced ischemia.* It is estimated that nearly three-quarters of ischemic episodes in patients with symptomatic ischemic heart disease are not associated with angina pectoris, and 10% to15% of AMIs are silent. It is important to recognize the presence of incipient congestive heart failure because the added stresses of anesthesia, surgery, fluid replacement, and pain may result in overt congestive heart failure.

A history of MI is an important piece of information. Using a discharge database of more than 0.5 million patients, it was shown that the postoperative MI rate in patients with a recent MI decreased substantially as the length of time from the prior MI to the time of surgery increased: less than 1 month _ 32.8%, 1 to 2 months _ 18.7%, 2 to 3 months _ 8.4%, and 3 to 6 months ⊥ 5.9%. The 30-day mortality also decreased as time since the recent MI increased.

The importance of the timing of a recent MI in relation to the proposed surgery may, however, be changing in this era of thrombolytic therapy, angioplasty/stents, and risk stratification. Although many patients with a history of MI continue to have myocardium at risk, others may not. If a stress test does not indicate residual myocardium at risk, the likelihood of reinfarction is low. The American Heart Association/American College of Cardiology (AHA/ACC) guidelines for perioperative cardiovascular evaluation suggest that more than 60 days should elapse after an MI before noncardiac surgery is undertaken in the absence of coronary intervention.

It is important to determine whether a patient has undergone cardiac revascularization with PCI and stent placement or CABG. Stent placement is routinely followed by postprocedure dual antiplatelet therapy to prevent acute coronary thrombosis and maintain the long-term patency of the stent. It is prudent to delay elective noncardiac surgery for 4 to 6 weeks after PCI with bare-metal stent placement and as long as 12 months with drug-eluting stent placement. Ideally, elective noncardiac surgery should be delayed for 6 weeks after CABG surgery.

The presence of aortic stenosis is associated with a two- to threefold increase in perioperative cardiac morbidity and mortality. Patients with critical aortic stenosis have the highest risk of cardiac decompensation after noncardiac surgery. Mitral valve disease is associated with a lesser risk. Regurgitant valve lesions have less risk than stenotic lesions. The presence of prosthetic heart valves should be noted since patients with these valves will require perioperative endocarditis prophylaxis and adjustment of their anticoagulation regimens.

The history should also elicit information relevant to coexisting noncardiac disease. For example, patients with ischemic heart disease are likely to have peripheral vascular disease. A history of syncope may reflect cerebrovascular disease, a seizure disorder, or cardiac dysrhythmias. Cough is often pulmonary rather than cardiac in origin. It may be difficult to differentiate dyspnea caused by cardiac dysfunction from that caused by chronic lung disease, although patients with ischemic heart disease more often complain of orthopnea and paroxysmal nocturnal dyspnea. Chronic obstructive pulmonary disease is likely in patients with a long history of cigarette smoking. Diabetes mellitus often coexists with ischemic heart disease. Renal insufficiency (creatinine level _ 2.0 mg/dL) increases the risk of perioperative cardiac events.

A history of pulmonary hypertension should also be determined. Patients with pulmonary artery hypertension are at an increased risk of cardiopulmonary complications after noncardiac surgery. Mortality rates of 4% to 26% and cardiorespiratory morbidity rates of 6% to 42% have been reported.

Medical treatment of ischemic heart disease is designed to decrease myocardial oxygen requirements, improve coronary blood flow, stabilize plaque, prevent thrombosis, and remodel the injured myocardium. These goals are achieved by the use of ⊥ blockers, nitrates, calcium entry blockers, statins, antiplatelet drugs, and ACE inhibitors. Effective ⊔ blockade is suggested by a resting heart rate of 50 to 60 beats per minute. Routine physical activity is expected to increase the heart rate by 10% to 20%. There is no evidence that ⊾ blockers enhance the negative inotropic effects of volatile anesthetics. ⊾ blocker therapy should be continued throughout the perioperative period. Atropine or glycopyrrolate can be used to treat excessive bradycardia caused by □ blockers during the perioperative period. Isoproterenol is the specific pharmacologic antagonist for excessive ⊐ blocker activity. The postoperative period is a time when inadvertent withdrawal of ⊐ blocker therapy may occur and result in rebound hypertension and tachycardia.

Significant hypotension has been observed in patients receiving long-term treatment with ACE inhibitors who undergo general anesthesia. It is generally recommended to withhold ACE inhibitors for 24 hours before surgery, especially those involving significant fluid shifts or blood loss. Hypotension attributable to ACE inhibitors is usually responsive to fluids or sympathomimetic drugs. If hypotension is refractory to these measures, treatment with vasopressin or one of its analogues may be required.

Antiplatelet drugs are an essential component in the pharmacotherapy of ACS and long-term management of ischemic heart disease. The use of dual antiplatelet therapy precludes neuraxial anesthesia and increases the risk of perioperative bleeding, which may then require platelet transfusion.

Physical Examination

The physical examination of patients with ischemic heart disease often yields normal findings. Nevertheless, signs of right and left ventricular dysfunction must be sought. A carotid bruit may indicate cerebrovascular disease. Orthostatic hypotension may reflect attenuated autonomic nervous system activity because of treatment with antihypertensive drugs. Jugular venous distention and peripheral edema are signs of right ventricular dysfunction. Auscultation of the chest may reveal evidence of left ventricular dysfunction such as an S_3 gallop or rales.

Specialized Preoperative Testing

Specialized preoperative testing should be limited to circumstances in which the results will affect perioperative patient management and outcomes. A conservative approach is recommended. Coronary revascularization before noncardiac surgery to enable the patient to "get through" the noncardiac procedure

is inappropriate. However, in a high-risk subset of patients, such as those with left main coronary artery disease, severe multivessel coronary artery disease, severe aortic stenosis, and/or ejection fraction less than 20%, coronary revascularization/valve replacement might be indicated. Currently there is overwhelming agreement that aggressive medical management to provide myocardial protection during the perioperative period is a critical element in the reduction of perioperative cardiovascular complications.

Specialized preoperative cardiac testing might include exercise ECG, stress echocardiography, nuclear stress imaging, and cardiac catheterization. Radionuclide ventriculography is rarely performed now, and high-speed CT, MRI, and PET scanning do not have an established role in preoperative cardiac risk stratification algorithms.

Exercise Electrocardiography

Physiologic exercise provides an estimate of functional capacity, blood pressure, and heart rate response to stress and detection of myocardial ischemia by ST-segment changes. A preoperative exercise stress test is appealing because perioperative increases in myocardial oxygen consumption and the development of myocardial ischemia are often accompanied by tachycardia. However, the utility of the exercise ECG can vary significantly. Preexisting ST-segment abnormalities hamper reliable ST-segment analysis, and treadmill testing has a rather low sensitivity (74%) and specificity (69%), comparable with information gleaned from daily clinical practice. Preoperative exercise stress testing is not indicated in patients with stable coronary artery disease and acceptable exercise tolerance.

Stress Echocardiography and Stress Nuclear Imaging

Pharmacologic stress testing with dobutamine, dipyridamole, adenosine, or regadenoson, and myocardial perfusion imaging with thallium 201 and/or technetium 99m and rubidium 82, can be used in patients undergoing noncardiac surgery who cannot perform enough exercise to detect stress-induced myocardial ischemia. Reversible wall motion abnormalities on echocardiography or reversible perfusion defects on radionuclide imaging suggest ischemia.

Myocardial perfusion imaging and dobutamine stress echocardiography before vascular surgery predict PMI or death with a positive predictive value of only 12% to 14% but a negative predictive value of 88% to 94%. Thus patients with a normal scan/echo have an excellent prognosis.

Selection of a noninvasive stress test should be based primarily on patient characteristics, local availability, and expertise in interpretation. Dobutamine stress echocardiography is the preferred test if there is an additional question regarding valvular function or left ventricular function.

CT and MRI

High-speed CT can visualize coronary artery calcification. IV administration of radiographic contrast media enhances the clarity of the images. MRI provides even greater image clarity and can delineate the proximal portions of the coronary arterial circulation. The benefit of noninvasive coronary CT angiography (CCTA) prior to noncardiac surgery is uncertain. CCTA-diagnosed coronary artery disease may overestimate risks, and it is not currently recommended by clinical practice guidelines for risk stratification prior to noncardiac surgery.

Biomarker Measurement

Preoperative measurement of biomarkers is an evolving area of investigation for perioperative risk assessment. Increased serum levels of B-type natriuretic peptide (BNP), a polypeptide released by cardiomyocytes in response to stretch, or the N-terminal pro-BNP (NT-proBNP) may be associated with increased perioperative cardiovascular risk. Though Canadian guidelines recommend measurement of NT-proBNP or BNP levels prior to noncardiac surgery in patients with a Revised Cardiac Risk Index (RCRI) of 1 or greater, or for those who are aged 65 years or older, AHA/ACC guidelines do not recommend such testing. Though increased levels of cardiac troponin have been associated with increased perioperative MACE, routine cardiac troponin screening should be avoided in unselected patients without symptoms of cardiac ischemia.

MANAGEMENT OF ANESTHESIA IN PATIENTS WITH KNOWN OR SUSPECTED ISCHEMIC HEART DISEASE UNDERGOING NONCARDIAC SURGERY

Preoperative management of patients with ischemic heart disease or risk factors for ischemic heart disease is geared toward the following goals: (1) determining the extent of ischemic heart disease and any previous interventions (CABG, PCI), (2) assessing the severity and stability of the disease, and (3) reviewing medical therapy and noting any drugs that can increase the risk of surgical bleeding or contraindicate use of a particular anesthetic technique. The first two goals are important in risk stratification.

Risk Stratification

For patients in stable condition undergoing elective major noncardiac surgery, six independent predictors of major cardiac complications have been identified and included in the Lee RCRI (Table 5.6). These six predictors are (1) high-risk surgery, (2) history of ischemic heart disease, (3) history of congestive heart failure, (4) history of cerebrovascular disease, (5) preoperative insulin-dependent diabetes mellitus, and (6) preoperative serum creatinine over 2.0 mg/dL. The more risk factors present in a patient, the greater the probability of perioperative cardiac complications such as cardiac death, cardiac arrest or ventricular fibrillation, complete heart block, AMI, and pulmonary edema (Fig. 5.5). These risk factors have been incorporated into the AHA/ACC guidelines for perioperative cardiovascular evaluation for noncardiac surgery. A principal theme of these guidelines is that preoperative intervention is rarely necessary simply to lower the risk of surgery. An intervention is indicated or not indicated regardless of the need for surgery. Preoperative testing should be performed only if the result is likely to influence perioperative management. Although no prospective randomized study has been conducted to prove the efficacy of these

TABLE 5.6 Cardiac Risk Factors in Patients Undergoing Elective Major Noncardiac Surgery

1. High-risk surgery
   - Abdominal aortic aneurysm
   - Peripheral vascular operation
   - Thoracotomy
   - Major abdominal operation
2. Ischemic heart disease
   - History of myocardial infarction
   - History of a positive finding on exercise testing
   - Current complaints of angina pectoris
   - Use of nitrate therapy
   - Presence of Q waves on ECG
3. Congestive heart failure
   - History of congestive heart failure
   - History of pulmonary edema
   - History of paroxysmal nocturnal dyspnea
   - Physical examination showing rales or S_3 gallop
   - Chest radiograph showing pulmonary vascular redistribution
4. Cerebrovascular disease
   - History of stroke
   - History of transient ischemic attack
5. Insulin-dependent diabetes mellitus
6. Preoperative serum creatinine concentration ¯2 mg/dL

Adapted from Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100:1043–1049.

guidelines, they offer a paradigm that has been widely adopted by clinicians. The 2014 AHA/ACC guidelines have been simplified from earlier versions. Rather than classifying patients into nine groups based on three clinical risk groups and three surgical risk groups, the 2014 AHA/ACC guidelines categorize patients into only two groups—low risk and elevated risk—based on the presence of clinical risk factors and the risk of the surgery. Patients with a less than 1% chance of MACE are categorized as low risk, whereas patients with a cumulative risk of MACE greater than 1% are categorized as elevated risk. Patients who have more than two RCRI risk factors are considered to be elevated risk.

There are various other risk stratification calculators (see Table 5.8, later), but the two most commonly used are the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) Myocardial Infarction and Cardiac Arrest (MICA) Risk Calculator and the ACS NSQIP Surgical Risk Calculator (http://riskcalculator.facs.org/). The 21-component NSQIP universal surgical risk calculator is more complex but may provide better predictive discrimination.

Though the 2014 AHA/ACC guidelines do not categorize clinical predictors of MACE into major, intermediate, and minor factors, some of the following clinical factors may significantly increase the risk of perioperative adverse cardiac events:

- **Unstable coronary syndromes:** acute (MI ≥ 7 days before examination) or recent MI (≥ 7 days but ≤ 1 month ago) with evidence of important ischemic risk by clinical symptoms or noninvasive study. It is suggested that more than 60 days should elapse after a recent MI before noncardiac surgery is undertaken (in the absence of coronary intervention).
- **Unstable or severe angina:** angina causing a marked limitation of ordinary physical activity at a normal pace or angina so severe as to prevent any physical activity without discomfort.
- **Decompensated heart failure:** patients with active heart failure have a significantly higher risk of postoperative death than do patients with coronary artery disease but no heart failure.
- **Severe valvular heart disease:** severe aortic stenosis or severe mitral stenosis. Left-sided regurgitant lesions convey an increased cardiac risk during noncardiac surgery but are better tolerated than stenotic valvular lesions.

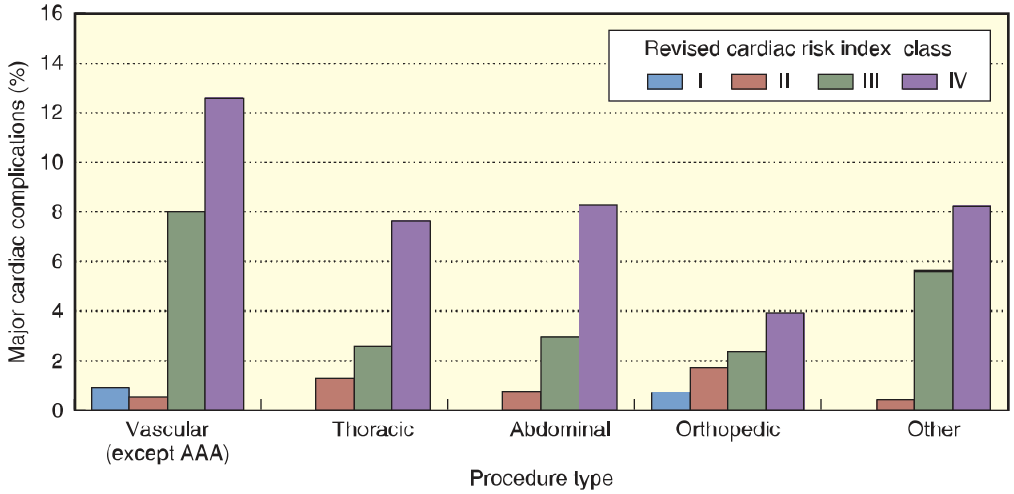

Fig. 5.5 Rates of major cardiac complications in patients in various Revised Cardiac Risk Index classes according to the type of surgery performed. Note that by definition, patients undergoing abdominal aortic aneurysm *(AAA)*, thoracic, and abdominal procedures are excluded from risk class I because these operations are all considered high-risk surgery. In all subsets there was a statistically significant trend toward greater risk with higher risk class. (Adapted from Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100:1043–1049.)

- **Significant dysrhythmias:** high-grade atrioventricular block, Mobitz type II atrioventricular block, third-degree heart block, and symptomatic supraventricular and ventricular tachydysrhythmias may increase operative risk.
- **Age:** considered a risk factor especially when it is associated with frailty; however, its exact role needs to be refined.

The AHA/ACC guidelines provide an algorithm for determining the need for preoperative cardiac evaluation. The first step assesses the urgency of the surgery. The need for emergency surgery takes precedence over the need for any additional workup (Fig. 5.6). Subsequent steps of the AHA/ACC guidelines integrate risk stratification according to risk classification, unstable clinical risk factors, and functional capacity. Patients who present for elective surgery and have any of the unstable clinical risk factors (unstable coronary syndrome, decompensated heart failure, significant dysrhythmias, severe valvular heart disease) may require delay of elective surgery, cardiologic evaluation, and optimization prior to elective surgery. Intensive preoperative management is necessary if surgery is urgent or emergent. For patients classified as low risk, further cardiac evaluation is not recommended, and patients can proceed to surgery. Patients stratified into the elevated-risk category and scheduled for elective surgery need to have their functional capacity determined.

Functional capacity or exercise tolerance can be expressed in METs. Oxygen consumption in a 70-kg, 40-year-old man in a resting state is 3.5 mL/kg/min or 1 MET. Perioperative cardiac risk is increased in patients with poor functional capacity (i.e., those who are unable to meet a 4-MET demand during normal daily activities). These individuals may be able to perform some activities, such as baking, slow ballroom dancing, golfing (riding in a cart), or walking at a speed of approximately 2 to 3 mph, but are unable to perform more strenuous activity without developing chest pain or significant shortness of breath. The ability to participate in activities requiring more than 4 METs indicates good functional capacity.

According to the AHA/ACC guidelines, patients stratified into the elevated-risk category but with a good functional capacity (14 METs) can proceed to surgery without further testing. Patients stratified into the elevated-risk category but with a low functional capacity or in whom functional capacity cannot be determined can be referred for pharmacologic stress testing if the testing will impact further management. If such testing is negative, this elevated-risk patient can proceed to surgery. If the stress test is abnormal, coronary angiography and revascularization can be considered, depending on the degree that the test is abnormal, or the patient can proceed to surgery with maximum medical management. Preoperative coronary angiography is most suitable for patients with stress test results suggesting significant myocardium at risk. The aim of the angiographic study would be to identify very significant coronary artery disease (i.e., left main or severe multivessel coronary artery disease). Further management in such a patient would be dictated by the patient's clinical condition, the overall risk of an intervention, and available resources.

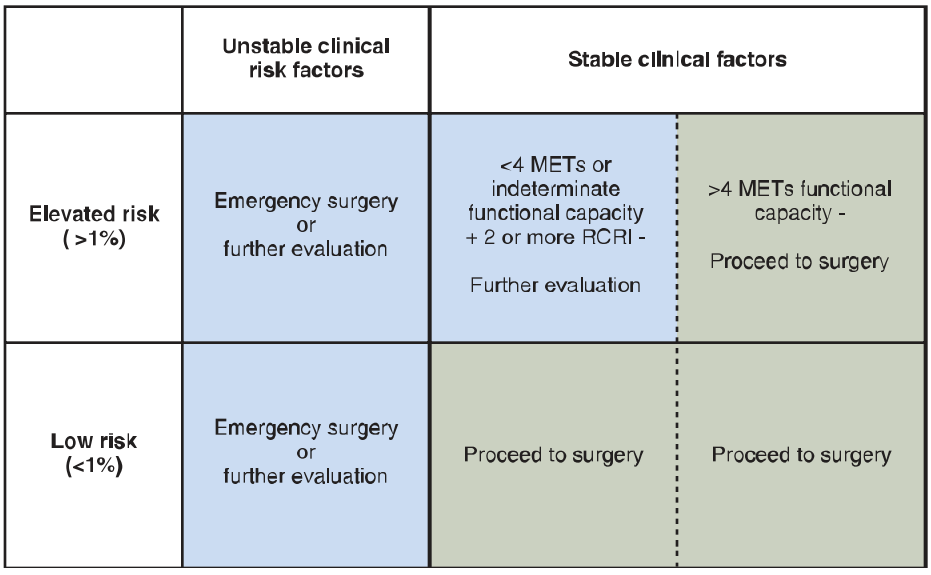

Fig. 5.6 Algorithm for preoperative assessment of patients with ischemic heart disease. The need for emergency surgery takes precedence over the need for additional workup. Patients who have any of the unstable clinical risk factors (unstable coronary syndrome, decompensated heart failure, significant dysrhythmias, severe valvular heart disease) may require delay of elective surgery, cardiologic evaluation, and optimization prior to elective surgery. Subsequent steps of the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines integrate risk stratification according to risk classification, number of clinical risk factors, and functional capacity. For patients classified as low risk, further cardiac evaluation is not recommended, and they can proceed to surgery. For patients who are stratified into elevated-risk category and presenting for elective surgery, the next step is to determine their functional capacity. Patients stratified into elevated-risk category with good functional capacity (4 METs) can proceed to surgery without further testing. Patients stratified into elevated-risk category with low functional capacity and/or in whom functional capacity cannot be determined can be referred for pharmacologic stress testing if the testing will impact further management. *MET,* Metabolic equivalent of the task; *RCRI,* Revised Cardiac Risk Index.

Management After Risk Stratification

The fundamental reason for risk stratification is to identify patients at increased risk so as to manage them with pharmacologic and other perioperative interventions that can lessen the risk and/or severity of perioperative cardiac events. Three therapeutic options are available prior to elective noncardiac surgery: (1) revascularization by cardiac surgery, (2) revascularization by PCI, and (3) optimal medical management.

In nonoperative settings, treatment strategies such as PCI (with or without stenting), CABG surgery, and medical therapy have proven efficacious in improving long-term morbidity and mortality. Patients with significant ischemic heart disease who come for noncardiac surgery are likely to be candidates for one or more of these therapies regardless of their need for surgery. Coronary interventions should be guided by the patient's cardiac condition and by the potential consequences of delaying surgery for recovery from the revascularization.

Coronary Artery Bypass Grafting

For CABG surgery to be beneficial before noncardiac surgery, the institutional risk of that particular noncardiac operation should be greater than the combined risk of coronary catheterization and coronary revascularization plus the generally reported risk of that noncardiac operation. The indications for preoperative surgical coronary revascularization are the same as those in the nonoperative setting.

Percutaneous Coronary Intervention

It was thought that PCI before elective noncardiac surgery could improve perioperative outcomes. However, PCI, which is accompanied by stenting and dual antiplatelet therapy, poses its own unique set of problems that need to be considered in patients who are scheduled to undergo elective noncardiac surgery. There is no value in preoperative coronary intervention in a patient with stable ischemic heart disease. Despite current guidelines, invasive coronary angiography before noncardiac surgery is common and preoperative revascularization is performed in 24% of these cases.

Pharmacologic Management

Most patients with stable coronary artery disease and/or risk factors for coronary artery disease will be managed pharmacologically, as will patients with significant ischemic heart disease who come for emergent or urgent surgery.

Several drugs have been used to reduce perioperative myocardial injury. These are drugs that have demonstrated efficacy in the management of coronary ischemia in the nonsurgical setting. Nitroglycerin may be helpful in the management of active perioperative ischemia. However, prophylactic use of nitroglycerin has not been shown to be efficacious in reducing perioperative morbidity and mortality.

blockers reduce myocardial oxygen consumption, improve coronary blood flow by prolonging diastole, improve the supply-demand ratio, stabilize cellular membranes, improve oxygen dissociation from hemoglobin, and inhibit platelet aggregation. blockers suppress perioperative tachycardia and appear most efficacious in preventing perioperative myocardial ischemia. In view of these beneficial effects, prophylactic use of blockers to decrease PMI has been explored in many trials. In 2014, the AHA/ACC conducted a systematic review on this topic. The main findings were (1) preoperative use of blockers was associated with a reduction in cardiac events, but there were little data to support the effectiveness of preoperative administration of blockers to reduce the risk of surgical death; and (2) a clear association exists between blocker administration and adverse outcomes such as bradycardia and stroke.

Currently the only class I recommendation by the AHA/ACC for perioperative blockers is to continue their use in patients who are already on blockers. blockers can be used in patients with elevated risk, especially in those with ischemia on preoperative stress testing or those with three or more RCRI factors. If blockers are to be used for prophylactic purposes, they should be slowly titrated (over 7 days prior to elective surgery), and acute administration of high-dose blockers in high-risk patients undergoing low-risk surgery is not recommended. Questions regarding the choice of blocker and the target heart rate are still unresolved. For ease of dosing and consistency of effect, longer-acting blockers, such as atenolol or bisoprolol, may be more efficacious in the perioperative period.

agonists such as clonidine decrease sympathetic outflow, blood pressure, and heart rate. Older studies suggested a possible beneficial effect of clonidine perioperatively, but more recent trials failed to show any statistically significant benefits of clonidine in reducing 30-day mortality or the risk of nonfatal MI in patients with atherosclerosis undergoing noncardiac surgery. Based on the AHA/ACC guidelines, agonists for prevention of cardiac events are not recommended in patients undergoing noncardiac surgery.

Statins are used for their lipid-lowering effects and are widely prescribed in patients with or at risk of ischemic heart disease. Statins also induce coronary plaque stabilization by decreasing lipid oxidation, inflammation, matrix metalloproteinase, and cell death. These so-called nonlipid or pleiotropic effects may prevent plaque rupture and subsequent MI in the perioperative period. Trials show that statins can reduce mortality significantly in noncardiac surgery (by 44%) and in vascular surgery (by 59%). Evidence to date suggests a protective effect of perioperative statin use on cardiac complications during noncardiac surgery. The AHA/ACC guidelines recommend continuing statin therapy in patients scheduled for noncardiac surgery.

Controlling hyperglycemia in patients undergoing cardiac surgery and in patients in intensive care units has been associated with improved outcomes. Recognizing that insulin has some beneficial nonmetabolic effects and noting the harmful effects of hyperglycemia, it is prudent to actively manage hyperglycemia with insulin during noncardiac surgery. This is especially important in patients who are at high risk of cardiac injury. The goal in this situation is to keep the perioperative glucose below 180 mg/dL.

Because several pathophysiologic mechanisms can trigger a PMI, it seems reasonable to think that multimodal therapy with

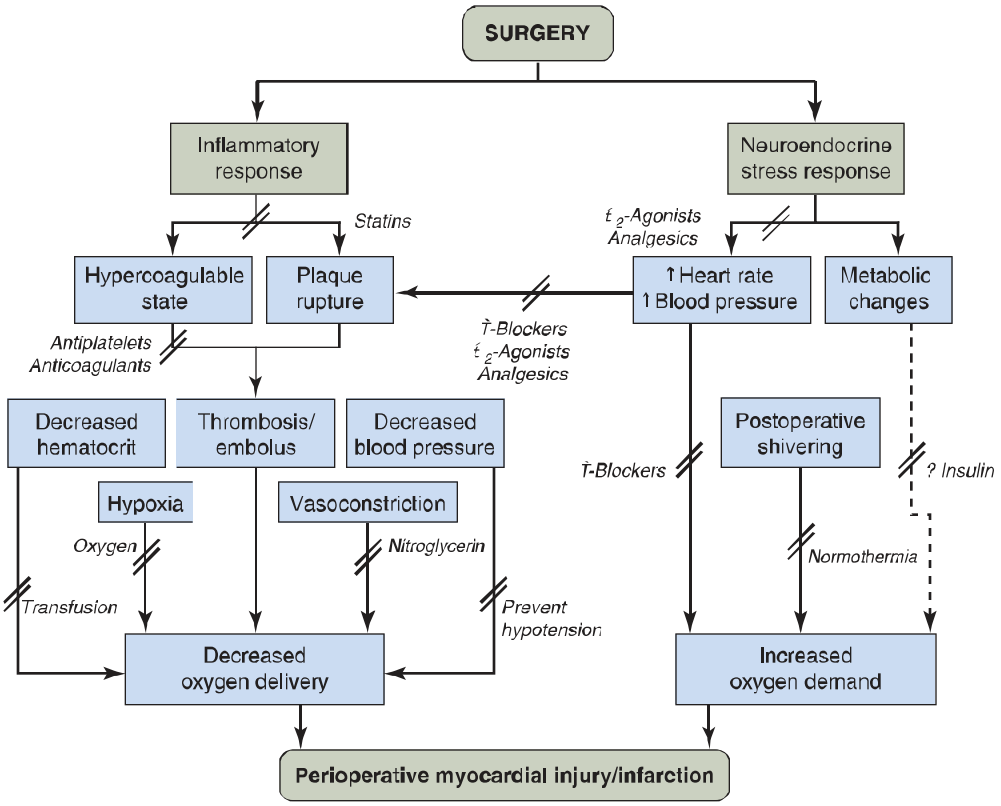

Fig. 5.7 Interventions that can modulate triggers of perioperative myocardial injury. ↑, Increased.

l blockers, statins, and insulin may be more beneficial than treatment with any single drug (Fig. 5.7).

Intraoperative Management

The basic challenges during induction and maintenance of anesthesia in patients with ischemic heart disease are to (1) prevent myocardial ischemia by optimizing myocardial oxygen supply and reducing myocardial oxygen demand, (2) monitor for ischemia, and (3) treat ischemia if it develops. Intraoperative events associated with persistent tachycardia, systolic hypertension, sympathetic nervous system stimulation, arterial hypoxemia, or hypotension can adversely affect the patient with ischemic heart disease (Table 5.7). Perioperative myocardial injury is closely associated with heart rate in vascular surgery patients. A rapid heart rate increases myocardial oxygen requirements and decreases diastolic time for coronary blood flow and therefore oxygen delivery. The increased oxygen requirements produced by hypertension are offset to some degree by improved coronary perfusion. Hyperventilation must be avoided because hypocapnia may cause coronary artery vasoconstriction. Maintenance of the balance between myocardial oxygen supply and demand is more important than which specific anesthetic technique or drugs are selected to produce anesthesia and muscle relaxation.

It is important to avoid persistent and excessive changes in heart rate and blood pressure. A common recommendation is to keep the heart rate and blood pressure within 20% of the normal awake value for that patient. However, many episodes of intraoperative myocardial ischemia occur in the absence of hemodynamic changes. These episodes may be due to regional decreases in myocardial perfusion. It is unlikely that this form of ischemia can be prevented by the anesthesiologist.

Induction of anesthesia in patients with ischemic heart disease can be accomplished with an IV induction drug.

TABLE 5.7 Intraoperative Events That Influence the Balance Between Myocardial Oxygen Delivery and Myocardial Oxygen Requirements

Decreased Oxygen Delivery
Decreased coronary blood flow
Tachycardia
Hypotension
Hypocapnia (coronary artery vasoconstriction)
Coronary artery spasm
Decreased oxygen content
Anemia
Arterial hypoxemia
Shift of the oxyhemoglobin dissociation curve to the left
Increased Oxygen Requirements
Sympathetic nervous system stimulation
Tachycardia
Hypertension
Increased myocardial contractility
Increased afterload
Increased preload

A meta-analysis of more than 6000 patients undergoing noncardiac surgery failed to demonstrate a difference in PMI rates between patients who received volatile anesthesia and patients who received total IV anesthesia. Tracheal intubation can be facilitated by administration of succinylcholine or a nondepolarizing muscle relaxant.

Myocardial ischemia may accompany the sympathetic stimulation that results from direct laryngoscopy and endotracheal intubation. Keeping the duration of direct laryngoscopy short (~15 seconds) is useful in minimizing the magnitude and duration of the circulatory changes associated with tracheal intubation. If the duration of direct laryngoscopy is not likely to be brief or if hypertension already exists, it is reasonable to consider administering drugs to minimize the sympathetic response. Laryngotracheal lidocaine, IV lidocaine, esmolol, fentanyl, remifentanil, and dexmedetomidine have all been shown to be useful for blunting the increase in heart rate evoked by tracheal intubation.

In patients with normal left ventricular function, tachycardia and hypertension are likely to develop in response to intense stimulation, such as during direct laryngoscopy or painful surgical stimulation. Achieving controlled myocardial depression using a volatile anesthetic may be useful in such patients to minimize the increase in sympathetic nervous system activity. Overall, volatile anesthetics may be beneficial in patients with ischemic heart disease because they decrease myocardial oxygen requirements and may precondition the myocardium to tolerate ischemic events, or they may be detrimental because they lead to a decrease in blood pressure and an associated reduction in coronary perfusion pressure. The current AHA guidelines state that "use of either a volatile anesthetic agent or total intravenous anesthesia is reasonable for patients undergoing noncardiac surgery, and the choice is determined by factors other than the prevention of myocardial ischemia and MI."

The use of nitrous oxide in patients with a history of coronary artery disease has been questioned since the early 1990s when animal and human studies showed an increase in pulmonary vascular resistance, diastolic dysfunction, and myocardial ischemia with its use. However, subsequent data showed that nitrous oxide did not increase the risk of death and cardiovascular complications or surgical site infection. Thus the use of nitrous oxide in patients with coronary artery disease is not contraindicated.

Patients with severely impaired left ventricular function may not tolerate anesthesia-induced myocardial depression. Opioids may then be selected as the principal anesthetic. The addition of nitrous oxide, a benzodiazepine, or a low dose of volatile anesthetic may be needed to supplement the opioid because amnesia cannot be insured with an opioid anesthetic.

Regional anesthesia is an acceptable technique in patients with ischemic heart disease. However, the decrease in blood pressure associated with epidural or spinal anesthesia must be controlled. Prompt treatment of hypotension that exceeds 20% of the preblock blood pressure is necessary. Potential benefits from the use of a regional anesthetic include excellent pain control, a decreased incidence of deep venous thrombosis in some patients, and the opportunity to continue the block into the postoperative period. However, the incidence of perioperative cardiac morbidity and mortality does not appear to be significantly different for general and regional anesthesia. The current guidelines recommend that the choice of anesthesia is best left to the discretion of the anesthesia care team, who will consider the need for postoperative mechanical ventilation, pulmonary/neuromuscular comorbidities, cardiovascular effects (including myocardial depression), the consequences of sympathetic blockade, and the dermatomal level of the procedure.

Muscle relaxants with minimal or no effect on heart rate and systemic blood pressure (vecuronium, rocuronium, cisatracurium) are attractive choices for patients with ischemic heart disease. The histamine release and resulting decrease in blood pressure caused by atracurium make this drug less desirable.

Though reversal of neuromuscular blockade with an anticholinesterase-anticholinergic drug combination can be safely accomplished in patients with ischemic heart disease, sugammadex, with its better risk profile, may be a superior choice in patients with ischemic heart disease. Glycopyrrolate, which has much less chronotropic effect and central effect than atropine, is preferred in these patients.

Monitoring

The type of perioperative monitoring is influenced by the complexity of the operative procedure and the severity of the ischemic heart disease. The most important goal in selecting monitoring methods is to select those that allow early detection of myocardial ischemia. Since most myocardial ischemia occurs in the absence of hemodynamic alterations, one should be cautious in endorsing routine use of expensive or complex monitors to detect myocardial ischemia.

The simplest, most cost-effective method for detecting perioperative myocardial ischemia is standard ECG. The diagnosis of myocardial ischemia focuses on changes in the ST segment, characterized as elevation or depression of at least 1 mm and T-wave inversions. The degree of ST-segment depression parallels the severity of myocardial ischemia. Because visual detection of ST-segment changes can be unreliable, computerized ST-segment analysis has been incorporated into ECG monitors. Traditionally, monitoring of two leads (leads II and V_5) has been the standard, but it appears that monitoring three leads (leads II, V_4, and V_5 [or V_3, V_4, and V_5]) may improve the ability to detect ischemia. There is also a correlation between the lead of the ECG that detects myocardial ischemia and the anatomic distribution of the diseased coronary artery (Tables 5.8 and 5.9). For example, the V_5 lead (fifth intercostal space in the anterior axillary line) reflects myocardial ischemia in the portion of the left ventricle supplied by the left anterior descending coronary artery (Fig. 5.8). Lead II is more likely to detect myocardial ischemia occurring in the distribution of the right coronary artery. Lead II is also very useful for analysis of cardiac rhythm disturbances.

Events other than myocardial ischemia that can cause ST-segment abnormalities include cardiac dysrhythmias, cardiac conduction disturbances, digitalis therapy, electrolyte abnormalities,

TABLE 5-8 Risk Scores and Calculators

			NATIONAL SURGICAL QUALITY IMPROVEMENT PROGRAM			
			Risk Calculators		Geriatric-Sensitive	
	Goldman Index of Cardiac Risk, 1977	Revised Cardiac Risk Index, 1999	Perioperative MI and Cardiac Arrest, 2011	Universal Surgical, 2013	Perioperative Cardiac Risk Index, 2017	Cardiovascular Risk Index, 2019
Criteria	• Aged ≥ 70 y (5 points) • Had an MI within 6 mo (10 points) • Jugular venous distention or a third heart sound on auscultation (11 points) • ≥ 5 PVCs/min (7 points) • Nonsinus rhythm or PAC on preoperative ECG (7 points) • Aortic stenosis (3 points) • Intraperitoneal, intrathoracic, or aortic surgery (3 points) • Any emergency surgery (4 points)	• Ischemic heart disease (1 point) • Cerebrovascular disease (1 point) • History of congestive heart failure (1 point) • Insulin therapy for diabetes (1 point) • Serum creatinine level ≥ 2.0 mg/dL (1 point) • Planned high-risk procedure (intraperitoneal, intrathoracic, or vascular surgery) (1 point)	• Age • ASA class • Preoperative function • Creatinine level • Procedure type: anorectal; aortic; bariatric; brain; breast; cardiac; ear, nose, or throat; foregut or hepatopancreatobiliary; gallbladder, appendix, adrenal, or spleen; intestinal; neck; obstetric or gynecologic; orthopedic; other abdomen; peripheral; vascular; skin; spine; thoracic; urological; or vein	• Age group • Sex • ASA class • Functional status • Emergency case • Steroid use for chronic condition • Ascites within 30 d preoperatively • System sepsis within 48 h preoperatively • Required ventilator • Disseminated cancer • Diabetes • Hypertension requiring medication • Prior cardiac event • Congestive heart failure within 30 d preoperatively • Dyspnea • Current smoker within 1 y • History of COPD • Dialysis • Acute kidney failure • BMI • CPT-specific linear risk	• Age • Sex • ASA class • High-risk surgery • History of heart failure • Stroke • Required insulin • Diabetes • Dialysis • Medications for hypertension • Current tobacco use • History of COPD • Functional status (partially vs totally dependent) • Creatinine level • Surgical category • Dyspnea • BUN level • Laparoscopic surgery	• Age ≥ 75 y (1 point) • History of heart disease (1 point) • Symptoms of angina or dyspnea (1 point) • Hemoglobin level < 12 mg/dL (1 point) • Vascular surgery (1 point) • Emergency surgery (1 point)
Score range	• Class I: 0-5 points (lowest risk) • Class II: 6-12 points • Class III: 13-25 points • Class IV: ≥ 26 points (highest risk)	• Class I: 0 points (lowest risk) • Class II: 1 point • Class III: 2 points • Class IV: ≥ 3 points (highest risk)	0-100% (0%, lowest risk; 100%, highest risk)	0-100% (0%, lowest risk; 100%, highest risk)	0-100% (0%, lowest risk; 100%, highest risk)	0 points (lowest risk) 1 point 2 points 3 points ≥ 3 points (highest risk)
Threshold denoting elevated risk	≥ Class II (≥ 6 points)	≥ 1 point	≥ 1%	≥ 1%	≥ 1%	≥ 2 points

Continued

TABLE 5-8 Risk Scores and Calculators—cont'd

			NATIONAL SURGICAL QUALITY IMPROVEMENT PROGRAM			
			Risk Calculators		Geriatric-Sensitive	
	Goldman Index of Cardiac Risk, 1977	Revised Cardiac Risk Index, 1999	Perioperative MI and Cardiac Arrest, 2011	Universal Surgical, 2013	Perioperative Cardiac Risk Index, 2017	Cardiovascular Risk Index, 2019
Outcome	Intraoperative or postoperative MI, pulmonary edema, VT, cardiac death	MI, pulmonary edema, ventricular fibrillation, complete heart block, cardiac death	Intraoperative or postoperative MI or cardiac arrest within 30 d	Cardiac arrest, MI, all-cause mortality within 30 d	Cardiac arrest, MI, all-cause mortality within 30 d	Death, MI, or stroke at 30 d
Derivation population	1001	1422	211410	1414006	584931	3284
Set ROC						
Derivation	0.61	0.76	0.88	0.90 (cardiac arrest or MI); 0.94 (mortality)		0.90
Validation	0.70	0.81; 0.75	0.87	0.88 (cardiac arrest or MI); 0.94 (mortality)	0.83 (0.76 in adults aged ≥65 y)	0.82

TABLE 5-9 Relationship of ECG Leads to Areas of Myocardial Ischemia

ECG Lead	Coronary Artery Responsible for Ischemia	Area of Myocardium That May Be Involved
II, III, aVF	Right coronary artery	Right atrium Right ventricle Sinoatrial node Inferior aspect of left ventricle Atrioventricular node
I, aVL	Circumflex coronary artery	Lateral aspect of left ventricle
V_3-V_5	Left anterior descending coronary artery	Anterolateral aspect of left ventricle

and hypothermia. However, in patients with known or suspected coronary artery disease, it is reasonable to assume that intraoperative ST-segment changes represent myocardial ischemia. The occurrence and duration of intraoperative ST-segment changes in high-risk patients are linked to an increased incidence of PMI and adverse cardiac events. Interestingly, the overall incidence of myocardial ischemia is lower in the intraoperative period than in the preoperative or postoperative period.

If pulmonary artery catheter monitoring is being used, intraoperative myocardial ischemia can manifest as an acute increase in pulmonary artery occlusion pressure (PAOP) due to changes in left ventricular compliance and left ventricular systolic performance. If myocardial ischemia is global or involves the papillary muscle, V waves may appear in the PAOP waveform. If only small regions of left ventricular myocardium become ischemic, overall ventricular compliance and pulmonary artery occlusion pressure will remain unchanged, so the pulmonary artery catheter is a relatively insensitive method of monitoring for myocardial ischemia. The pulmonary artery diastolic pressure is even less sensitive than the pulmonary artery occlusion pressure in detecting a change in left ventricular compliance. Right heart catheterization is therefore not recommended as an intraoperative ischemia monitor.

The development of new regional ventricular wall motion abnormalities seen on transesophageal echocardiography (TEE) is the accepted standard for the intraoperative diagnosis of myocardial ischemia. These regional wall motion abnormalities can occur before ECG changes are seen. However, segmental wall motion abnormalities may also occur in response to events other than myocardial ischemia. The limitations of TEE include its cost, the need for extensive training in interpreting the images, and the fact that the transducer cannot be inserted until after induction of anesthesia. There is then a critical period during which myocardial ischemia may develop, but this monitor is not in place to detect it. The AHA/ACC guidelines recommend the use of TEE intraoperatively or perioperatively to determine the cause of an acute, persistent, and life-threatening hemodynamic abnormality. However, its use as an ischemia monitor in noncardiac surgery is less validated and should only be considered in patients at high risk for developing myocardial ischemia during major noncardiac surgery. Routine use of intraoperative TEE during noncardiac surgery to monitor for myocardial ischemia is not recommended.

Intraoperative Management of Myocardial Ischemia

Treatment of myocardial ischemia should be instituted when there are 1-mm ST-segment changes on ECG. Prompt drug

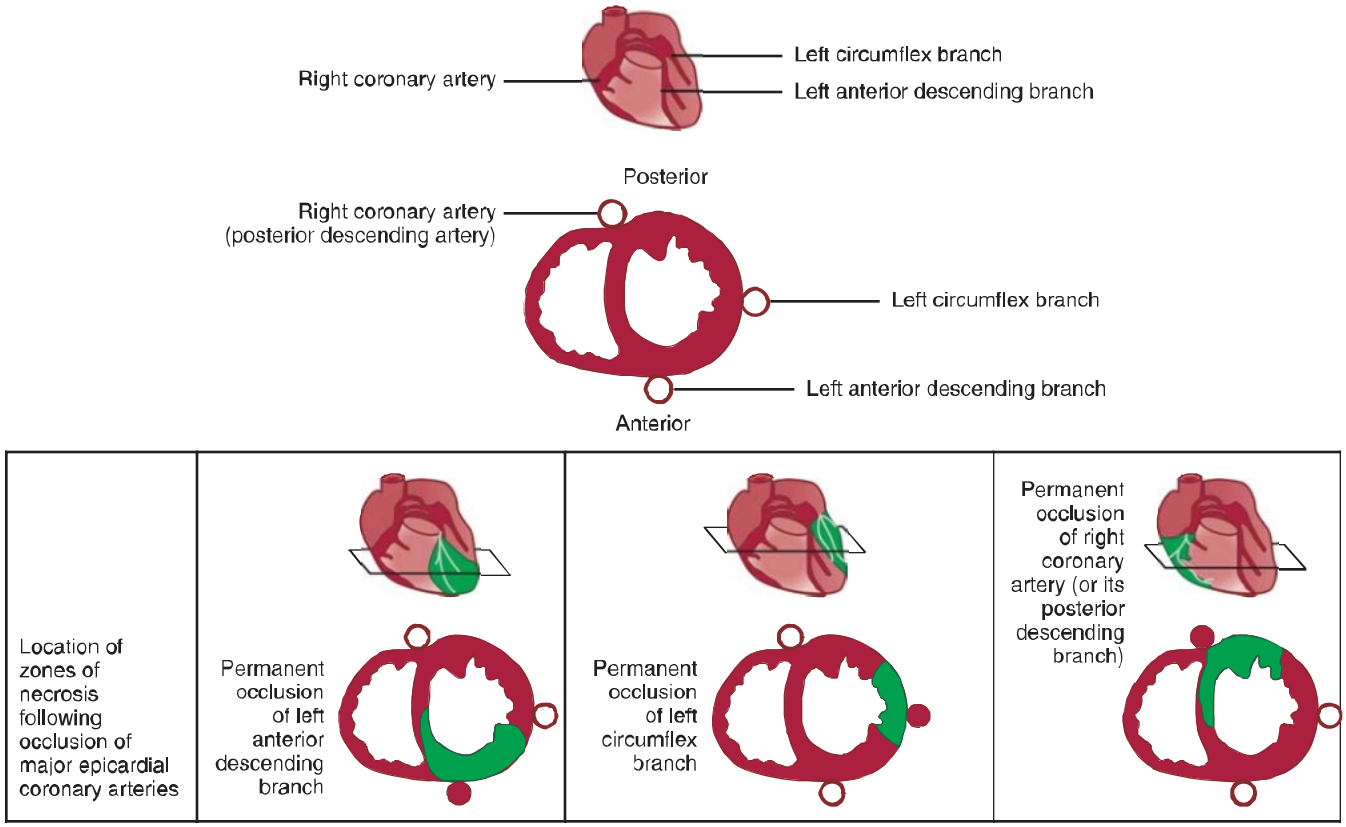

Fig. 5.8 Correlation of sites of coronary occlusion and zones of necrosis. (From Antman EM. ST-segment myocardial infarction: pathology, pathophysiology, and clinical features. In: Bonow RO, Mann DL, Zipes DP, et al, eds, *Braunwald's Heart Disease*. Philadelphia, PA: Saunders; 2012 [fig. 54-4].)

treatment of adverse changes in heart rate and/or blood pressure is indicated. Nitroglycerin is an appropriate choice when myocardial ischemia is associated with a normal or modestly elevated blood pressure. In this situation the nitroglycerin-induced coronary vasodilation and decrease in preload improve subendocardial blood flow, but the nitroglycerin-induced decrease in afterload does not decrease systemic blood pressure to the point that coronary perfusion pressure is jeopardized. A persistent increase in heart rate in the setting of normal or high blood pressure can also be treated by administration of a ⊥ blocker such as esmolol.

Hypotension is treated with inotropic drugs to restore coronary perfusion pressure. In addition to administration of inotropic drugs, judicious fluid infusion can be useful to help restore blood pressure. Regardless of the treatment, prompt restoration of blood pressure is necessary to maintain pressure-dependent flow through narrowed coronary arteries. In an unstable hemodynamic situation, circulatory support with inotropes, or mechanical circulatory support devices, may be necessary. It may also be necessary to plan for early postoperative cardiac catheterization.

Postoperative Management

Although significant advances have been made in researching and refining preoperative evaluation and risk management strategies, evidence-based strategies that can be adopted in the postoperative period to improve outcome have not yet been developed.

The goals of postoperative management are the same as those for intraoperative management: prevent ischemia, monitor for myocardial injury, and treat myocardial ischemia or infarction. Any situation that leads to prolonged and significant hemodynamic perturbations can stress the heart. Intraoperative hypothermia may predispose to shivering on awakening, leading to abrupt and dramatic increases in myocardial oxygen requirements. Pain, hypoxemia, hypercarbia, sepsis, and hemorrhage also lead to increased myocardial oxygen demand and/or decreased oxygen delivery. The resulting oxygen supply-demand imbalance in patients with ischemic heart disease can precipitate myocardial ischemia, infarction, or death. Although most adverse cardiac events occur within the first 48 hours postoperatively, delayed cardiac events can occur within the first 30 days and can be the result of secondary stresses. It is imperative that patients taking ¯ blockers and statins continue to receive these drugs throughout the perioperative period.

Prevention of hypovolemia and hypotension is necessary postoperatively, and not only an adequate intravascular volume but also an adequate hemoglobin concentration must be maintained (_7 g/dL [L8 g/dL in patients ⊥80 years]). Oxygen content and oxygen delivery depend significantly on the concentration of hemoglobin in blood. The degree of anemia that can be safely tolerated in patients with ischemic heart disease remains to be defined.

The timing of weaning from mechanical ventilation and tracheal extubation requires careful consideration. Early extubation

is possible and desirable in many patients so long as they fulfill the criteria for extubation. However, patients with ischemic heart disease can become ischemic during emergence from anesthesia and/or weaning from mechanical ventilation. Any increase in heart rate and/or blood pressure must be managed promptly. Pharmacologic therapy with a □ blocker or a combined □ and □ blocker (e.g., labetalol) or a calcium channel blocker (e.g., nicardipine) can be very helpful.

Continuous ECG monitoring is useful for detecting postoperative myocardial ischemia, which is often silent. Postoperative myocardial ischemia predicts adverse in-hospital and long-term cardiac events. It should be identified, evaluated, and managed, preferably in consultation with a cardiologist.

CARDIAC TRANSPLANTATION

Cardiac transplantation is most often performed in patients with end-stage heart failure due to an ischemic or nonischemic cardiomyopathy, adult congenital heart disease, valvular heart disease, or a failing prior heart transplant. Preoperatively the ejection fraction is often less than 20%. Irreversible pulmonary hypertension is a contraindication to cardiac transplantation, and most centers do not consider candidates older than age 70 or with a life expectancy less than 2 years. Active infection, recent pulmonary thromboembolism with pulmonary infarction, irreversible renal or hepatic dysfunction, and active or recent (¯ 5 years) solid organ or hematologic cancer are considered relative contraindications to heart transplantation.

Management of Anesthesia

Patients may come for cardiac transplantation with inotropic, vasodilator, or mechanical circulatory support. Additionally, they may have implanted antidysrhythmic devices (pacemaker, automatic implantable cardioverter-defibrillator [AICD) and invasive hemodynamic monitors. Antidysrhythmic devices should be interrogated and reprogrammed to a mode that is not affected by electrical cautery. These devices are typically explanted and extracted during excision of the patient's heart. At times that may be challenging, and the leads may have to be incorporated into the vessel. Patients are also on standard heart failure medications such as ACE inhibitors, ARBs, Γ blockers, hydralazine, and nitrates. Refractory hypotension and vasoplegia may be encountered in the perioperative period. Most patients will not be in a fasting state and should be considered as having a full stomach. Patients can be anesthetized using a balanced anesthetic technique. The primary goals of induction are maintenance of contractility, systemic vascular resistance, and preload while minimizing the negative inotropic effects of induction and preventing aspiration or an acute increase in pulmonary vascular resistance. Nondepolarizing neuromuscular blocking drugs that do not cause histamine release are usually selected. Many patients undergoing cardiac transplantation have coagulation disturbances due to passive congestion of the liver as a result of chronic congestive heart failure, or they may be on warfarin. Coagulopathy can be managed by administration of vitamin K, fresh frozen plasma (FFP), or prothrombin complex concentrate. Due to immunologic sensitization, transfusion-related acute lung injury (TRALI), and volume required to reverse anticoagulation, some institutions now avoid FFP and prefer prothrombin complex concentrate (PCC) if available.

The operative technique includes cardiopulmonary bypass and anastomosis of the aorta, pulmonary artery, and left and right atria. Immunosuppressive drugs are usually begun during the preoperative period. Intravascular catheters must be placed using strict aseptic technique. It is necessary to withdraw the central venous or pulmonary artery catheter into the superior vena cava when the native heart is removed. The catheter can then be repositioned into the donor heart. These catheters are often inserted into the central circulation via the left internal jugular vein so that the right internal jugular vein is available when needed to perform endomyocardial biopsies during the postoperative period. TEE is used to monitor cardiac function intraoperatively.

After cessation of cardiopulmonary bypass, an inotropic drug may be needed briefly to maintain myocardial contractility and heart rate. Therapy to lower pulmonary vascular resistance may also be necessary and may include administration of a pulmonary vasodilator such as nitric oxide, a prostaglandin, or a phosphodiesterase inhibitor. The denervated transplanted heart initially assumes an intrinsic heart rate of about 110 beats per minute, which reflects the absence of normal vagal tone. Stroke volume responds to an increase in preload by the Frank-Starling mechanism. These patients tolerate hypovolemia poorly. The transplanted heart does respond to direct-acting catecholamines, but drugs that act by indirect mechanisms, such as ephedrine, have a much less intense effect. Vasopressin may be needed to treat severe hypotension unresponsive to catecholamines. The heart rate does not change in response to administration of anticholinergic or anticholinesterase drugs. About 25% of patients develop bradycardia after cardiac transplantation that requires insertion of a permanent cardiac pacemaker.

Postoperative Complications

Right heart failure after cardiac transplantation occurs frequently and is responsible for approximately 20% of the early deaths after this procedure. Acute right heart failure may require urgent mechanical circulatory support and pulmonary vasodilation to prevent further hemodynamic compromise.

Cardiac transplant patients may require Γ-adrenergic stimulants for 3 to 4 days after transplantation. Early postoperative morbidity related to heart transplantation surgery usually involves sepsis and/or rejection. The most common early cause of death is opportunistic infection as a result of immunosuppressive therapy. Transvenous right ventricular endomyocardial biopsies are performed to provide early warning of asymptomatic allograft rejection. Congestive heart failure and development of dysrhythmias are late signs of rejection. Immunotherapy after cardiac transplantation typically involves corticosteroids and calcineurin inhibitors such as cyclosporine or tacrolimus. Cyclosporine treatment can be associated with drug-induced hypertension that is often resistant to antihypertensive therapy. Nephrotoxicity is another complication of cyclosporine and tacrolimus therapy. Long-term corticosteroid use may result in skeletal demineralization and glucose intolerance.

Late complications of cardiac transplantation include development of coronary artery disease in the allograft and an increased incidence of cancer. Diffuse obliterative coronary arteriopathy affects cardiac transplant recipients over time, and the ischemic sequelae of this form of coronary artery disease are the principal limitations to long-term survival. This arterial disease is restricted to the allograft and is present in about half of cardiac transplant recipients after 5 years. The accelerated appearance of this coronary artery disease likely reflects a chronic rejection process in the vascular endothelium. This process is not unique to cardiac allografts and is thought to be analogous to the chronic immunologically mediated changes seen in other organ allografts (bronchiolitis obliterans in the lungs, vanishing bile duct syndrome in the liver). The clinical sequelae of this obliterative coronary artery disease include myocardial ischemia, left ventricular dysfunction, cardiac dysrhythmias, and sudden death. The prognosis for transplant recipients with angiographically established obliterative coronary artery disease is poor.

Any medical regimen involving long-term immunosuppression is associated with an increased incidence of cancer, especially lymphoproliferative and cutaneous cancers. Malignancy is responsible for a significant portion of the mortality of heart transplant patients. Most posttransplantation lymphoproliferative disease is related to infection with the Epstein-Barr virus.

Anesthetic Considerations in Heart Transplant Recipients

Heart transplant patients present unique anesthetic challenges because of the hemodynamic function of the transplanted denervated heart, the side effects of immunosuppressive therapy, the risk of infection, the potential for drug interactions (given the complex drug regimens), and the potential for allograft rejection.

Allograft rejection results in progressive deterioration of cardiac function. The presence and degree of rejection should be noted preoperatively. The presence of infection must also be noted because infection is a significant cause of morbidity and mortality in these patients. Invasive monitoring requires the use of strict aseptic technique. When hepatic and renal function are normal, there is no contraindication to the use of any anesthetic drug.

The transplanted heart has no sympathetic, parasympathetic, or sensory innervation initially. After a variable period of 6 to 12 months, partial reinnervation of the transplanted heart has been shown to occur. The loss of vagal tone results in a higher-than-normal resting heart rate. Two P waves may be detectable on the ECG. The native sinus node remains intact if a cuff of atrium is left in place to permit surgical anastomosis to the grafted heart. Because the native P wave cannot traverse the suture line, it has no influence on the chronotropic activity of the heart. Carotid sinus massage and the Valsalva maneuver have no effect on heart rate. There is no sympathetic response to direct laryngoscopy and tracheal intubation, and the denervated heart has a blunted heart rate response to light anesthesia or intense pain. The transplanted heart is unable to increase its heart rate immediately in response to hypovolemia or hypotension but responds instead with an increase in stroke volume via the Frank-Starling mechanism. The needed increase in cardiac output is dependent on venous return until the heart rate increases after several minutes in response to the effect of circulating catecholamines. Because _- and L-adrenergic receptors are intact on the transplanted heart, the heart will eventually respond to circulating catecholamines.

Cardiac dysrhythmias may occur in heart transplant patients, perhaps reflecting a lack of vagal innervation and/or increased levels of circulating catecholamines. At rest, the heart rate reflects the intrinsic rate of depolarization of the donor sinoatrial node in the absence of any vagal tone. First-degree atrioventricular block (an increased PR interval) is common after cardiac transplantation. Some patients may require a cardiac pacemaker for treatment of bradydysrhythmias. A surgical transplantation technique that preserves the anatomic integrity of the right atrium by using anastomoses at the level of the superior and inferior vena cava rather than at the midatrial level results in better preservation of sinoatrial node and tricuspid valve function. Afferent denervation renders the cardiac transplant patient incapable of experiencing angina pectoris in response to myocardial ischemia.

Response to Drugs

Catecholamine responses are different in the transplanted heart because the intact sympathetic nerves required for normal uptake and metabolism of catecholamines are absent. The density of ¯ and ¯ receptors in the transplanted heart is unchanged, however, and responses to direct-acting sympathomimetic drugs are intact. Epinephrine, isoproterenol, and dobutamine have similar effects in normal and denervated hearts. Indirect-acting sympathomimetics such as ephedrine have a blunted effect in denervated hearts.

Vagolytic drugs such as atropine do not increase the heart rate. Neostigmine is well known to cause bradycardia and even cardiac arrest when used for neuromuscular blockade reversal, although the exact mechanism has been unclear. Preadministration of glycopyrrolate and the ready availability of direct chronotropic agents are essential when administering neostigmine to these patients. Sugammadex presents a good alternative to neostigmine because it is devoid of significant cardiac effects.

Preoperative Evaluation

At presentation, heart transplant recipients may have ongoing rejection manifesting as myocardial dysfunction, accelerated coronary atherosclerosis, or dysrhythmias. All preoperative drug therapy must be continued, and proper functioning of a cardiac pacemaker must be confirmed. Cyclosporine-induced hypertension may require treatment with calcium channel blocking drugs or ACE inhibitors. Cyclosporine or tacrolimus-induced nephrotoxicity may present as an increased creatinine concentration. In such cases, anesthetic drugs excreted mainly by renal clearance mechanisms should be avoided. Proper hydration is important and should be confirmed preoperatively because heart transplant patients are preload dependent.

Management of Anesthesia

Experience suggests that heart transplant recipients undergoing noncardiac surgery have monitoring and anesthetic requirements

similar to those of other patients undergoing the same surgery. Intravascular volume must be maintained because these patients are preload dependent and the denervated heart is unable to respond to sudden shifts in blood volume with an increase in heart rate. TEE may be considered if the planned procedure is associated with large fluid shifts. General anesthesia is usually selected because there may be an impaired response to the hypotension associated with spinal anesthesia. Epidural anesthesia can be performed under close hemodynamic monitoring. Anesthetic management must include avoidance of significant vasodilation and acute reductions in preload. Although volatile anesthetics may produce myocardial depression, they are usually well tolerated in heart transplant patients who do not have significant heart failure. Despite reports of cyclosporine-induced enhanced neuromuscular blockade, it does not appear that these patients require different dosing of muscle relaxants than normal patients. Monitoring of neuromuscular blockade with a peripheral nerve stimulator will clarify any unusual dosing requirements. Careful attention must be paid to appropriate aseptic technique because of the increased susceptibility to infection.

KEY POINTS

- Exercise ECG is most likely to indicate myocardial ischemia when there is at least 1 mm of horizontal or downsloping ST-segment depression during or within 4 minutes after exercise. The greater the degree of ST-segment depression, the greater the likelihood of significant coronary disease. When the ST-segment abnormality is associated with angina pectoris and occurs during the early stages of exercise and persists for several minutes after exercise, significant coronary artery disease is very likely.
- Noninvasive imaging tests for the detection of ischemic heart disease are used when exercise ECG is not possible or when interpretation of ST-segment changes would be difficult. Administration of atropine, infusion of dobutamine, institution of cardiac pacing, or administration of a coronary vasodilator such as adenosine or dipyridamole creates cardiac stress. After stress is induced, either echocardiography to assess myocardial function or radionuclide imaging to assess myocardial perfusion is performed.
- blockers are the principal drug treatment for patients with angina pectoris. Long-term administration of blockers decreases the risk of death and myocardial reinfarction in patients who have had an MI, presumably by decreasing myocardial oxygen demand.
- Patients with acute coronary syndrome (ACS) can be categorized based on a 12-lead ECG. Patients with ST-segment elevation at presentation are considered to have STEMI. Patients who have ST-segment depression or nonspecific ECG changes can be classified based on the level of cardiac-specific troponins. Elevation of cardiac-specific biomarkers indicates NSTEMI. If levels of cardiac-specific biomarkers are normal, unstable angina (UA) is present.
- STEMI occurs when coronary blood flow decreases abruptly. This decrease in blood flow is attributable to acute thrombus formation at a site where an atherosclerotic plaque fissures, ruptures, or ulcerates, creating a local environment that favors thrombogenesis. Typically, vulnerable plaques (i.e., those with rich lipid cores and thin fibrous caps) are most prone to rupture. The plaques that rupture are rarely of a size that cause significant coronary obstruction. By contrast, flow-restrictive plaques that produce stable angina pectoris and stimulate development of collateral circulation are less likely to rupture.
- The primary management goal of STEMI is reestablishment of blood flow in the obstructed coronary artery as soon as possible. This can be achieved by reperfusion therapy or coronary angioplasty with or without placement of an intracoronary stent.
- Administration of blockers after AMI is associated with a significant decrease in early (in-hospital) and long-term mortality and myocardial reinfarction. Early administration of blockers can decrease infarct size by decreasing heart rate, blood pressure, and myocardial contractility. In the absence of specific contraindications, it is recommended that all patients receive intravenous blockers as soon as possible after AMI.
- NSTEMI and UA result from a reduction in myocardial oxygen supply. With an NSTEMI, rupture or erosion of an atherosclerotic coronary plaque leads to thrombosis, inflammation, and vasoconstriction. Embolization of platelets and clot fragments into the coronary microvasculature leads to microcirculatory ischemia and infarction and results in elevation of cardiac biomarker levels.
- Most postoperative MIs are NSTEMIs and can be diagnosed by ECG changes and/or release of cardiac biomarkers. Two different pathophysiologic mechanisms may be responsible for perioperative MI (PMI). One is related to acute coronary thrombosis; the other, which is more common, is the consequence of increased myocardial oxygen demand in the setting of compromised myocardial oxygen supply.
- AMI (1–7 days previously), recent MI (8–30 days previously), and UA are associated with the highest risk of PMI, MI, and cardiac death.
- Coronary artery stent placement (drug-eluting or bare-metal stent) is routinely followed by dual antiplatelet therapy to prevent acute coronary thrombosis and maintain long-term patency of the stent. Elective noncardiac surgery should be delayed for at least 30 days after PCI with bare-metal stent placement and for at least 6 months after PCI with drug-eluting stent placement and 12 months after PCI with drug-eluting stent placement after ACS.
- Preoperative use of blockers has been associated with a reduction in cardiac events in the perioperative period. A clear association exists between blocker administration and adverse outcomes such as bradycardia and stroke. Currently the only class I recommendation for perioperative

blocker use by the AHA/ACC is to continue use in patients who are already taking them. blockers can also be used in patients with elevated risk, especially those who have demonstrated ischemia on preoperative stress testing but should be started at least 1 week prior to surgery and slowly titrated.

- Current AHA/ACC guidelines state that "use of either a volatile anesthetic agent or total intravenous anesthesia is reasonable for patients undergoing noncardiac surgery, and the choice is determined by factors other than the prevention of myocardial ischemia and MI."
- The transplanted heart has no sympathetic, parasympathetic, or sensory innervation for 6 to 12 months, and the loss of vagal tone results in a higher-than-normal resting heart rate. Carotid sinus massage and the Valsalva maneuver have no effect on heart rate. There is minimal sympathetic response to direct laryngoscopy and tracheal intubation, and the denervated heart has a blunted heart rate response to light anesthesia or intense pain. The transplanted heart is unable to increase its heart rate immediately in response to hypovolemia or hypotension. It responds instead with an increase in stroke volume via the Frank-Starling mechanism. The needed increase in cardiac output is then dependent on venous return. After several minutes, the heart rate increases in response to the effect of circulating catecholamines. Because - and -adrenergic receptors are intact on the transplanted heart, it eventually responds to circulating catecholamines.

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6

Valvular Heart Disease

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OUTLINE

INTRODUCTION

The burden of valvular heart disease in developed countries is steadily increasing with current estimates of an overall prevalence of 2.5% in the United States who have moderate or severe valvular disease, increasing to 13% prevalence in those older than 75 years of age. Since the overall incidence of valvular heart disease increases with age, the need for cardiac surgery or percutaneous valvular interventions has increased in aging populations. While significant advances have been made in recent years with regard to diagnosis and treatment options, these patients still face significant perioperative morbidity and mortality.

Valvular heart disease results in the development of hemodynamic changes on the left- and/or right-sided chambers that are initially tolerated well as a result of compensatory adaptations, but eventually lead to decompensation and thus symptom onset. An in-depth understanding of the pathophysiology and clinical progression of the disease is required by those caring for these patients to optimize perioperative care. Appropriate workup for patients with valvular heart disease includes a thorough history for evaluation of causes and symptoms, and assessment of the valvular pathology by physical examination along with appropriate noninvasive and invasive diagnostic tests to accurately quantify the severity of the valve dysfunction and associated pathologies, if present.

Degenerative valve disease is the most common form of valvular heart disease in Western countries whereas rheumatic heart disease (RHD) accounts for the majority of valvular pathology in developing countries. Aortic stenosis (AS) due to calcific disease and mitral regurgitation (MR) due to primary causes such as degenerative disease, or secondary causes such as ischemic heart disease, are the most commonly encountered valvular lesions in Western countries. Patients may present with both stenotic and regurgitant lesions affecting a single heart valve, or can have more than one affected. These lesions will

produce pressure and/or volume overload within the heart chambers thus altering normal physiology. Anesthetic management requires an understanding of the likely effects of drug-induced changes to the cardiac rhythm, heart rate, preload, afterload, and myocardial contractility as well as the changes to systemic and pulmonary vascular resistance relative to the pathophysiology of the specific valvular lesion.

STENOTIC VS REGURGITANT LESIONS

Each valvular lesion will impart unique hemodynamic consequences on the upstream and downstream heart chambers and/or vessels. The narrowed orifice of the affected valve obstructs blood flow across the valve, during systole in aortic and pulmonary valves, and diastole in mitral and tricuspid valves, which results in increased pressure proximal to the affected valve. As blood reaches the stenotic valve, there is flow convergence causing the blood to eject with increased velocity through the orifice with a simultaneous pressure drop and thus consequent increase in the pressure gradient across the valve. Valvular obstruction can be classified as either fixed, defined as a constant degree of obstruction to blood flow throughout the cardiac cycle as seen in patients with AS, or dynamic, defined as a variable degree of obstruction dependent on the phase of the cardiac cycle as seen in patients with hypertrophic obstructive cardiomyopathy.

Regurgitant lesions cause pathologies that result in volume overload that leads to chamber dilation and eccentric hypertrophy in the originating chamber. The affected chamber can initially compensate for this increased volume load, but eventually function declines once the compensatory mechanism is exhausted and irreversible failure subsequently occurs.

Multiple and mixed valvular heart disease are becoming increasingly prevalent conditions. The hemodynamic and clinical consequences of valvular heart lesions may be modulated by the presence of another concomitant stenotic or regurgitant lesion on the same valve, termed *mixed valvular heart disease,* or on another valve, termed *multiple valvular heart disease.* The consequences will depend on the complex interplay of several factors: the specific combination of the lesions present, the severity and timing of onset of each individual lesion, the loading conditions, and ventricular systolic and diastolic performance. Multiple valvular disease is most often acquired, and the most frequent associations are AS with aortic regurgitation (AR), AS with MR, and AR with MR.

STRUCTURAL AND FUNCTIONAL RESPONSE OF LEFT VENTRICLE TO PRESSURE AND/OR VOLUME OVERLOAD

Valvular heart disease results in unique hemodynamic changes to the Left ventricle (LV). Despite the LV being a complex structure, it can only respond to these changes using three basic mechanisms: (1) activation of the Frank-Starling mechanism, (2) use of the adrenergic neurohormonal systems, and (3) chamber remodeling. Each of these processes has both beneficial and maladaptive effects, and the symptom onset will depend on their interplay.

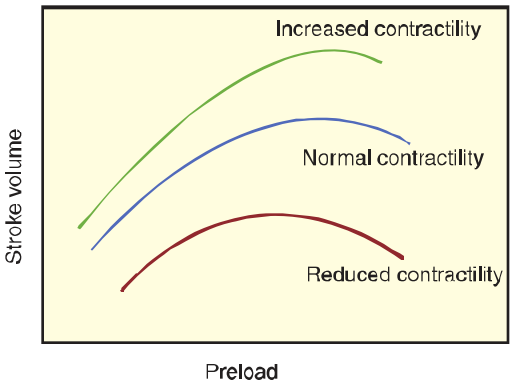

Fig. 6.1 The Frank-Starling curve shows us how changes in venous return cause the ventricle to move up or down along a single Frank-Starling curve; the slope of that curve is defined by the existing conditions of afterload and inotropy.

The LV generates pressure and displaces a volume of blood into the systemic circulation. The three factors determining LV performance are the preload (venous return, end-diastolic volume), myocardial contractility (the force generated at any given end-diastolic volume), and afterload (aortic impedance and wall stress). The relationship between LV pressure generation and volume ejection can be expressed as a plot of LV pressure versus LV volume, better known as the Frank-Starling curve. In ventricles with normal cardiac function, there is a positive correlation between increased cardiac filling pressures and increased myocardial performance. As cardiac function declines, this relationship is shifted to the right and flattened so that further increases in the left heart filling pressures lead to minimal increases in cardiac output (Fig. 6.1). Initial reductions in LV performance are then countered with activation of neurohumoral systems resulting in increased fluid retention, increasing both sarcomere length and contractility. While this response is initially compensatory, it will eventually transition to a maladaptive one as the sarcomere is overstretched and the number of cross bridges that can form is reduced linearly with increasing length. With diastolic dysfunction, there is also an upward shift in the end-diastolic pressure-volume relationship that occurs because a higher pressure is required to achieve the same volume.

LV remodeling is another important response to valvular heart disease. Remodeling is defined as a structural heart change that occurs to meet the increased demand due to increased hemodynamic load or neurohormonal activation. Stresses typically include pressure overload as seen in AS or volume overload as seen in regurgitant lesions. While initially remodeling is a compensatory measure, it will ultimately transition to worsening cardiac function with continued stress. The three general patterns of remodeling are (1) concentric LV remodeling that occurs in response to pressure overload, (2) eccentric LV hypertrophy due to volume overload, or (3) mixed hypertrophy that may occur due to mixed valvular lesions. Factors affecting the degree of remodeling include decreased contractility due to ischemia, increased vascular resistance, and neurohormonal activation.

Each valvular lesion will create its own unique set of loading conditions that will cause specific structural and functional

changes to facilitate compensation. Faced with similar stressors and lesions, patients will exhibit significant differences in the compensatory response suggesting a great deal of modulation downstream from the initial mechanical signal. Ascertaining when these changes go from being compensatory to maladaptive is crucial in deciding when to intervene in valvular heart disease.

EVALUATION OF VALVULAR HEART DISEASE

History should focus on questions designed to evaluate exercise tolerance, which will give an indication of cardiac reserve. Patients are generally classified according to the criteria established by the New York Heart Association (NYHA) (Table 6.1). The presence of angina should also be screened for in the history, as this may occur even in the absence of coronary artery disease (CAD). This generally reflects increased myocardial oxygen demand due to ventricular hypertrophy where the metabolic demands of the thickened muscle mass may exceed the ability of even patent coronary arteries to deliver adequate amounts of oxygen, causing angina-type symptoms.

Physical examination should focus on signs of heart failure, which can be left sided (i.e., pulmonary edema) and/or right sided (i.e., dependent edema or ascites). The presence of a heart murmur reflecting turbulent blood flow across the valve should also be detected and appreciated in a patient with clinically significant valvular heart disease. The character, location, intensity, and direction of radiation of a heart murmur provide clues to the location and severity of the valvular lesion.

The electrocardiogram (ECG) of a patient with valvular disease often exhibits characteristic changes that reflect either the direct insult or the compensatory remodeling from the primary lesion. Broad and notched P waves (P mitrale) suggest the presence of left atrial enlargement typical of mitral valve disease. LV and right ventricular (RV) hypertrophy can be diagnosed by the presence of left or right axis deviation and high voltage. Other common ECG findings include dysrhythmias, conduction abnormalities, and evidence of active ischemia or previous myocardial infarction.

The cornerstone of diagnosis of valvular heart disease is Doppler echocardiography (Table 6.2). In addition to diagnosis, echocardiography can also be used to noninvasively monitor the lesion and help guide decision making for interventions. It is critical in determining the indication and timing of surgery as well as making intraoperative decisions about whether a valve should be repaired or replaced. Three-dimensional echocardiography is also rapidly being incorporated into the evaluation of patients with valvular heart disease and is becoming the standard of care in a multitude of circumstances, including assessing suitability of repair in mitral valve surgery and measurement of the LV outflow tract in patients with AS or the mitral area in patients with mitral stenosis (MS). Stress echocardiography can be of use in certain situations such as distinguishing true severe AS from pseudosevere and assessing LV flow reserve when the pressure gradient is low and LV ejection fraction is reduced.

Cardiac catherization is currently recommended in situations where noninvasive evaluation is inconclusive or discordant with clinical findings. While most assessments, such as assessing the valve area using the Gorlin equation, are unaffected by valvular disease, other standardized techniques such as assessing cardiac output by either thermodilution or the Fick method must be interpreted with caution as disease states such as severe tricuspid regurgitation (TR) and low cardiac output can affect the accuracy of these results.

Computed tomography (CT) is increasingly used to assess the aortic valve calcium score when there is evidence of low-flow, low-gradient AS, and preserved LV ejection fraction. High calcium scores are consistent with an increase in the likelihood of severe AS. CT is also routinely used in procedural planning for patients undergoing transcatheter aortic valve replacement (TAVR) to size the LV outflow tract and determine the optimal size valve to implant.

Cardiac magnetic resonance imaging (MRI) is an evolving tool in the diagnosis of valvular heart disease. It has particular utility in the diagnosis of regurgitant lesions as well as measurement of ventricular volumes and systolic function. Cardiac MRI allows for accurate identification of serial changes in ventricular volumes, mass, and function. These changes reflect the global burden of the evolving valvular pathology and may have the potential to help determine the optimal time for surgical intervention.

Regardless of what method is used to evaluate patients with valvular heart disease, it is crucial to perform periodic evaluation of any patient with valvular heart disease. This is important because when patients start to develop symptoms, they will have a higher risk of perioperative adverse events. Performing periodic evaluation to track disease progression helps optimize timing of surgical intervention and thus improves perioperative outcomes.

TABLE 6.1 New York Heart Association Functional Classification of Patients With Heart Disease

Class	Description
I	Asymptomatic
II	Symptoms with ordinary activity but comfortable at rest
III	Symptoms with minimal activity but comfortable at rest
IV	Symptoms at rest

TABLE 6.2 Utility of Echocardiography in the Evaluation of Valvular Heart Disease

Determine significance of cardiac murmurs
Identify hemodynamic abnormalities associated with physical findings
Determine transvalvular pressure gradient
Determine valve area
Determine ventricular ejection fraction
Diagnose valvular regurgitation
Evaluate prosthetic valve function

AORTIC STENOSIS

Etiology

Age-related degenerative AS is by far the most common cause among adults in the United States, while rheumatic heart disease is the most common worldwide. The prevalence of AS increases with advancing age, with over 30% of adults over age 65 years exhibiting some degree of aortic sclerosis, and 2% overall having severe grade valvular stenosis often requiring intervention. On histology, these valves appear thickened, inflamed, and calcified. This degenerative process of the aortic valve has been compared to atherosclerosis with endothelial dysfunction, lipid deposition, and oxidative changes that stimulate inflammation and lead to fibrosis and calcification. Risk factors for the development of calcific AS are similar to those of atherosclerosis and include systemic hypertension, hypercholesterolemia, diabetes mellitus, smoking, and male gender.

Bicuspid aortic valve (BAV) is the second most common cause for the development of AS in the United States and has a prevalence of 1% to 2%. The abnormal valve architecture makes the leaflets susceptible to constant low shear stress that over time leads to thickened and calcified leaflets that generally tend to occur in the fifth or sixth decade; trileaflet aortic valves rarely develop degenerative calcific AS before the sixth or seventh decade of life. Other pathologies associated with BAV include aortic root dilation, aortic coarctation, and AR.

RHD is characterized by fusion of the commissures between the leaflets, fibrosis, and calcification, with a resultant narrowing of the valve orifice. Rheumatic AS very commonly affects the mitral valve as well; as a result, most patients with rheumatic AS also have an isolated or combined mitral lesion, including stenosis or regurgitation. Other rarer causes of AS include metabolic diseases (i.e., Fabry disease), systemic lupus erythematous, or alkaptonuria.

Pathophysiology

The decrease in aortic valve area causes an obstruction to LV forward flow, which requires a compensatory increase in LV pressure to maintain stroke volume. The initial response to this increased pressure is concentric hypertrophy, which reduces wall stress as demonstrated by Laplace's law of wall tension. The LV remodeling process can accommodate the pressure overload for many years before it eventually becomes maladaptive, and LV function begins to decline with chamber dilation and a reduction in cardiac output. A mean gradient of greater than 40 mm Hg or a valve area of less than 1 cm^2 is characteristic of severe disease. Cardiac output, requiring significant compensation already to remain normal at rest, may lack the cardiac reserve to rise in response to exercise. Angina may occur in these patients even in the absence of CAD. This is due to mismatch between a consistent supply of oxygen meeting the increased demand secondary to concentric LV hypertrophy and the increase in myocardial work necessary to offset the afterload produced by the stenotic valve. Myocardial ischemia can also result from compression of the subendocardial vessels by the increased LV pressure. Syncope may occur in these patients and is usually associated with exertion as exercise-induced vasodilation in the presence of an obstruction with a fixed cardiac output can result in hypotension and reduced cerebral perfusion.

Clinical Manifestations and Diagnosis

The onset of symptoms in patients with AS does not occur until late in the disease because the hypertrophied left ventricle can produce the elevated pressures necessary to maintain an adequate stroke volume. When symptoms do occur, this generally signifies severe disease and often heralds the need for intervention due to the significant mortality that is associated with untreated, severe AS.

The classic triad of symptoms associated with AS include exertional dyspnea, chest pain, and syncope. Dyspnea typically occurs as a result of diastolic dysfunction, caused by elevated LV filling pressures in the noncompliant, hypertrophied left ventricle. Chest pain and syncope occur due to a mismatch between myocardial oxygen supply and demand from the thickened myocardium and the inability to augment cardiac output through the stenotic valve. Symptoms related to LV failure are generally not present until the advanced stages of AS when it is associated with LV systolic dysfunction.

On physical examination, cardiac auscultation will reveal a characteristic systolic murmur that is best appreciated in the aortic area and may radiate to the neck, mimicking a carotid bruit. The intensity of the murmur does not necessarily correlate with the severity of the murmur. Pulsus parvus et tardus is another sign associated with AS in which palpation of the carotid pulse rises slowly to a delayed and sustained peak. While this physical finding is specific to AS, it is often difficult to appreciate in the elderly with stiffened arterial walls that can mask this finding. Other nonspecific findings include splitting of S_2 due to prolonged LV ejection across the stenotic valve and an audible S_4 at the apex reflecting LV hypertrophy.

Diagnostic investigations should begin with ECG, which may have evidence of LV hypertrophy and, in advanced cases, ST depression and T-wave inversion in the lateral leads. Chest radiograph may show a prominent ascending aorta due to post–stenotic aortic dilation, and aortic valve calcification may be identified on the lateral film.

Transthoracic echocardiography with Doppler examination is the test of choice for the diagnosis and monitoring of patients with AS. Key findings include whether it is a trileaflet or bileaflet aortic valve, thickening and calcification of the valvular leaflets with decreased mobility, LV hypertrophy, and LV systolic or diastolic dysfunction (Fig. 6.2A–B). Valve area and transvalvular pressure gradients can also be estimated with Doppler (see Fig. 6.2C). Stress echocardiography may be required in a subset of patients with reduced LV function and low flow AS.

Cardiac catherization with invasive measurement of transvalvular gradients may be useful if there is a discrepancy between the clinical and echocardiographic findings. Coronary angiogram is also often indicated to detect for CAD in patients who are being considered for operative intervention due to its high prevalence in this population. CT is increasingly used to assess the aortic valve calcium score, which correlates well with the likelihood of severe AS.

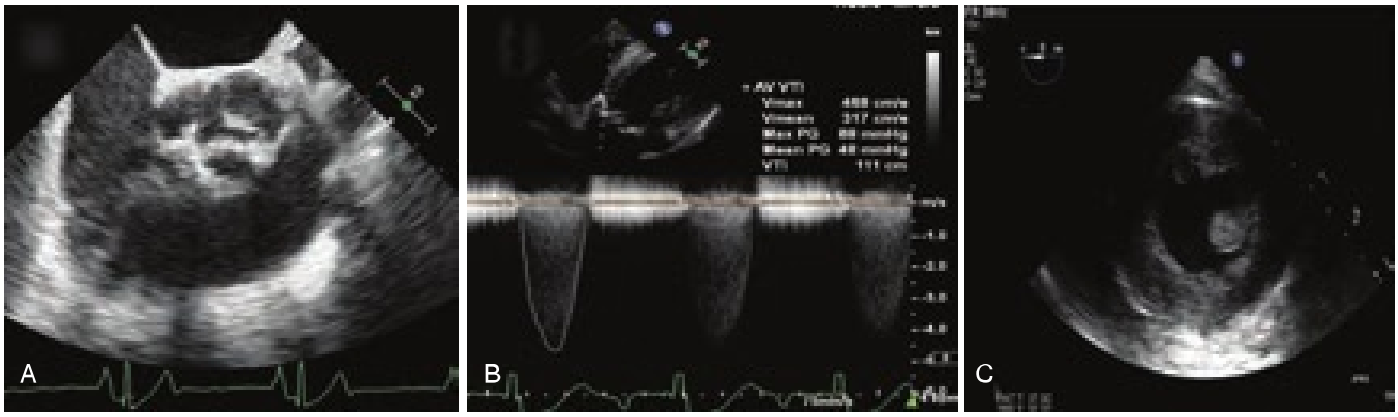

Fig. 6.2 Transesophageal echocardiography images of patient with characteristic features of severe aortic stenosis. (A) Midesophageal short-axis view showing severely calcified aortic valve with a small valve area. (B) Deep transgastric view with continuous wave Doppler through aortic valve showing high peak velocity along with high peak and mean gradients. (C) Transgastric short-axis view showing compensatory concentric left ventricular hypertrophy.

Timing and Type of Intervention

Patients with AS have a long latent period in which the onset of symptoms is prevented by compensatory measures and survival is similar to patients without AS. However, once symptoms develop, survival declines dramatically with mortality approaching 75% within 3 years of symptom onset unless the aortic valve is replaced (Fig. 6.3). Asymptomatic patients should be followed carefully for the development of symptoms and have serial echocardiograms to quantitatively monitor for deteriorating LV function. Risk stratification using a combination of serial echocardiography and additional testing to help determine the degree of AS may help to identify patients who would benefit from valve replacement before symptom onset.

Surgical aortic valve replacement (SAVR) and TAVR are the mainstays of treatment for severe AS. As clinical experience and evidence of good long-term outcomes is growing with TAVR, its use is steadily increasing over SAVR. The decision to proceed with SAVR or TAVR should be made on a case-by-case basis and involve a multidisciplinary heart valve team taking into account a multitude of factors: the patient's life expectancy, frailty, comorbidities, specific anatomy, valves, and personal preferences. The type of treatment suitable for patients is often informed by their surgical risk as defined by the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM). In low-risk surgical patients, the decision between SAVR or TAVR is uncertain, and the decision to proceed with one over the other should be made based on individualized risk-benefit assessment. Current guidelines recommend TAVR over SAVR in low-risk surgical patients who meet all four of the following criteria: (1) age is over 65 years, (2) transfemoral TAVR is feasible, (3) aortic valve is trileaflet, and (4) absence of high-risk anatomic features such as adverse aortic root, low coronary ostia height, or LV outflow tract calcification. For patients who lack one or more of these four criteria, SAVR is

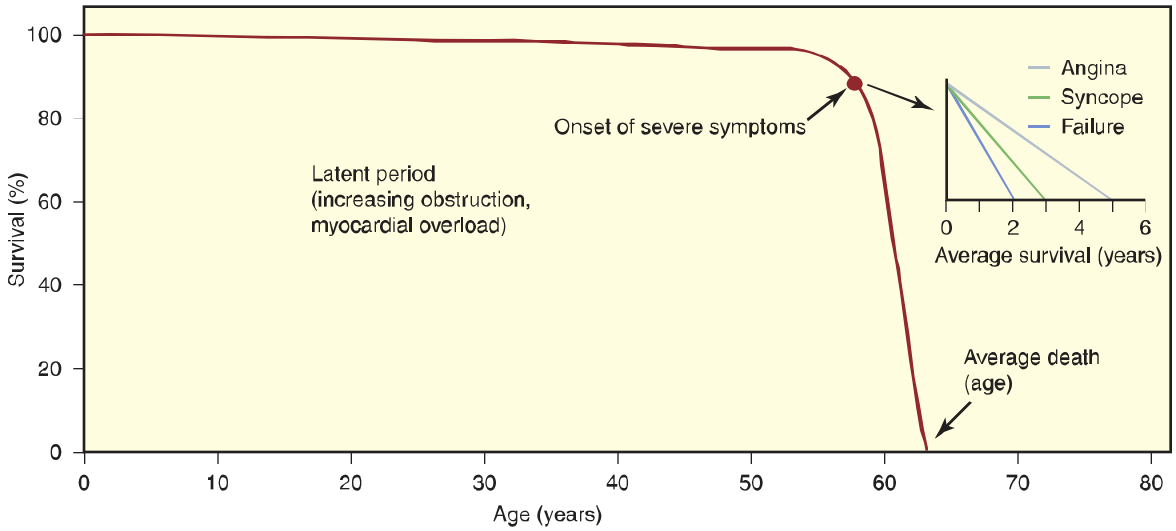

Fig. 6.3 In patients with aortic stenosis after a long latent asymptomatic period, during which time survival is almost normal compared to those patients without aortic stenosis, survival declines precipitously once symptoms develop.

preferred. In intermediate-risk patients, if TAVR is feasible and high anatomic features (i.e., adverse aortic root, low coronary ostia height, heavily calcified bicuspid aortic valve, and severe LV outflow tract calcification) are absent, TAVR is recommended. In high-risk patients, TAVR is the intervention of choice.

Medical therapy does not prevent the progression of AS, but it is useful in patients who are not suitable candidates for valve replacement. The therapy typically focuses on treatment of concurrent cardiovascular conditions along with prevention or treatment of superimposed diseases such as atrial fibrillation (Afib), CAD, and heart failure that often exacerbate the effects of valve obstruction. Optimal hemodynamic conditions should be maintained as much as possible, and any symptoms that develop should be treated promptly. Physical activity should be curtailed or even avoided in these patients. Medications that alter preload, contractility, and afterload should be used with caution.

Percutaneous aortic balloon valvotomy (PABV) is occasionally performed in adolescents and young adults with congenital, noncalcific AS. It is not routinely used as an intervention in adults with severe calcific AS because of high restenosis rates, embolic complications, and the potential development of AR. In rare cases, PABV may be used in patients with severe LV dysfunction and cardiogenic shock as a bridge to surgical intervention.

Intraoperative Management

Patients with AS who are undergoing noncardiac surgery are at high risk for perioperative complications. An appropriate preoperative investigation should ascertain the severity of AS, and anesthetic management of these patients should include maintenance of sinus rhythm, a normal heart rate, and maintenance of adequate preload, afterload, and contractility (Table 6.3).

Normal sinus rhythm should be preserved as much as possible because filling of the hypertrophic, noncompliant left ventricle depends significantly on the left atrial contraction during end diastole that is lost in conditions such as atrial fibrillation. Loss of atrioventricular synchrony will result in reduced LV filling and lead to a dramatic decrease in stroke volume and blood pressure. Avoiding both tachycardia and excessive bradycardia is important. With tachycardia, the decrease in diastolic filling time will result in inadequate oxygen delivery to the hypertrophied left ventricle. With bradycardia, the heart will have inadequate cardiac output as these patients cannot compensate by increasing stroke volume due to the stenotic valve.

Maintaining adequate preload with volume resuscitation is paramount as these patients are generally preload dependent; fluid boluses should be titrated according to either clinical assessment or ideally by a goal-directed method such as transesophageal echocardiography (TEE) or other invasive parameters. Hypotension should ideally be prevented or at least treated promptly with an α-adrenergic vasoconstrictor such as phenylephrine. This will increase the systemic vascular resistance (SVR) without the chronotropic side effects associated with other medications such as epinephrine or dobutamine. Avoiding doses of anesthetic agents that might cause significant depression of myocardial contractility such as high doses of propofol or volatile anesthetic agents is important in maintaining cardiac output.

General anesthesia is often selected in preference to epidural or spinal anesthesia because the sympathetic blockade produced by neuraxial anesthesia can lead to significant hypotension as a result of severely impaired preload. Induction of general anesthesia can be achieved with a combination of intravenous (IV) induction agents that do not decrease SVR or myocardial contractility such as opioids, benzodiazepines, and etomidate. Propofol can be utilized with caution at reduced doses in combination with other induction agents with prompt prevention or treatment of the anticipated drop in SVR. Maintenance of anesthesia is generally accomplished with a combination of volatile anesthetics and opioids.

Monitoring of patients with AS must include a five-lead ECG that can reliably detect cardiac arrhythmias and ischemia. The decision to proceed with invasive monitoring such as invasive arterial monitoring or TEE should be made based on severity of the disease and the complexity of the surgery.

TABLE 6.3 Anesthetic Considerations in Patients With Aortic Stenosis

Maintain normal sinus rhythm
Avoid bradycardia or tachycardia
Avoid hypotension
Optimize intravascular fluid volume to maintain venous return and left ventricular filling

AORTIC REGURGITATION

Etiology

Aortic regurgitation (AR) occurs as a result of incomplete coaptation of the aortic valve leaflets in diastole and may be caused by disease processes that affect the aortic valve leaflets, aortic root, or both. Common causes of leaflet abnormalities include congenital abnormalities of the aortic valve (i.e., bicuspid valves), rheumatic disease, infective endocarditis, calcific degeneration, and myxomatous degeneration. Abnormalities of the aortic root include idiopathic aortic root dilatation, hypertension-induced annuloaortic ectasia, aortic dissection, Marfan syndrome, Ehlers-Danlos syndrome, or aortitis occurring as a result of syphilitic infection, rheumatoid arthritis, or ankylosing spondylitis. AR has also been described as a complication in patients undergoing PABV or TAVR. The majority of these lesions produce chronic AR, with slow, insidious LV dilatation. In contrast, acute AR is almost always a result of either infective endocarditis or aortic dissection.

Pathophysiology

The inability of the aortic valve leaflets to remain competent during diastole results in a portion of the LV stroke volume leaking back into the left ventricle from the aorta (Fig. 6.4A). This regurgitant volume results in increased LV end-diastolic volume and pressure. As a compensatory measure, the left ventricle responds with eccentric hypertrophy, with an increase in

LV mass with normal relative wall thickness. The combination of LV eccentric hypertrophy along with LV chamber enlargement increases the total stroke volume. The magnitude of the regurgitant volume depends on the heart rate and SVR. The heart rate affects the time available for the regurgitant flow to occur, and the SVR impacts the pressure gradient across the aortic valve. Thus the regurgitant volume can be reduced by inducing tachycardia and peripheral vasodilation.

The LV remodeling that occurs due to the increase in LV pressure and volume overload is initially adaptive as the forward stroke volume and systemic blood flow are maintained with little to no change in filling pressures or cardiac output despite the regurgitation. Eventually as the lesion progresses, these adaptive measures will fail, and the ejection fraction and decline in forward flow results in symptom onset. The reduction in LV function that occurs in the advanced stages of AR often precedes symptom onset and should prompt intervention.

While patients with chronic AR have adequate time to develop compensatory measures to deal with the increased volume and pressure overload, this is not the case with acute AR. With acute AR, there is a sudden increase in LV volume and pressure, which typically results in coronary ischemia. Rapid deterioration can occur with impaired LV function leading to heart failure (Fig. 6.4).

Clinical Manifestations and Diagnosis

Patients with chronic AR may remain asymptomatic for an extended period of time due to adequate compensation with adaptive mechanisms. Some patients may develop symptoms related to the increased LV size and stroke volume, experienced as an uncomfortable awareness of their heartbeat, particularly noticed when lying down, or head pounding due to increased stroke volume. Exertional dyspnea is usually an early symptom of decompensation and is related to the gradual decline in systolic function. More severe symptoms of heart failure such as orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema may develop without appropriate intervention. Angina may also occur even in the absence of CAD and often occurs at night, due to bradycardia with subsequent fall in the diastolic blood pressure and increased regurgitant volume. The drop in diastolic blood pressure reduces coronary perfusion pressure and results in angina-type symptoms.

Physical examination in patients with severe AR centers on examination of peripheral pulses, precordial inspection and palpation, and auscultation of the heart. Signs that are present due to AR are generally related to increased stroke volume. The arterial pulse rises sharply and collapses abruptly with a widened pulse pressure, known as the Corrigan pulse. A pistol shot pulse may be heard over the femoral arteries, known as Traube sign. Capillary pulsations can also be appreciated in the fingertips or lips, which is known as Quincke pulses. Palpation of the heart in chronic, severe AR reveals a heaving, laterally displaced LV impulse and an apical diastolic thrill. The murmur of AR is a high-pitched, blowing decrescendo murmur that is often loudest along the left sternal border. A low-pitched middiastolic rumble, known as the Austin Flint murmur, may be audible in severe AR due to the high-frequency fluttering of the anterior mitral valve leaflet caused by the AR jet.

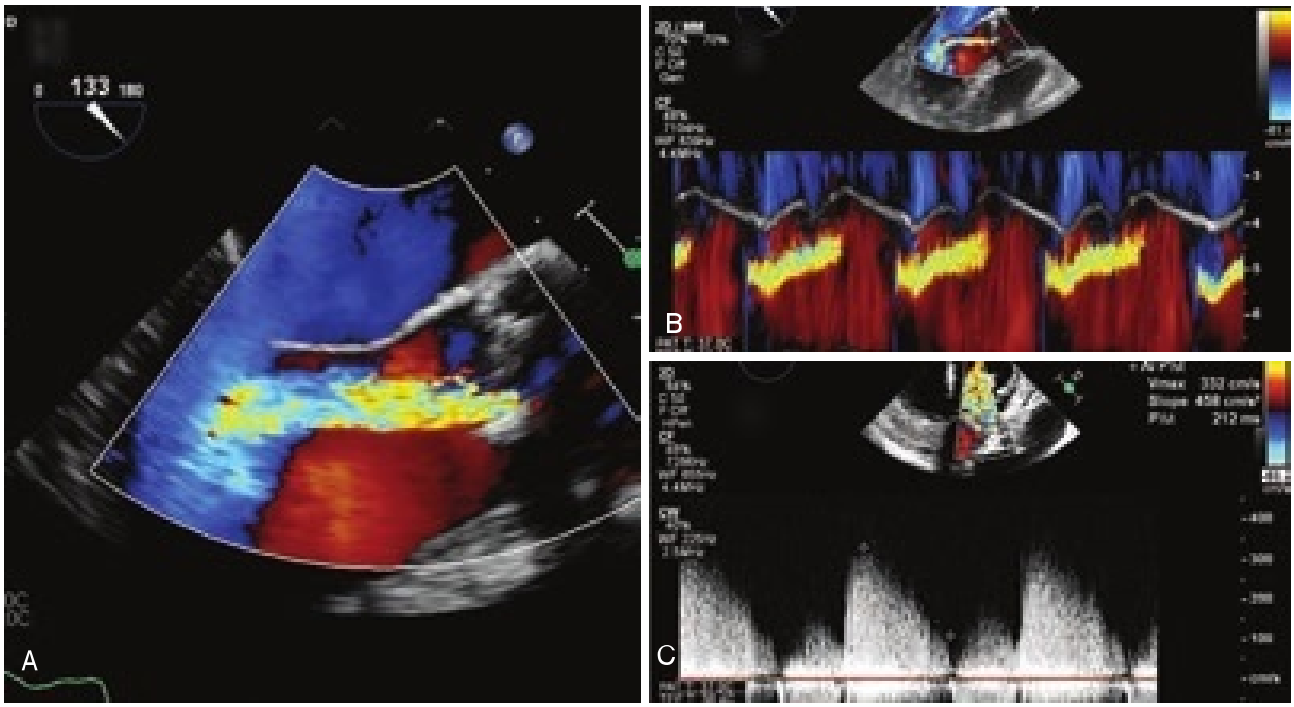

Fig. 6.4 Transesophageal echocardiography images of a patient with aortic regurgitation showing (A) regurgitant flow into the left ventricular outflow tract (LVOT) during diastole, (B) M-mode placed in the LVOT during diastole allowing measurement of the regurgitant jet width as a percentage of overall LV outflow tract width (Perry index), and (C) pressure half-time measurement obtained in the deep transgastric window.

In patients with chronic AR, there will be evidence of LV enlargement and hypertrophy on both the chest radiography and ECG. Echocardiography is the gold standard for diagnosis, evaluation, and surveillance of AR. Anatomic abnormalities of the aortic valve such as congenital abnormalities, leaflet perforations, or prolapse along with abnormalities of the aortic root and annulus can be identified on echocardiography. LV size, volume, and function can be easily measured, with Doppler interrogation used to assess the severity of regurgitation. To quantify the severity of AR, there are several methods available: (1) the Perry index, which measures the regurgitant jet width as a percentage of overall LV outflow tract width (Fig.6.4B) (2) regurgitant fraction, the percentage of stroke volume that returns to the left ventricle from the aorta during diastole; or (3) pressure half-time, the time it takes for the initial maximal pressure gradient in diastole to fall by 50% Fig. 6.4C. In patients with severe AR, a rapid drop in the pressure gradient occurs. Cardiac catheterization can also be used in the assessment of AR, generally in patients with angina to rule out CAD as a cause.

Timing and Type of Interventions

Medical treatment of AR should be based around decreasing systolic hypertension and LV wall stress while preserving or improving LV function. Although reducing afterload with medical therapy can reduce the severity and improve symptoms, there is little evidence that this approach delays the need for surgical intervention. Commonly used medication classes for managing AR include diuretics, angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers.

Surgical intervention should ideally occur before the onset of LV dysfunction or decompensation. Indications for intervention include symptomatic heart failure, nonspecific symptoms with poor performance on an exercise stress test, and evidence of LV dysfunction or severe LV dilatation with or without symptoms. The type of surgical intervention will depend on the etiology of the AR. Aortic valve replacement is often the treatment of choice for pathologies of the valve itself; aortic root replacement with either aortic valve replacement or a valve-sparing procedure is needed when the etiology is related to the aortic root. In patients with acute AR, immediate surgical intervention is required because the acute volume overload will rapidly result in heart failure. Alternatives to aortic valve replacement with a prosthetic valve include pulmonic valve autograft, known as the Ross procedure, and aortic valve reconstruction. Percutaneous interventions for pure native AR have been discouraged because specific anatomic features can compromise device success and procedural safety.

Intraoperative Management

Hemodynamic goals for patients with AR undergoing noncardiac surgery should focus on maintaining forward LV stroke volume. Bradycardia should be avoided as this will increase the duration of diastole, allowing for more time for AR to occur causing acute LV volume and pressure overload. Abrupt increases in SVR should be avoided, as this can precipitate LV failure by increasing the transvalvular gradient and therefore the regurgitant volume. Overall, modest increases in heart rate and modest decreases in SVR are preferable hemodynamic goals during anesthesia. Although biventricular function typically remains intact in patients with moderate to severe AR through compensatory mechanisms, the balance is often tenuous, and anesthetic-induced myocardial depression may cause decompensation. When patients do develop or present with LV failure, the primary treatment involves vasodilators to reduce afterload and inotropes to improve contractility and increase forward flow.

Induction of anesthesia for patients with mild to moderate AR can be achieved with induction agents such as propofol slowly titrated in doses that reduce or maintain a low normal SVR to minimize regurgitant flow, while maintaining adequate cardiac output and myocardial oxygen delivery. Blunting the sympathetic response to laryngoscopy and the subsequent hypertension is also important and can be achieved with a short-acting opioid medication.

Maintenance of anesthesia is often best achieved with a volatile anesthetic because of the beneficial vasodilatory effects that reduce afterload and decrease AR volume. Combining with nitrous oxide with or without opioid helps to control sympathetic hypertension from surgical stimulus. High doses of volatile anesthetic should be avoided due to the potential for myocardial depression and resultant hypotension. In patients with severe LV dysfunction, high-dose opioid anesthesia may be preferred to optimize hemodynamics, however, opioid-induced bradycardia should be avoided.

Adequate preload should be maintained with judicious use of IV fluids. Mechanical ventilation should focus on maintaining normal oxygenation and carbon dioxide elimination while providing adequate time for venous return. Emergence from anesthesia and weaning from controlled mechanical ventilation should be a gradual and controlled process. Acute increases in SVR around this period should be controlled with short-acting agents such as nitroglycerin, hydralazine, or labetalol as abrupt increases in SVR may cause hemodynamic deterioration.

Surgery in patients with asymptomatic AR may not require invasive monitoring, and standard monitoring to detect rhythm disturbances with the noninvasive blood pressure monitor cycled at regular intervals is generally adequate. In patients with moderate to severe AR undergoing extensive surgery, invasive monitoring is generally required, and intraoperative TEE is typically helpful if available.

MITRAL STENOSIS

Etiology

Mitral stenosis is most often associated with RHD, which is a major public health problem in developing countries. In the Western world, widespread use of programs for the early detection and treatment of streptococcal pharyngitis have reduced the incidence of RHD and thus the incidence of rheumatic MS. In many populations, RHD more commonly affects females more than males. Involvement of the mitral valve is present in approximately 90% of individuals with RHD, of which 25% have pure MS, 40% have mixed MS and MR, and 25% have multiple valvular disease. Rheumatic MS is a chronic condition;

it is not typically seen during the first episode of acute rheumatic carditis but generally manifests 20 to 30 years after the initial insult.

Less common causes for MS include severe mitral annular calcification, radiation-associated valve disease, carcinoid syndrome, left atrial myxoma, rheumatoid arthritis, systemic lupus erythematous, and iatrogenic MS after mitral valve repair surgery.

Pathophysiology

The normal mitral valve orifice has an area of 4 to 6 cm^2, and MS generally develops when the area is reduced to less than 2 cm^2. Changes to the mitral valve apparatus that occur over time include (1) fusion of the leaflet commissures; (2) thickening, fibrosis, and calcification of the leaflet cusps; and (3) thickening, fusion, and shortening of the chordae tendinae. Leaflet thickening and calcification occur primarily due to the chronic stress of turbulent flow through a deformed valve. The net result leads to a narrowing at the apex of a funnel-shaped, "fish-mouth" valve.

The hemodynamic consequence is resistance to transmitral flow and attenuation of the atrial contribution to LV filling. Consequently, there is an increase in left atrial volume and pressure that is not only dependent on the severity of the MS, but also on cardiac output and heart rate. In patients with mild to moderate MS, left atrial pressures are only minimally elevated at rest but may increase with exercise or conditions that increase heart rate, such as Afib, and consequently produce symptoms. In more severe forms of MS, left atrial pressures are usually significantly elevated at rest, which leads to pulmonary hypertension, right heart failure, and symptoms at rest. LV function is generally preserved, and adaptive changes occur in the left atrium, such as myocardial hypertrophy, interstitial fibrosis, and geometric remodeling to help counteract the increase in the left atrial pressure.

Clinical Manifestations and Diagnosis

Patients with MS generally present with exertional dyspnea with or without decreased exercise tolerance. These symptoms are generally slow to progress due to the nature of RHD, and many patients are slow to recognize the symptoms because the progression of the disease is often accompanied by a gradual reduction in activity. Symptoms are primarily related to the extent and severity of valvular stenosis, as it impacts the left atrial pressure, pulmonary pressures, pulmonary vascular resistance, and cardiac output. Dyspnea occurs as pulmonary venous pressure increases causing transudation of fluid into the pulmonary interstitial space. There is a decrease in pulmonary compliance, which causes increased work of breathing and therefore leads to progressive dyspnea on exertion. Over time, changes in pulmonary vasculature result in pulmonary hypertension, which can progress to right-sided heart failure.

Other less common clinical presentations due to high pulmonary pressures and vascular congestion include hemoptysis, chest pain, ascites, and lower extremity edema. Atrial enlargement may lead to new onset Afib and hoarseness if there is left atrial compression of the recurrent laryngeal nerve, known as Ortner syndrome. Thromboembolism may be another presentation due to blood stasis in the left atrium causing thrombus development. While the symptoms of MS develop gradually over time, any stressor (i.e., sepsis, fever, emotional stress, pregnancy) can markedly increase the transmitral pressure gradient and precipitate the onset of symptoms. This occurs by the stressor increasing the cardiac output, which raises transmitral flow, or causing tachycardia, which decreases diastolic filling time.

Physical examination in patients with MS may reveal pulmonary rales, peripheral edema, ascites, an elevated jugular venous pressure, and congestive hepatomegaly. Classically patients with severe disease will develop cutaneous vasodilation resulting in pinkish-purple patches on the cheeks, known as mitral facies. On auscultation, the opening snap that is characteristic of MS occurs early in diastole; it is best appreciated during expiration and is followed by a low-pitched rumbling diastolic murmur that is best heard at the apex with the patient in the left lateral decubitus position.

Chest radiograph may reveal left atrial enlargement, which presents as straightening of the left heart border and elevation of the left mainstem bronchus. The "double density" sign of an enlarged left atrium with mitral calcification and evidence of pulmonary edema or pulmonary vascular congestion may also be seen. On the ECG, left atrial enlargement may be evident as broad, notched P waves as well as findings of Afib.

Echocardiography is the diagnostic test of choice to assess the anatomy of the mitral valve, including the degree of leaflet thickening, calcification, changes in mobility, and extent of involvement of the subvalvular apparatus (see Fig. 6.5A). The severity of MS is assessed by calculation of the mitral valve area and using Doppler echocardiography to measure transmitral gradients or pressure half-time (see Fig. 6.5B). Pressure half-time measures the time interval in milliseconds between the maximum mitral gradient in early diastole and the time point where the gradient is half the maximal initial value; the presumption is that as the valve becomes more stenotic, the pressure half-time increases. Echocardiography also allows evaluation of cardiac chamber dimensions, pulmonary hypertension, LV and RV function, assessment of other valves that may be affected with RHD, and examination of the left atrial appendage for the presence or absence of thrombus. Stress testing, cardiac catheterization, and cardiac MRI may be indicated if there is inconsistency between resting Doppler echocardiographic findings and clinical presentation.

Timing and Type of Intervention

In the absence of correction of the stenotic lesion, MS is generally a slowly progressive disease initially, but progresses more rapidly after symptom onset. In general, a valve area less than 2.5 cm^2 must be present before exertional dyspnea occurs; a valve area less than 1.5 cm^2 is generally required before symptoms develop at rest. Patients with MS should be followed by clinical examination and echocardiography until (1) symptoms start to interfere with daily activities, (2) Afib develops, or (3) pulmonary hypertension becomes severe, at which time they should be referred for surgical or percutaneous intervention.

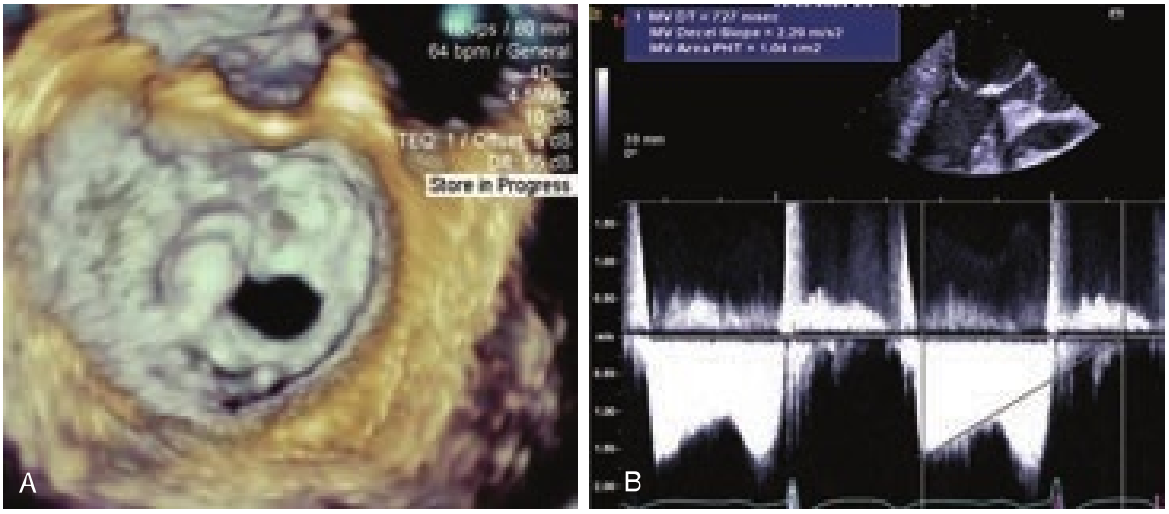

Fig. 6.5 Transesophageal echocardiography images of a patient with severe rheumatic heart disease of the mitral valve showing (A) three-dimensional image displaying heavily calcified leaflets with mitral annular calcification and the classic fish-mouth view, and (B) transmitral flow and calculation of the pressure half-time to estimate mitral valve area.

Medical treatment is based around secondary prevention of rheumatic fever with antibiotic prophylaxis and the treatment of complications as they occur. Diuretics along with a salt-restricted diet are the mainstay for treating symptoms of pulmonary congestion. If Afib develops, aggressive medical therapy to control the rate or rhythm is paramount because a rapid heart rate reduces mitral inflow time, thereby increasing left atrial pressure and reducing cardiac output. This is achieved with medications such as β blockers, digoxin, or nondihydropyridine calcium channel blockers. Anticoagulation is required for patients with MS and Afib or a history of thromboembolism due to the risk of embolic stroke.

Percutaneous mitral balloon valvotomy is a good treatment option for suitable patients as this has been shown to achieve durable results. Ideal candidates for this procedure are younger patients with more pliable mitral valve leaflets with little calcification, no left atrial thrombus, and no more than mild MR. With this procedure, the mitral valve area is doubled and there is a significant reduction of the transmitral gradient and symptoms. In patients not suitable for balloon valvulotomy, surgical commissurotomy or valve replacement is performed. Due to the long-term complications associated with mitral valve replacement, it should only be considered in those patients with a mitral valve area less than 1 cm^2 and severe symptoms despite maximum medical therapy.

Intraoperative Management

Patients with MS should be medically optimized with adequate heart rate control and management of volume overload prior to proceeding with elective noncardiac surgery. Medications used for heart rate control should be continued up to the time of surgery. The decision to proceed with general or neuraxial anesthesia should be based on the surgical procedure. If neuraxial anesthesia is to be performed, the patient should stop the anticoagulation per guideline recommendations. Epidural anesthesia is generally considered to be safer over spinal anesthesia, as this can be slowly titrated to effect and hemodynamics controlled more closely. Regardless of the choice of anesthetic, intraoperative management for noncardiac surgery in patients with MS should focus on the prevention and treatment of events that can decrease cardiac output or produce pulmonary edema (Table 6.4).

Induction of anesthesia can be achieved using any induction agent with the exception of ketamine, which should be avoided because of its propensity to increase heart rate. Short-acting β blockers or opioids should be used around times of sympathetic stimulation to avoid excessive tachycardia. Maintenance of anesthesia can be achieved by combining a volatile anesthetic agent with an intravenous opioid. Nitrous oxide should be avoided, since this agent increases pulmonary vascular resistance. New onset of Afib or other tachyarrhythmias should be promptly treated with cardioversion or rate control. When ventilating patients with MS, special attention should be paid to avoiding hypoxemia and hypercarbia, as these will precipitate right heart failure in vulnerable patients. If right heart failure does occur, it should be treated promptly with inotropic and pulmonary vasodilating agents. Judicious fluid management should be utilized as excessive fluid administration or placement in the Trendelenburg position increases central blood volume and can precipitate acute heart failure. Sudden decreases in SVR should also be avoided as these are generally poorly tolerated due to the reflex tachycardia associated with

TABLE 6.4 Intraoperative Events That Have a Significant Impact on Mitral Stenosis

Sinus tachycardia or a rapid ventricular response during atrial fibrillation
Marked increase in central blood volume, as associated with overtransfusion or head-down positioning
Drug-induced decrease in systemic vascular resistance
Hypoxemia and hypercarbia that may exacerbate pulmonary hypertension and evoke right ventricular failure

hypotension causing decreased cardiac output. When treating hypotension, pure α vasoconstrictors such as phenylephrine or vasopressin may be considered, since they have minimal effects on pulmonary artery pressure.

Patients with MS undergoing surgical intervention will require monitoring that depends on the complexity of the operative procedure and the magnitude of physiologic impairment caused by the MS. For patients with mild to moderate MS who are asymptomatic, monitoring should be no different than for those patients without valvular heart disease. For patients with symptoms undergoing major surgery, invasive monitoring (i.e., continuous invasive blood pressure monitoring) should be considered. If available, TEE should also be considered to guide intraoperative therapy.

MITRAL REGURGITATION

Etiology

Mitral regurgitation is a common valvular disorder that arises from abnormalities of any part of the mitral valve apparatus, which consists of the anterior and posterior mitral valve leaflets, the annulus, chordae tendineae, papillary muscle, and the subadjacent LV myocardium (Fig. 6.6). The spectrum of MR varies from acute forms, in which rapid deterioration of myocardial function can occur, to more chronic forms that have a slow and indolent course.

Acute MR most often occurs as a sequelae of CAD, in which myocardial ischemia and infarction cause papillary muscle dysfunction and, in some cases, papillary muscle rupture. The posteromedial papillary muscle is more susceptible to rupture, as it has blood supply from a single artery, whereas the anterolateral papillary muscle has a dual supply. Other causes of acute MR include chordae tendineae rupture caused by myxomatous disease of the mitral valve or acute rheumatic fever, infective endocarditis, balloon valvuloplasty, or a penetrating chest injury.

Chronic MR may be due to a primary abnormality of one or more components of the valvular apparatus or secondary to another cardiac disease. Causes of MR can be grouped into three types based on leaflet motion, according to Carpentier classification scheme (Fig. 6.7). In type I, there is normal leaflet motion, and MR is due to either annular dilatation or leaflet perforation. Annular dilatation occurs as a result of disease processes that result in LV dilatation such as dilated cardiomyopathy or AR. Leaflet perforation is generally the result of infective endocarditis. In type II, there is excessive leaflet motion that occurs as a result of papillary muscle rupture, chordal rupture, redundant chordae, or mitral valve prolapse with myxomatous degeneration and fibroclastic disease being the disease processes involved. In type III, there is restricted leaflet motion, which can further be subdivided into type IIIa, where leaflet motion is restricted in both systole and diastole (i.e., RHD), and type IIIb, in which leaflet motion is restricted in diastole (i.e., ischemic cardiomyopathy). With type IIIb, there is disruption of the normal geometric relationship between the mitral valve leaflets, papillary muscles, and left ventricle.

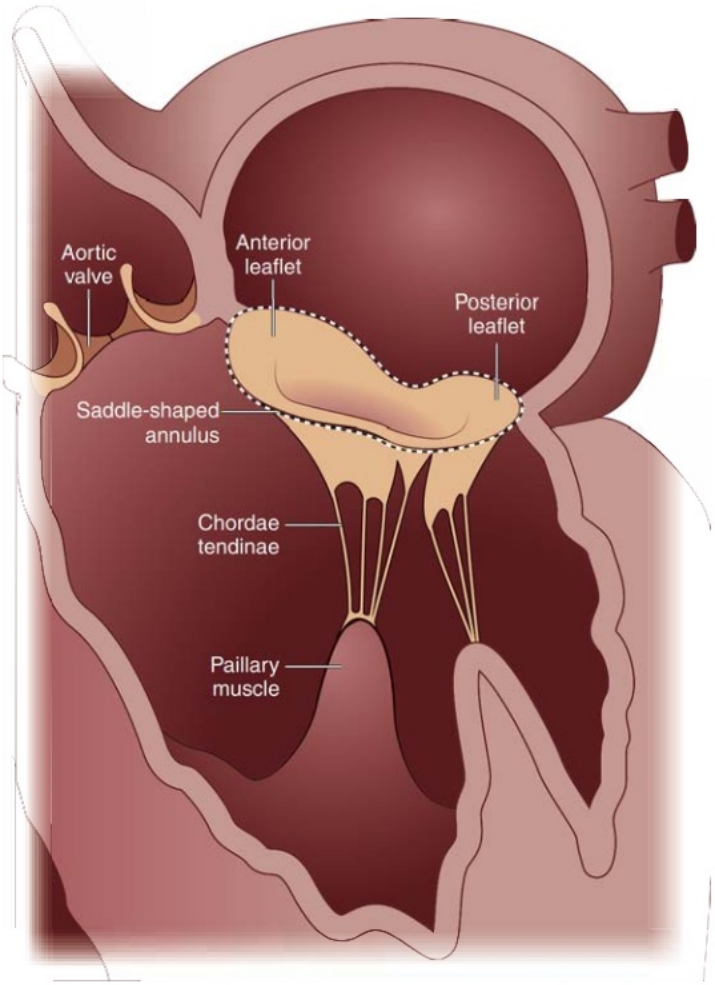

Fig. 6.6 Illustration of the mitral valve apparatus showing the anterior and posterior mitral valve leaflets along with the subvalvular suspension network comprised of chordae tendineae and papillary muscles.

Pathophysiology

The primary hemodynamic consequence of MR is a diminished forward stroke volume as a portion of each stroke volume is regurgitated back into the left atrium through the incompetent mitral valve, ultimately causing a decreased cardiac output. Left atrial dilatation and eccentric hypertrophy of the left ventricle mark signs of the gradual development of chronic MR. Dilatation of the left ventricle is compensatory, as it maintains an adequate LV end-diastolic pressure despite the increased volume and thus preserves cardiac output by an overall increase in forward stroke volume. The onset of LV dysfunction and symptoms of heart failure manifest when LV dilatation and hypertrophy can no longer meet the necessary forward LV stroke volume to maintain adequate cardiac output. The dilatation and increased pressure seen in the left atrium is further exacerbated by mitral valve annular dilatation with a resultant increase in the regurgitant volume. Ultimately the increased pressure in the left atrium is reflected on the right side with elevated pulmonary artery pressures, pulmonary congestion, and eventual RV dysfunction. Increased left atrial volume also results in high risk for the development of Afib and thrombus formation, both of which add significant morbidity to these patients.

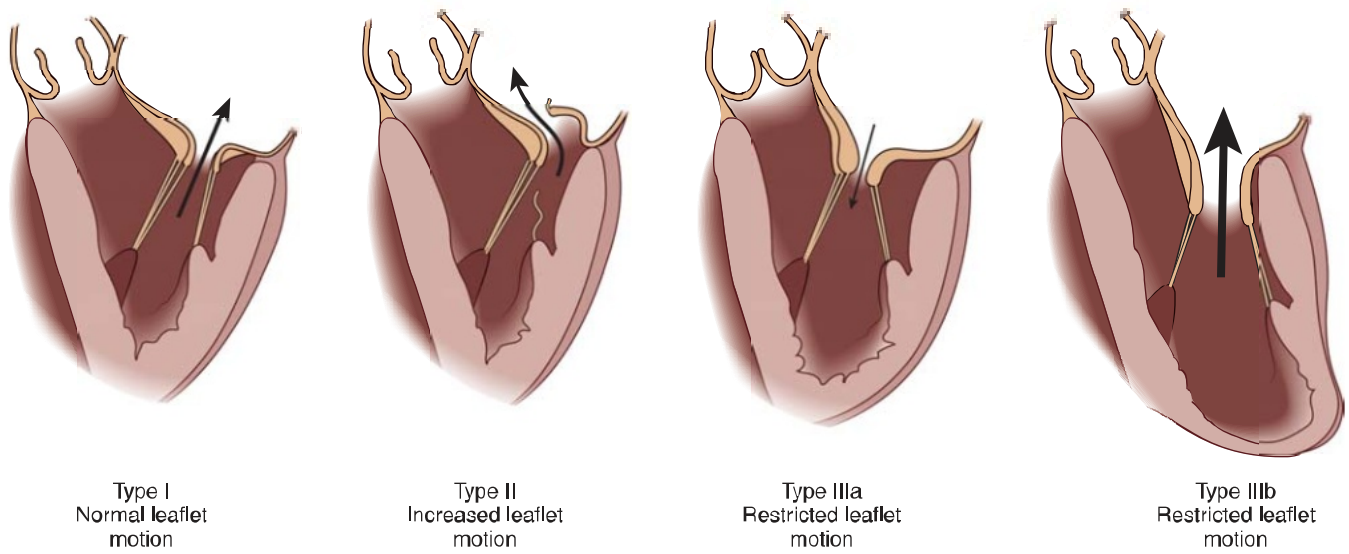

Fig. 6.7 Carpentier classification scheme for the etiology of mitral regurgitation. Type I: normal leaflet motion, type II: excessive leaflet motion, type IIIa: restricted leaflet motion (systole and diastole), type IIIb: restricted leaflet motion (systole).

Patients with acute MR often present with biventricular failure. Left-sided failure occurs, as there is inadequate forward stroke volume to maintain adequate cardiac output. There will be a compensatory increase in heart rate in an effort to maintain cardiac output, but this results in the incomplete emptying of the left ventricle, raising LV volume and end-diastolic pressure and further exacerbating LV dysfunction. The rapid pressure rise in the noncompliant left atrium results in an acute rise in pulmonary pressures leading to pulmonary edema and ultimately right-sided failure.

Clinical Manifestations and Diagnosis

The severity of symptoms associated with MR is dependent on the severity of the regurgitation, its rate of progression, the pulmonary artery pressure, presence of arrhythmias, and associated cardiac disease. Patients with mild to moderate primary MR are generally asymptomatic until LV cavity enlargement results in systolic dysfunction or there is new onset pulmonary hypertension or Afib. The symptoms most commonly present include exertional dyspnea and fatigue due to a combination of a decrease in forward stroke volume and an increase in left atrial pressure from the regurgitant jet that causes pulmonary hypertension and its sequelae. Palpitations are also common and may signify the onset of Afib. Patients with severe acute or chronic MR will develop symptomatic heart failure with pulmonary congestion and edema. The decline in LV function seen at this stage is often irreversible, which is why serial monitoring of patients is essential to ensure early intervention.

Clinical examination of patients with MR may reveal a blowing, holosystolic murmur with a reduced S_1; sometimes this may be accompanied by a rumbling middiastolic murmur from the large volume of blood entering the left ventricle. Enlargement of the left ventricle results in a brisk or hyperdynamic apical impulse that is typically laterally displaced. In severe disease, signs of left- and right-sided heart failure may also be present.

Diagnostic tests should begin with an ECG and chest radiograph, which may reveal evidence of left atrial and left ventricular hypertrophy. ECG may also reveal new-onset Afib that is associated with MR. Echocardiography with Doppler is the test of choice for the diagnosis, severity assessment, and surveillance of MR. Both transthoracic and TEE can be used to (1) classify the cause of MR according to the Carpentier classification, (2) assess its severity with the use of Doppler and other methods, and (3) assess geometric changes associated with MR such as chamber dilatation, hypertrophy, and function. In addition, echocardiography can be used to assess for associated adverse sequelae such as left atrial appendage clot in patients with Afib and evidence of pulmonary hypertension with or without RV dysfunction. Three-dimensional echocardiography and quantitative mitral valve modeling are increasingly becoming routine practice in assessing mitral valve pathologies as it provides high-resolution images of the valvular apparatus, thus allowing precise diagnosis of the pathology involved and determining suitability for surgical repair, surgical replacement, or percutaneous intervention (Fig. 6.8).

Timing and Type of Interventions

Medical therapy has a limited role to play in the treatment of primary MR as it does not address the disease process. Patients with secondary MR and those with decompensated primary MR should have therapies directed to treating their heart failure symptoms such as diuretics, β blockers, and ACE inhibitors. Concomitant heart disease such as hypertension and CAD should be addressed if present.

The decision for surgical intervention is determined by a number of factors, including MR severity, symptom severity, LV function, Afib, degree of pulmonary hypertension, and feasibility of valve repair. In asymptomatic patients with primary MR, surgical intervention is warranted in those with an LV ejection fraction of 30% to 60% or an LV end-systolic dimension greater

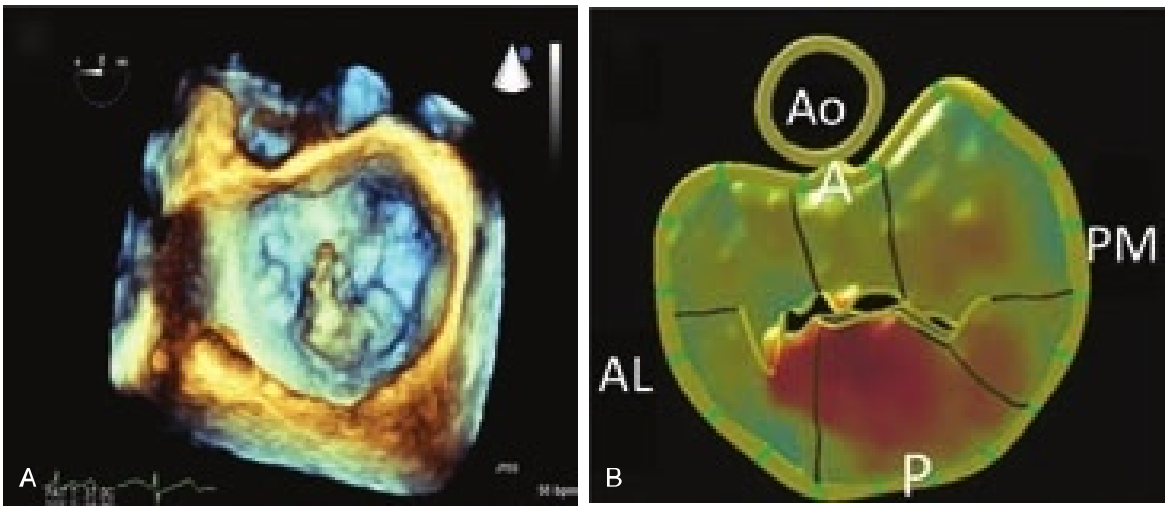

Fig. 6.8 (A) Three-dimensional transesophageal echocardiography view of the mitral valve with a flail at the P2 region as seen from the "surgeons view" or "en-face view" where the valve is being viewed from the left atrial perspective with the aortic valve in the 12 o'clock position and the left atrial appendage in the 9 o'clock position. (B) Parametric model of the mitral valve depicting the P2 flail. *Ao*, Aorta; *A*, anterior; *PM*, posteromedial; *P*, posterior; *AL*, Anterolateral.

than 40 mm. New-onset Afib or pulmonary hypertension may also justify the need for intervention. In symptomatic patients with severe primary MR, surgical intervention is undertaken if the LV ejection fraction is greater than 30% and LV end-systolic dimension is less than 55 mm. For patients with secondary MR unresponsive to medical therapy, isolated mitral valve surgery is not suggested unless they are undergoing cardiac surgery for a concurrent condition such as CAD. If it is feasible, mitral valve repair should be attempted over replacement in patients undergoing surgical intervention, as repair avoids the need for long-term anticoagulation associated with valve replacement and preserves the subvalvular apparatus to maintain LV performance.

Transcatheter mitral valve repair (TMVR) is a minimally invasive treatment option for select patients with severe MR in whom open surgery is not an option due to prohibitive surgical risk. An edge-to-edge leaflet repair device (e.g., MitraClip) is the most common minimally invasive transcatheter device used for mitral valve repair (Fig. 6.9). This device is based on the Alfieri edge-to-edge repair, which involves suturing together the middle segments of the anterior and posterior mitral valve leaflets, thereby creating a "double-orifice" mitral regurgitant area. The MitraClip system uses a clip that is delivered percutaneously via groin access; a transseptal puncture is performed to cross the intraatrial septum. The MitraClip steerable catheter is then advanced into the left atrium and lined up with the mitral valve. The clip is advanced into the left ventricle and then slowly drawn back under echocardiography guidance to grasp the leaflets at the site of regurgitation. By grasping both the anterior and posterior leaflets, this increases the coaptation between the regurgitant leaflets, reducing the degree of MR. There is good evidence showing effectiveness of this procedure with clinical studies demonstrating reduction in the severity of MR, reduced left ventricular and left atrial volumes, and improved exercise

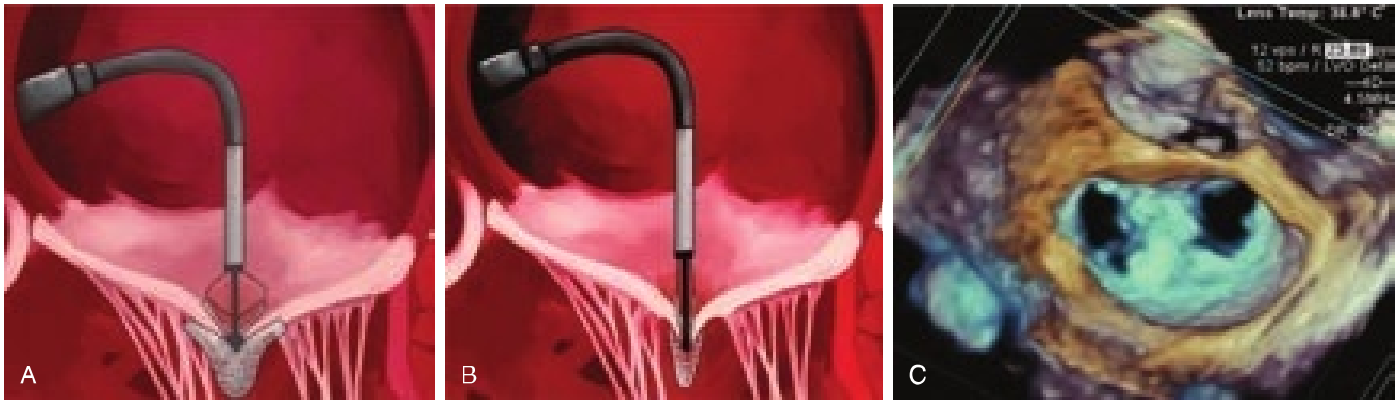

Fig. 6.9 Percutaneous MitraClip procedure for treatment of mitral regurgitation. (A) Left atrium is accessed via a transseptal puncture through groin access, and the clip delivery system is positioned below the mitral valve leaflets at the point of maximal regurgitation. (B) Both the anterior and posterior portions of the mitral valve leaflets are grasped by the MitraClip. (C) Three-dimensional transesophageal echocardiography view of the end result depicting the double-orifice valve.

TABLE 6.5 Anesthetic Considerations in Patients With Mitral Regurgitation

Prevent bradycardia
Prevent increases in systemic vascular resistance
Minimize drug-induced myocardial depression
Maintain cardiac output

tolerance and quality of life. This option may be considered in those patients with prohibitively high risk for open surgery or patients with severe secondary MR not responsive to medical therapy.

Intraoperative Management

Intraoperative management of patients with MR undergoing noncardiac surgery should focus on maintaining forward stroke volume and cardiac output by reducing the regurgitant fraction (Table 6.5). Maintenance of a normal to slightly increased heart rate is generally recommended, and bradycardia should be avoided as this will result in LV volume overload. Afterload reduction is desired in these patients as increased afterload results in an increase in the regurgitant fraction and consequent decrease in the forward stroke volume. For this reason, the decrease in SVR associated with neuraxial and regional anesthesia may be of benefit. If LV dysfunction ensues, afterload reduction with a vasodilator drug, with or without an inotropic agent, will improve LV function.

Induction of anesthesia can be achieved with any induction agent as they all produce vasodilation, which reduces the regurgitant fraction. Short-acting agents to mitigate the sympathetic response to laryngoscopy should be used so as to avoid acute increases in SVR. Maintenance of anesthesia is best achieved with volatile agents owing to their vasodilatory effects coupled with minimally negative inotropic effects. In patients with severe MR and LV dysfunction, an opioid-based anesthetic is an excellent option because of the minimal myocardial depression that opioids induce.

Mechanical ventilation should be adjusted to ensure adequate oxygenation and ventilation as hypoxia or hypercapnia can result in RV dysfunction. The appropriate ventilator mode and settings must provide sufficient time between breaths for adequate venous return. Maintenance of euvolemia is important to maintain adequate preload without causing LV volume overload and precipitating heart failure symptoms.

With regard to monitoring, patients with asymptomatic mild to moderate MR do not require invasive monitoring. Patients with severe or symptomatic MR require invasive monitoring (i.e., pulmonary artery catheter, TEE) to measure the adequacy of cardiac output, guide fluid therapy, and assess the hemodynamic response to anesthetic agents and vasodilating drugs.

TRICUSPID STENOSIS

Tricuspid stenosis (TS) is an uncommon valvular abnormality in developed countries that is usually found in combination with TR and other valvular lesions. RHD is the most common cause of TS. Even less common causes of acquired TS include carcinoid syndrome, infective endocarditis, hypereosinophilic syndromes, right atrial tumors causing functional stenosis, and congenital causes not previously diagnosed in childhood.

The tricuspid valve is the largest cardiac valve with a normal valve area of 7 to 9 cm^2 in the typical adult. As a result, symptoms are slow to progress with a long asymptomatic period prior to symptom onset. When stenosis does develop, there is a persistent diastolic pressure gradient between the right atrium and right ventricle. As the right atrial pressure increases, the right atrium dilates, and forward blood flow decreases. As a result, patients develop symptoms associated with systemic venous congestion such as jugular venous distension, ascites, and peripheral edema. Other clinical features may include shortness of breath and fatigue that occur as a result of obstruction to tricuspid flow, which ultimately limits cardiac output. Due to the fact that TS rarely occurs in isolation, the symptoms and signs of other valvular lesions that are present may be more prominent. Consequently, TS is often not suspected as the primary lesion.

Investigations of patients with suspected TS should include a physical exam assessing for jugular venous distension, hepatomegaly, hepatic pulsations, ascites, peripheral edema, and anasarca. Since TS usually coexists with other valvular lesions, examination findings may not be specific and predictable. Laboratory tests should be obtained to evaluate for liver function and a chest radiograph to assess for pulmonary edema. ECG may reveal tall, peaked P waves in leads II, III, and aVF consistent with right atrial enlargement. Like most valvular lesions, the diagnosis of TS is generally based on echocardiography findings that typically reveal leaflets that are thickened with limited leaflet mobility, reduced separation of the leaflet tips, and diastolic doming of the valve. A valve area of less than 1 cm^2 and a pressure gradient of more than 5 mm Hg are indications of severe TS. Echocardiography is also useful for assessing other valvular lesions that are typically associated with TS.

Since TS is a mechanical disorder, it is generally better managed with valve intervention by surgical repair, valve replacement, or percutaneous balloon valvuloplasty. Medical management is centered around managing symptoms; loop diuretics are the mainstay of treatment to prevent symptoms of systemic venous congestion.

Anesthetic management of patients with isolated TS should focus on maintenance of high preload to maintain forward flow across the valve, high afterload, and adequate contractility. In patients with coexisting valvular disease, the anesthetic management will often depend on the type of coexisting valvular lesion. Similarly, monitoring for these patients is often dictated by other valvular lesions, but arterial and central venous pressure monitoring should be considered along with TEE if it is available. In general, insertion of a pulmonary artery catheter through the stenotic tricuspid valve can be troublesome and is not always warranted.

TRICUSPID REGURGITATION

Etiology

Tricuspid regurgitation in adults is more commonly a secondary lesion due to tricuspid annular dilatation with or without

leaflet tethering. This often occurs as a result of RV ischemia, severe pulmonary hypertension, or dilated cardiomyopathy, which ultimately leads to RV pressure and volume overload. Primary causes of TR occur much less frequently and include infective endocarditis, carcinoid syndrome, RHD, tricuspid valve prolapse, and Ebstein anomaly. Implantable device leads that cross the tricuspid valve may also cause acute or chronic TR. The cause of lead-associated TR include changes in RV geometry as a result of chronic pacing, direct impingement on leaflet motion, foreign body inflammation of the leaflets, infective endocarditis, and thrombosis. Tricuspid valve disease is often associated with diseases of the mitral or aortic valve.

Pathophysiology

TR is characterized by blood flowing through an incompetent tricuspid valve into the right atrium during RV systole that results in right atrial volume overload. The high compliance of the right atrium and vena cava results in only a minimal increase in right atrial pressure, even in the presence of a large regurgitant volume, however when the TR is severe, right atrial and venous pressures increase and can result in signs and symptoms of right-sided heart failure. As a consequence of chronic RV overload, these patients frequently develop RV systolic dysfunction and a low forward cardiac output.

Clinical Manifestations and Diagnosis

Symptoms and signs related to TR may not be present until the advanced stages of the disease. When symptoms do develop, they tend to be related to right heart failure and include fatigue, edema, ascites, and painful hepatosplenomegaly. Patients may also have a sensation of pulsation in the neck with severe disease.

Physical findings associated with severe TR include a holosystolic murmur along the left sternal border that intensifies with inspiration, jugular venous distension with the presence of V waves, peripheral edema, ascites, and hepatomegaly.

ECG may reveal right axis deviation and signs of RV hypertrophy. Chest radiography may show an enlarged right heart border and obliteration of the retrosternal window. Echocardiography is the diagnostic test of choice for evaluation of TR. It enables evaluation of the severity of TR, valve morphology, right chamber sizes, and RV function. Pulmonary pressures can also be estimated with echocardiography, and any concomitant left heart disease can be assessed.

Timing and Type of Intervention

Medical therapies for severe TR have limited effect, since many patients present late. Medications should be directed toward treating the underlying cause of the functional TR to improve symptoms. Diuretic therapy and limiting salt and fluid intake are the mainstay of treatment for managing right-sided heart failure symptoms. When pulmonary hypertension is present, medications directed at treating this (i.e., endothelin receptor antagonists, phosphodiesterase inhibitors) may improve symptoms.

Timing of surgical intervention for TR remains controversial; however, delayed surgery must be avoided given the risk of irreversible RV damage, organ failure, and overall poor outcomes. Current guidelines recommend surgical intervention in patients with severe functional TR undergoing left-sided surgery. Intervention should be considered in patients with mild or moderate TR with a dilated tricuspid annulus undergoing left-sided surgery. Isolated tricuspid valve surgery is suggested for patients with severe primary TR with symptoms unresponsive to medical therapy, preferably before the onset of significant RV dysfunction and organ failure. For patients with severe TR with minimal symptoms, the guidelines are less clear but include a weak recommendation for intervention if there is evidence of progressive RV dilatation or RV dysfunction.

When surgical intervention is required, annuloplasty is the preferred treatment for functional TR. Annuloplasty is ideal because it targets the pathophysiologic hallmark of functional TR, annular dilatation. Tricuspid valve replacement may be required if leaflet anatomy is not amenable to repair; however, overall mortality for these patients is high, so repair should be the preferred procedure when possible.

Percutaneous interventions on the tricuspid valve are evolving as a treatment option. Currently, these interventions are being undertaken in patients who have severe TR with intractable symptoms of right heart failure and are deemed prohibitively high surgical risks. The current transcatheter therapies that are available to improve TR include (1) the off-label transfer of the MitraClip technique to the tricuspid valve to perform an edge-to-edge repair and reduce the degree of TR, (2) percutaneous deployment of a specially designed band along the anterior and posterior portion of the tricuspid annulus to reduce annular size and severity of TR, and (3) implantation of a bioprosthetic valve into the inferior vena cava or superior vena cava, which does not address the severity of TR but may provide symptomatic relief by reducing the caval backflow and hepatorenal congestion. The efficacy of these percutaneous interventions is currently being studied in various clinical trials and may provide a good treatment option for patients with severe disease who are not suitable for surgery and fail to respond to maximal medical therapy.

Intraoperative Management

Management of anesthesia for patients with TR will largely depend on the management of other valvular or ischemic lesions that may be present and precipitating the TR. The presence of complications related to TR such as RV failure and pulmonary hypertension must also be considered. Management should focus on maintenance of intravascular fluid volume and maintaining the central venous pressure in the high-normal range to facilitate adequate RV preload and ventricular filling. Normal-to-high heart rates are beneficial in these patients to sustain forward flow and prevent peripheral congestion. The failing right ventricle may require inotropic support and is exquisitely sensitive to increases in afterload. Any increase in pulmonary artery pressure should be treated promptly to maintain forward flow and cardiac output. Inodilators such as milrinone and dobutamine are particularly useful in these patients. Aggravating factors of RV failure such as hypercarbia, hypoxia, and hypotension should be avoided, and ventilation should be optimized to avoid overdistension and a drop in venous return.

Peripheral nerve blocks are a good option for patients with severe TR; however, sedation for the procedure should be used with great caution, as oversedation can result in hypercarbia and hypoxia, leading to worsening of RV function. Neuraxial anesthesia should also be used with caution, as abrupt changes in SVR may adversely impact RV perfusion and function.

For patients undergoing general anesthesia without RV dysfunction or pulmonary hypertension, induction can be achieved with standard induction agents. In the presence of RV dysfunction or pulmonary hypertension, agents that do not result in myocardial depression along with blunting of the sympathetic response to laryngoscopy are preferable. Maintenance of anesthesia can be achieved with volatile anesthetic agents. Nitrous oxide is usually avoided as it can result in an increase in pulmonary vascular resistance and worsening of the transvalvular gradient.

Monitoring of patients with TR will be dependent on the presence or absence of RV dysfunction and pulmonary hypertension as well as the expected duration of the surgery. For patients with severe disease and presence of mild to moderate symptoms, an intraarterial catheter and central venous catheter should be used to promptly detect and treat hemodynamic disturbances while allowing for monitoring of central venous pressure trends and guiding fluid therapy. For patients with severe symptoms with RV dysfunction or pulmonary hypertension, consideration should be given for advanced monitoring with a pulmonary artery catheter or TEE, if available, to guide intraoperative decision making.

PULMONIC STENOSIS

Pulmonic stenosis (PS) is a disorder generally encountered in the pediatric population and is congenital in over 95% of cases, with 80% of these cases presenting with isolated PS and the remainder associated with other complex congenital heart diseases. Less common causes that may result in PS in adulthood include carcinoid syndrome and RHD.

Obstruction to pulmonary blood flow can occur at three locations: valvular, subvalvular, or supravalvular. RV hypertrophy and pressure overload will develop as the right ventricle tries to compensate; however, the right ventricle's capacity to compensate is much less than the left ventricle. Pulmonary hypertension will progressively worsen as symptoms gradually develop.

Many patients with mild or moderate PS may remain asymptomatic for a prolonged period of time and will only start to develop symptoms with severe obstruction. When symptoms do develop, they may range from mild exertional dyspnea to signs and symptoms of right heart failure, depending upon the severity of obstruction and degree of myocardial compensation. Inability to augment pulmonary blood flow during exertion will often lead to exercise-induced symptoms of dyspnea, syncope, and chest pain.

Physical findings are generally related to the severity of the obstruction and include (1) a crescendo-decrescendo systolic murmur that is loudest at the upper left border and radiates to the suprasternal notch and left neck (a loud and late peaking murmur is suggestive of severe valvular obstruction), (2) prominent RV systolic impulse with a left parasternal heave, and (3) an ejection click or ejection sound that decreases in intensity with inspiration.

Echocardiography is the diagnostic test of choice for evaluating PS. Valvular anatomy, localization of the stenosis, assessment of severity, and evaluation of coexisting pathology can all be evaluated with echocardiography. The characteristic thickened leaflets with doming in systole can be visualized, and the severity can be quantified based on the transvalvular pressure gradient that relies on calculating the transpulmonic velocity. Coexisting pulmonic regurgitation (PR) and the elevation in RV systolic pressure can also be quantified. Cardiac MRI is another diagnostic modality that can be utilized to quantify the severity of PS when image quality on echocardiography is inadequate.

Balloon valvuloplasty is the procedure of choice for patients with significant PS with good outcomes in treating both the congenital and acquired forms. Surgical intervention may be required in some patients with anatomic features that make balloon valvuloplasty unsuitable. Percutaneous pulmonic valve implantation is another method that has evolved to treat patients with PS; good outcomes paired with postponing the need for open heart surgery in these patients who often have significant comorbidities make this an attractive treatment option.

Anesthetic management of patients with PS should aim to preserve RV preload and contractility while avoiding further increases in pulmonary vascular resistance. General anesthesia is employed in these patients with the induction and maintenance of anesthesia achieved with agents that do not cause excessive myocardial contractility while also blunting the sympathetic response to surgery.

PULMONIC REGURGITATION

PR may be classified into physiologic, primary, and secondary causes. Physiologic PR is common in the general population and is typically of no clinical significance. Primary PR is most commonly iatrogenic caused by interventional procedures to treat RV outflow obstruction. Other causes of primary PR include infective endocarditis and carcinoid syndrome–related heart disease. Secondary PR occurs in patients with a structurally normal pulmonic valve who have pulmonary artery dilation with or without pulmonary arterial hypertension.

PR is initially well tolerated but will eventually lead to RV volume overload with consequential RV enlargement, RV dysfunction, and functional TR. Chamber enlargement also results in atrial and ventricular arrhythmias. As RV function deteriorates, the cardiac output starts to decrease. Symptoms such as exertional dyspnea and fatigue will then begin to develop.

The diagnosis of PR is often made by echocardiography, which can indicate the likely mechanism, cause, and severity of valve disease. Echocardiography is also a way to measure the hemodynamic effects of the valvular lesion and assess for associated disorders such as pulmonary artery hypertension.

Surgical or percutaneous intervention should always be considered for patients with symptomatic, severe PR. For

asymptomatic patients, surgical repair or replacement should also be considered in those who have (1) mild or moderate RV dysfunction, (2) severe RV dilation, or (3) progressive reduction in exercise tolerance.

Anesthetic management for patients with PR is generally guided by the degree of RV dysfunction and pulmonary artery hypertension that is present. Optimizing RV function while avoiding increases in pulmonary artery pressure is paramount. In the presence of severe disease, invasive monitoring and TEE should be used when available.

PREVENTION OF INFECTIVE ENDOCARDITIS

Guidelines for the prevention of infective endocarditis (IE) have been by the American Heart Association (AHA) for the past half-century. Recent literature on the incidence of IE, efficacy of antibiotic prophylaxis for the prevention of IE, as well as trends in antibiotic resistance and antibiotic-associated adverse events have led to changes in guideline recommendations for antibiotic prophylaxis in recent years. The most recent guidelines (2017) are based on the fact that IE is much more likely to occur as a result of frequent exposure to bacteria associated with daily activities than from bacteria associated with invasive procedures. The guidelines suggest that IE prophylaxis should be administered not to individuals with a high cumulative lifetime risk of contracting IE but rather to individuals at highest risk of adverse outcomes if they should develop IE. This includes patients with (1) prosthetic heart valves, including transcatheter implanted prostheses and homografts; (2) prosthetic material used for cardiac valve repair, such as annuloplasty rings and chords; (3) previous IE; (4) unrepaired cyanotic congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device; and (5) cardiac transplant with valve regurgitation due to a structurally abnormal valve. Prophylaxis in these high-risk populations is recommended for all dental procedures involving manipulation of gingival tissue or perforation of oral mucosa and procedures involving the respiratory tract, infected skin, or musculoskeletal system. Prophylactic antibiotics solely to prevent IE are no longer recommended for genitourinary or gastrointestinal procedures, and similarly patients with mitral valve prolapse no longer warrant antibiotic prophylaxis.

PROSTHETIC HEART VALVES

Types of Prosthetic Heart Valves

Prosthetic valves can be either mechanical or bioprosthetic and the decision to use one over the other depends on various factors, including the expected longevity of the patient, the ability of the patient to comply with anticoagulation therapy, the anatomy and pathology of the underlying valvular disease, and the experience of the operating surgeon. The ideal prosthetic valve should be nonthrombogenic, chemically inert, preserve blood elements, and allow for physiologic blood flow. In reality, prosthetic valves that are implanted do not possess any of the aforementioned characteristics, and they themselves are associated with their own problems known as prosthetic valve disease.

Mechanical valves are composed primarily of metal or carbon alloys and are classified according to their structure, such as caged-ball, single tilting disk, or bileaflet tilting disk valves. Mechanical valves are highly thrombogenic and require long-term anticoagulation. Bileaflet tilting disk valves include the St. Jude medical valve, which consists of two semilunar discs attached to a rigid ring, offering a large effective orifice area and thus avoiding patient-prosthesis mismatch. Thrombotic risk is low if there is good patient adherence to anticoagulation.

Bioprosthetic valves are usually xenografts (porcine aortic valves or cryopreserved, mounted bovine pericardium), but homografts from humans can also be used in complicated aortic valve endocarditis. Bioprosthetic valves are beneficial because they usually do not require long-term anticoagulation therapy and are less thrombogenic; however, durability is significantly less than that of mechanical valves. Due to the lower durability of bioprosthetic valves and because these valves last longer in older patients, they are usually recommended for patients over 65 years of age and when anticoagulation is better avoided. They are also indicated for women who expect to become pregnant or patients who may be noncompliant with anticoagulation therapy.

Complications Associated With Prosthetic Heart Valves

The incidence of serious complications in appropriately managed patients with prosthetic heart valves is approximately 3% per year. The frequency at which complications occur is dependent on the type of valve implanted (mechanical vs bioprosthetic), the heart valve where it is positioned, and adequacy of anticoagulation. The most frequent complications encountered in patients with prosthetic heart valves include valve obstruction (which may be caused by valve thrombosis, pannus formation, bioprosthetic valve fibrosis, prosthesis-patient mismatch, and/or calcification), valvular and paravalvular regurgitation, IE, hemolytic anemia, and bleeding complications related to antithrombotic therapy.

Assessment of Prosthetic Heart Valves

All patients with prosthetic heart valves should have a detailed clinical history taken and a physical examination performed prior to any surgical intervention. New or progressive symptoms such as shortness of breath, fatigue, or angina-type symptoms may allude to valvular dysfunction and should be followed up with further studies to quantify valve function. Likewise, the appearance of a new murmur or a change in the characteristics of an existing murmur should prompt further investigation. When further investigation is warranted, echocardiography with Doppler interrogation is the diagnostic test of choice. Either transthoracic or TEE can be used to ensure the prosthetic valve is well seated, there is normal leaflet motion, no evidence of thrombus, vegetation or pannus formation, normal valvular gradients, and that no paravalvular leak is present.

Antithrombotic Therapy for Prosthetic Heart Valves

Patients with prosthetic valves require some form of long-term anticoagulation to reduce the risk of thromboembolic events, which are the most frequent complications associated with mechanical valves. By contrast, these complications are rare in biologic valves where structural failure is more common. Systemic embolization occurs at a frequency of approximately 0.7% to 1% per patient per year in patients with mechanical valves who are treated with vitamin K antagonist anticoagulation. If no anticoagulation is used, this risk increases to 4% per year per patient. For patients with mechanical valves, anticoagulation will take the form of vitamin K antagonist therapy along with daily low-dose aspirin. The goal international normalized ratio (INR) varies with valve position and type and presence of risk factors, but in general an INR above 2 is required. Patients with surgically placed bioprosthetic valves should have anticoagulation with low-dose aspirin and a vitamin K antagonist for the first 3 to 6 months, and then, if there are no risk factors for thrombus formation, anticoagulation can be continued with aspirin alone.

Discontinuation of anticoagulant therapy may be required around the time of surgery in patients with prosthetic heart valves; however, this discontinuation places the patient at significant risk of thrombus formation, so the risk of hemorrhage from continuation of anticoagulation therapy should be weighed against the risk of thrombus formation. When anticoagulation is required to be discontinued, the vitamin K antagonist should be stopped 3 to 5 days prior to the procedure to allow normalization of the INR; as soon as the INR is subtherapeutic, intravenous unfractionated or low-molecular-weight heparin (LMWH) should be administered and continued until the day before or the day of surgery. The heparin can then be restarted postoperatively when the risk of bleeding has been reduced and should be continued until effective anticoagulation is again achieved with oral therapy.

KEY POINTS

- The burden of valvular heart disease is steadily increasing, especially in the elderly over 75 years of age who have a 13% prevalence of moderate or severe valvular disease.
- Multimodal imaging is key for preprocedural assessment of the valvular lesions and proper risk stratification for patients.
- Aortic stenosis and mitral regurgitation are the two most common lesions due to degenerative, calcific changes and ischemia, respectively.
- Cardiac valve lesions typically produce either pressure overload (mitral stenosis, aortic stenosis) or volume overload (mitral regurgitation, aortic regurgitation) on the left atrium or left ventricle.
- Pressure overload due to fixed obstructions (i.e., aortic stenosis) can cause compensatory changes, including ventricular remodeling, typically causing hypertrophy. Angina can occur in patients with valvular heart disease even in the absence of coronary artery disease as the ventricular hypertrophy will raise the myocardial oxygen demand beyond the capacity of even patent coronary arteries.
- The cornerstone of diagnosis and subsequent monitoring of any valvular lesion is echocardiography with Doppler interrogation, which will establish the pathogenesis, mechanism, severity, progression, and repercussions of the valvular lesion.
- Cardiac lesions that cause pressure overload (i.e., aortic or mitral stenosis) require a relatively slower heart rate to prolong diastole and improve chamber filling and coronary blood flow. Cardiac lesions that cause volume overload (i.e., aortic or mitral regurgitation) are optimized by reducing the regurgitant fraction by having relatively faster heart rates to reduce diastolic times and afterload reduction to help forward flow.
- Management of anesthesia in patients with aortic stenosis includes maintenance of preload, systemic vascular resistance, normal sinus rhythm, and avoiding tachycardia.
- AR can either be acute (ischemic or infective endocarditis) or chronic (bicuspid valves, IE, rheumatic disease, etc.) in nature. Intraoperative management usually involves reducing regurgitant volume and maintaining CO by inducing relative tachycardia and peripheral vasodilation.
- Mitral stenosis is most often associated with rheumatic heart disease. MS leads to attenuation of the atrial contribution to LV filling that worsens with exercise. Management of anesthesia in patients with mitral stenosis includes maintaining normal HR, preventing volume overload to prevent pulmonary edema, and avoiding hypoxemia and hypercarbia to prevent right heart failure.
- Mitral regurgitation (MR) is typically due to ischemia in acute MR and a variety of causes with chronic MR (dilated cardiomyopathy, AR, infective endocarditis, myxomatous degeneration, ischemic cardiomyopathy, etc.). Intraoperative management should focus on maintaining forward stroke volume and cardiac output by reducing the regurgitant fraction with normal to slightly increased heart rate and afterload reduction.
- Tricuspid stenosis (TS) is a valvular abnormality most commonly caused by rheumatic heart disease. Anesthetic management in isolated TS should focus on maintenance of high preload to maintain forward flow across the valve, high afterload, and adequate contractility.
- Tricuspid regurgitation (TR) is more commonly secondary to tricuspid annular dilatation due to RV ischemia, severe pulmonary hypertension, or dilated cardiomyopathy. Ultimately, RV pressure and volume overload cause symptoms of right-sided heart failure and low cardiac output. Anesthetic management should focus on maintenance of intravascular fluid volume and maintaining the central venous pressure in the high-normal range to facilitate adequate RV preload and ventricular filling. Normal-to-high heart rates are beneficial in these patients to sustain forward flow. The

failing RV may require inotropic support and is exquisitely sensitive to increases in afterload.

- Disorders of the pulmonic valve are generally congenital in origin, and patients often remain asymptomatic for a prolonged period of time. When symptoms do develop, they are generally related to RV dysfunction and pulmonary hypertension.
- Mechanical valves are very durable, lasting at least 20 to 30 years, whereas bioprosthetic valves last about 10 to 15 years. Mechanical valves are highly thrombogenic and require long-term anticoagulation. Bioprosthetic valves have a low thrombogenic potential; long-term anticoagulation is often not necessary.
- The most recent guidelines (2017) suggest that IE prophylaxis should be administered not to individuals with a high cumulative lifetime risk of contracting IE, but rather to individuals at highest risk of adverse outcomes if they should develop IE.

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7

Congenital Heart Disease

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OUTLINE

Congenital heart disease (CHD) occurs in approximately 4 to 10 cases per 1000 live births. These numbers do not include bicuspid aortic valves, which would double or triple the incidence. Overall, CHD accounts for approximately a third of all congenital defects. Moreover, in developed countries, CHD has become the principal cause of heart failure in children, with 10% to 15% having other associated congenital anomalies of the skeletal, genitourinary, or gastrointestinal system. The incidence of CHD in children has remained constant over the last few decades. However, as therapeutic options have increased life expectancy, the overall prevalence of adults with CHD has steadily increased. It is estimated that in the United States, more adults than children are currently living with CHD. This trend is reflected in an ever-rising number of patients presenting for cardiac surgery, including primary repair, revision of a prior operation, conversion to a more modern operation, or treatment of long-term sequelae, or undergoing noncardiac surgery that is unrelated to their congenital cardiac defect. Fortunately, fewer than a dozen lesions, most of them acyanotic, comprise almost 90% of CHD encountered in adulthood (Table 7.1).

It is common for physicians to diagnose CHD in utero during the routine fetal anatomy ultrasonography screen. Diagnosing CHD post utero has evolved from fairly crude methods (auscultation, chest x-rays, and phenotypical appearance) to highly sophisticated imaging modalities such as echocardiography, cardiac catheterization, and magnetic resonance imaging (MRI). These techniques also make it possible to (1) accurately visualize minute details of cardiac function, blood flow, and driving pressures and (2) predict (to a certain extent) the perioperative course and long-term prognosis. Patients with milder forms of CHD may go undiagnosed in the perinatal period, and instead be diagnosed only later in life. Diagnosis may occur when an incidental heart murmur is detected on physical examination, or during the workup of conditions such as failure to thrive, feeding intolerance, or new-onset arrhythmias. Any provider caring for such patients needs to be aware of the many problems that can occur with CHD (Table 7.2).

CONGENITAL HEART LESIONS

Acyanotic Congenital Heart Disease

Shunting Lesions

Acyanotic shunting lesions are principally characterized by blood flow that shunts from left to right inside the heart or the proximal great vessels (Table 7.3). This shunting leads to increased pulmonary blood flow that then increases pulmonary vascular resistance, leading to intimal hyperplasia and vascular remodeling. All these effects cumulate in pulmonary hypertension, right ventricular hypertrophy, and, eventually, congestive heart failure. In general, the younger the patient at the time of surgical repair, the greater the likelihood that pulmonary vascular resistance will normalize. Survival in such patients is usually excellent, especially if shunting is restrictive. However, if the defect is not repaired until the patient is in his or her late teens or adulthood, and shunting involves more than one-third of cardiac output, long-term sequelae are highly likely, including

TABLE 7.1 Classification and Incidence of Congenital Heart Disease

Disease	Incidence (%)
Acyanotic Defects	
Shunting lesions	
Ventricular septal defect	37
Atrial septal defect	9
Patent ductus arteriosus	8
Atrioventricular septal defect	4
Stenotic lesions	
Pulmonary stenosis	8
Aortic stenosis	4
Coarctation of the aorta	4
Cyanotic Defects	
Tetralogy of Fallot	4
Transposition of the great vessels	3
Hypoplastic left heart	3
Hypoplastic right heart	2

TABLE 7.2 Common Problems Associated With Congenital Heart Disease

Cardiac
Dysrhythmias
Conduction defects
Pulmonary hypertension (Eisenmenger syndrome)
Endocarditis
Heart failure

Pulmonary
Cyanosis
Altered response to hypoxia or hypercarbia
Decreased lung compliance
Chronic lung disease
Hemoptysis
Airway compression

Vascular
Prior cannulation sites complicating the ability to gain vascular access

Renal
Chronic renal insufficiency
Renal failure

Hepatobiliary
Cholelithiasis
Hepatic congestion
Protein-losing enteropathy

Central Nervous System
Brain abscesses
Seizures
Strokes
Paradoxical emboli
Developmental status

Peripheral Nervous System
Phrenic nerve paralysis
Recurrent nerve paralysis

Hematologic
Erythrocytosis (hyperviscosity syndrome)
Abnormal coagulation studies
Thromboembolism
Coagulopathy

Musculoskeletal
Higher incidence of scoliosis

Miscellaneous
Decreased exercise tolerance
Failure to thrive and feeding difficulties in children

the development of pulmonary hypertension, ventricular remodeling, and congestive heart failure.

Atrial Septal Defect

Atrial septal defects (ASDs) account for the majority of congenital heart lesions detected in adults. Small ASDs do not usually cause symptoms for decades and therefore frequently remain undiagnosed until adulthood.

Depending on the embryologic origin and location of the defect in the interatrial septum and the specific point of shunting, one can differentiate four different types of ASDs (Fig. 7.1). An ostium primum defect occurs when the ostium primum fails to fuse with the endocardial cushions. The result is a defect in the interatrial septum that is located caudally just above the atrioventricular valves. The ostium secundum defect, the most common type of ASD (75% of all ASDs), is located in the middle of the interatrial septum in the same location as the foramen ovale and varies from a single opening to a fenestrated septum. The two remaining ASDs, the sinus venosus defect (located at either the superior vena cava or the inferior vena cava junction) and the unroofed coronary sinus (opening of the coronary sinus into the left atrium via its crossing behind the heart), occur with the least frequency. Importantly, ASDs do not always present in isolation but can be part of complex syndromes, each associated with other specific lesions. Specifically, ostium primum defects are associated with a cleft mitral valve and/or mitral regurgitation, ostium secundum defects are associated with mitral valve prolapse and/or regurgitation, sinus venous defects are associated with anomalous right pulmonary venous return, and an unroofed coronary sinus is associated with a persistent left superior vena cava.

Regardless of the type of ASD, the resulting physiologic changes depend on the degree of net blood shunting from the left to the right atrium. The degree of shunting, in turn, depends not only on the pressure difference between the two chambers but also on the size of the lesion and the relative compliance of the ventricles. The resulting, mostly left-to-right, shunt increases pulmonary blood flow and causes volume overloading of the lung, right ventricle, and right atrium. Smaller defects result in minor shunts that are mostly

TABLE 7.3 Congenital Heart Defects Resulting in Left-to-Right Shunting

- Atrial septal defect
  - Ostium primum defect
  - Ostium secundum defect
  - Sinus venosus defect
  - Unroofed coronary sinus
- Ventricular septal defect
  - Subarterial ventricular septal defect
  - Perimembranous ventricular septal defect
  - Inlet ventricular septal defect
  - Muscular ventricular septal defect
- Patent ductus arteriosus
- Aortopulmonary fenestration

without hemodynamic consequences and can be tolerated well into adulthood. Larger ASDs that allow more than a 50% increase in pulmonary blood flow can have severe consequences such as pulmonary hypertension, ventricular remodeling, and dysrhythmias.

Similar to many other congenital heart lesions, diagnosis in asymptomatic patients is often initiated after auscultation of a heart murmur. An electrocardiogram (ECG) might reveal signs of right axis deviation and an incomplete right bundle branch block (RBBB) from right ventricular strain. A chest x-ray may show enlarged pulmonary arteries, prominent lung vasculature, and cardiomegaly. The diagnosis is confirmed by using echocardiography to determine the location of the ASD, the degree of shunting, the direction of blood flow, and associated cardiac anomalies.

Signs and symptoms. Patients can present with increasing dyspnea on exertion, decreased exercise tolerance, fatigue, heart failure, palpitations, or embolic stroke. However, many patients with ASDs will remain asymptomatic for years. Smaller defects with a ratio of pulmonary to systemic blood flow (Qp:Qs ratio) of less than 1.5:1 usually remain asymptomatic and do not require further intervention. Shunt lesions with a Qp:Qs ratio greater than 1.5:1 should be considered for closure to prevent long-term sequelae. Depending on the location and size of the ASD, the lesion can be closed percutaneously using a septal occlusion device in the catheterization suite or surgically with a primary or patch closure either via sternotomy or minimally invasive thoracotomy.

Management of anesthesia. For general management strategies, including anesthetic management, see "Balancing Pulmonary and Vascular Resistance (Qp:Qs)" later in the chapter. Management of patients undergoing ASD closure depends largely on the chosen intervention. A percutaneous ASD closure can be conducted with standard American Society of Anesthesiology (ASA) monitoring and the patient under general anesthesia or deep sedation, whereas a surgical ASD repair requires all the routine monitors, access for cardiopulmonary bypass, and the capacity to treat/manage potential postoperative heart block.

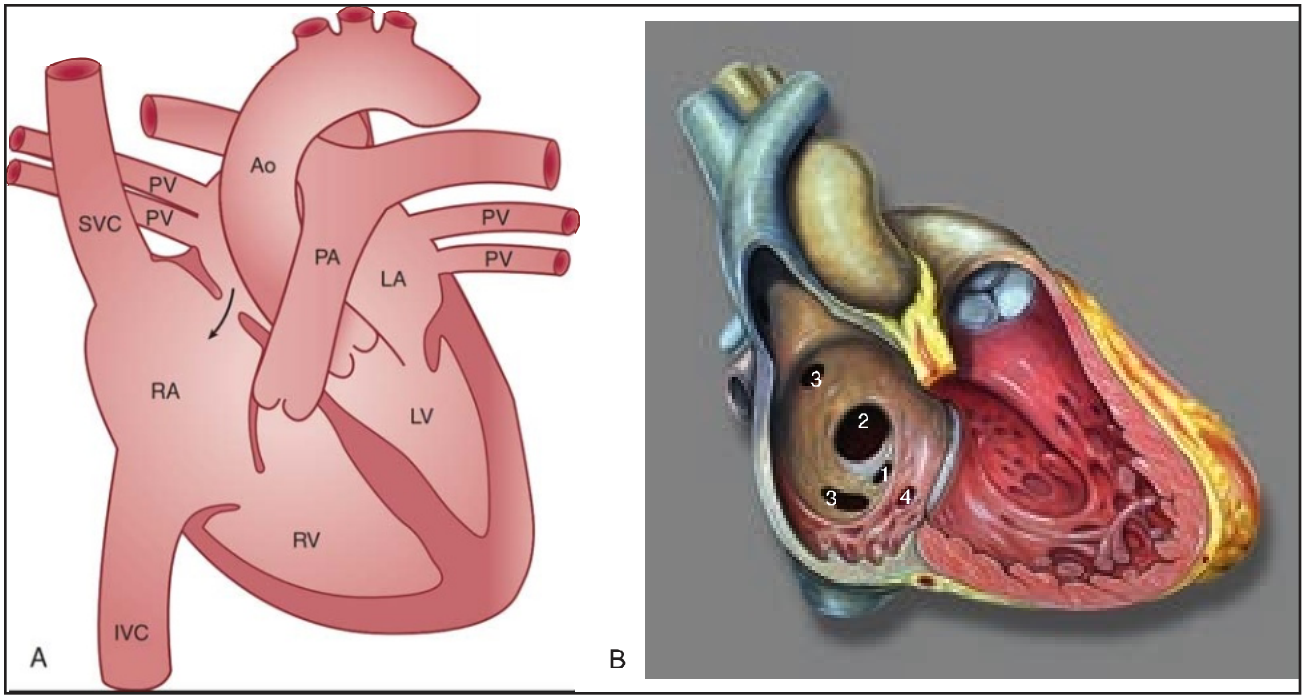


Fig. 7.1 Atrial septum defect. (A) Secundum atrial septal defect, in which blood flows left to right across the atrial septum along a pressure gradient. (B) Schematic drawing of the locations of atrial septal defects: (1) septum primum defect, (2) septum secundum defect, (3) sinus venosus defects, (4) unroofed coronary sinus. *Ao*, Aorta; *IVC*, inferior vena cava; *LA*, left atrium; *LV*, left ventricle; *PA*, pulmonary artery; *PV*, pulmonary vein; *RV*, right ventricle; *SVC*, superior vena cava. (http://radiopaedia.org/images/25224 by Patrick Lynch).

Ventricular Septal Defect

When excluding bicuspid aortic valves, ventricular septal defects (VSDs) are the most prevalent form of CHD in children, comprising 30% of cases. Because of the high spontaneous closure rate, however, especially for muscular septal defects, VSDs in adults are rare. The classification of VSDs can be confusing because each of the four different lesions has multiple names according to its location in the interventricular septum (Fig. 7.2). A VSD type I, also called subarterial, supracristal, outlet, subpulmonic, or infundibular VSD, is located high in the interventricular septum just below the pulmonic valve and above the crista terminalis. The most common VSD (more than two-thirds of all VSDs) is the type II VSD, also called the perimembranous or infracristal VSD, which is located lower in the septum just below the crista terminalis. A type III VSD, also called inlet or canal type VSD, is located just below the mitral and tricuspid valve. The last type of VSD, type IV or muscular VSD, is located deep in the muscular portion of the ventricular septum and can range from a single perforation to multiple holes of different sizes. Similar to ASDs, certain types of VSDs are associated with different lesions. Type I VSDs are associated with aortic insufficiency caused by prolapse of the aortic valve cusp. Type II VSDs are associated with tricuspid valve aneurysms or insufficiency caused by entrapment of the valve leaflets. Type III VSDs are associated with a cleft mitral valve or tricuspid valve and are part of the complete atrioventricular canal defect. Lastly, type IV VSDs can be associated with a multitude of different lesions but have the highest probability of closing spontaneously with time.

Signs and symptoms. The severity of signs and symptoms depends on the size of the defect, the pressure difference between the ventricles, and the ratio of pulmonary to systemic vascular resistance. Small defects with a Qp:Qs ratio of 1.4:1 or less usually remain asymptomatic and do not result in major sequelae (e.g., pulmonary hypertension or heart failure). These defects are usually referred to as restrictive VSDs, as the amount of shunting is restricted by the size of the defect. Moderately restrictive VSDs with a Qp:Qs ratio of 1.4:1 to 2.2:1 or nonrestrictive VSDs with a Qp:Qs ratio greater than 2.2:1 can result in an equalization of left and right ventricular systolic pressures that causes both volume and pressure overload of the pulmonary circulation. Over time, the pulmonary vasculature starts to remodel, resulting in increased pulmonary vascular resistance and pulmonary hypertension. Eventually a decrease in the Qp:Qs ratio results, leading to shunt reversal (Eisenmenger syndrome). Consequently, patients become progressively hypoxic as blood shunts right to left across the VSD and bypasses the lungs. Such patients are no longer candidates for VSD closure, as right heart failure would inevitably ensue. Over time, even in the absence of advanced disease and Eisenmenger syndrome, patients with moderate-restrictive or unrestrictive VSDs develop left ventricular failure and pulmonary hypertension, putting them at increased perioperative risk. Therefore it is important to diagnose patients early and perform a VSD closure before pulmonary vascular resistance increases to such high levels that closure is no longer possible.

With increasing size of the defect, the ECG can demonstrate signs of left atrial and left ventricular hypertrophy, as well as right

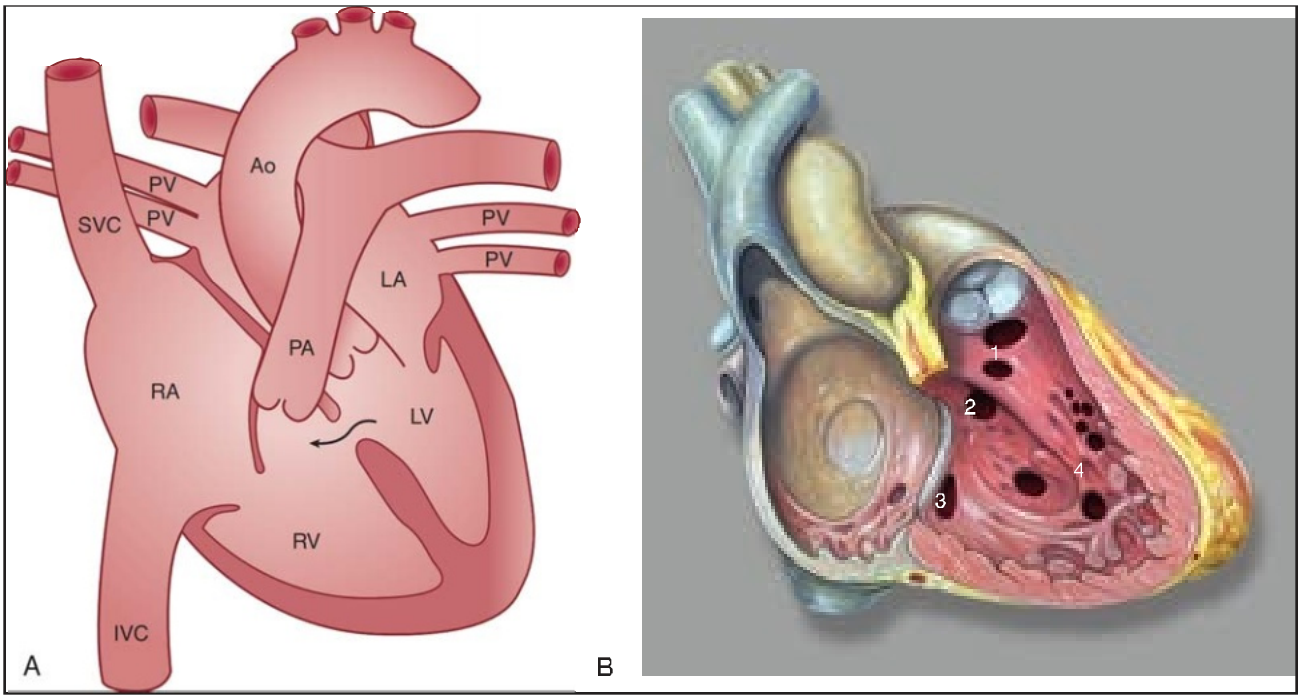


Fig. 7.2 Ventricular septal defect. (A) Schematic depiction of a ventricular septal defect resulting in a left-to-right shunting lesion. (B) Locations of the different types of ventricular septal defects: (1) outlet, (2) perimembranous, (3) inlet, (4) muscular. *Ao*, Aorta; *IVC*, inferior vena cava; *LA*, left atrium; *LV*, left ventricle; *PA*, pulmonary artery; *PV*, pulmonary vein; *RV*, right ventricle; *SVC*, superior vena cava. (http://commons.wikimedia.org/wiki/File:Heart_right_vsd.jpg by Patrick Lynch.)

ventricular strain. Similarly, chest x-rays will show an enlarged cardiac silhouette. Echocardiography with color Doppler is most commonly used to evaluate the presence, directionality, and severity of a VSD. Other more invasive techniques include cardiac catheterization and angiography to measure the amount of intracardiac shunting, intravascular and intracavitary pressures, and pulmonary and systemic vascular resistance.

Management of anesthesia. The most conservative summary would probably be to treat a patient with a VSD of unknown severity like a patient with congestive heart failure and pulmonary hypertension. For general management strategies and anesthetic management, refer to "Balancing Pulmonary and Vascular Resistance (Qp:Qs)" later in the chapter.

Small VSDs can occasionally be closed percutaneously in older children and adults, otherwise surgical closure is performed. Children who undergo surgical VSD closure generally tolerate it very well.

Patent Ductus Arteriosus (PDA)

During fetal development, the ductus arteriosus provides vascular communication between the left pulmonary artery and the descending aorta just distal to the left subclavian artery. In utero, it allows oxygenated placental blood returning to the fetus to flow from the systemic venous circulation to the systemic arterial circulation; therefore the blood does not have to traverse the pulmonary vascular bed of the nonventilated lungs (right-to-left shunt). Within the first 24 hours after delivery, the ductus arteriosus begins to close and is completely sealed off within the first month of life. However, in some patients (especially in preterm babies), the ductus arteriosus does not close normally and instead remains patent, allowing blood to flow between the pulmonary arterial and systemic arterial vasculature (Fig. 7.3). Over time, as pulmonary vascular resistance decreases, the flow of blood across the PDA occurs predominantly from the high-pressure aorta to the low-pressure pulmonary artery, resulting in a left-to-right shunt. The amount of blood shunting left to right depends on the resistance across the PDA (dependent on the diameter and length), the pressure difference between the aorta and the pulmonary artery, and both the pulmonary and systemic vascular resistance.

Signs and symptoms. Most patients with a PDA have only a mild or moderate left-to-right shunt, but symptoms of pulmonary overcirculation can develop over time. When the left-to-right shunt is substantial, patients can develop pulmonary hypertension that leads to heart failure, failure to thrive, aneurysmal dilatation of the ductus, and, in longstanding disease, Eisenmenger syndrome. Diagnosis and quantification can be established with echocardiography.

Management of anesthesia. Most patients in whom the ductus fails to close spontaneously will require closure during the neonatal period, especially those born before 28 weeks of gestation. Many can be closed medically with indomethacin, which decreases the production of prostaglandins that keep the ductus open. However, side effects of the drug may preclude its use in some patients. In such cases, the ductus is closed with either a device or surgical ligation. Minimally invasive device closure is performed by interventional cardiology in the catheterization suite and usually requires only percutaneous arterial and venous access. When device closure is not feasible, surgical ligation is carried out via a left thoracotomy without cardiopulmonary bypass. When severe pulmonary hypertension is present, ductal closure may precipitate acute right heart failure, contraindicating closure.

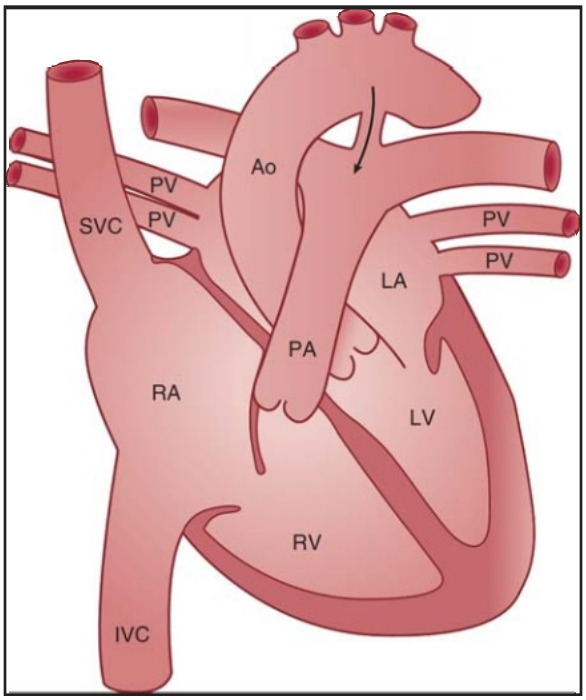


Fig. 7.3 Patent ductus arteriosus (PDA). Schematic depiction of a PDA connecting the distal aortic arch to the pulmonary artery (PA). This connection results in a left-to-right shunt, with blood flowing from the aorta (Ao) to the PA. IVC, Inferior vena cava; LA, left atrium; LV, left ventricle; PV, pulmonary vein; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

For general management strategies and anesthetic management, see "Balancing Pulmonary and Vascular Resistance (Qp:Qs)" later in the chapter. During surgical ligation of the ductus arteriosus, single lung ventilation is rarely required; rather the surgeon gently retracts the lung out of the field. This action can lead to a temporary drop in oxygen saturation, given the high incidence of lung disease with poor lung compliance in premature infants. Often, the decrease in oxygen saturation may be minimized with ventilator adjustments. Ligation of the ductus results in an immediate increase in diastolic blood pressure. Adverse events include hoarseness (due to recurrent laryngeal nerve injury), hemidiaphragm paralysis (due to phrenic nerve injury), chylothorax (due to thoracic duct injury), and reopening of the ductus.

Obstructive Lesions

Obstructive lesions are characterized by an increased resistance to blood flow around the level of the cardiac valves or the outflow tracts. In this section we will discuss the major left-sided obstructive lesion of the heart (aortic stenosis), its counterpart on the right side of the heart (pulmonic stenosis), and coarctation of the aorta (preductal and postductal). Increased pressure

is required to overcome the stenosis, which leads to either left-sided or right-sided concentric hypertrophy and ultimately heart failure.

Aortic stenosis. Stenosis of the left ventricular outflow tract can be due to subvalvular, valvular, or supravalvular aortic stenosis (AS). Valvular AS is frequently the result of a bicuspid aortic valve, which is present in approximately 2% of all newborns in the United States.

Patients with bicuspid aortic valves are generally not born with a stenosed valve. Rather, because the aortic valve has two (instead of the normal three) cusps, blood flow is more turbulent, leading to endothelial disruption and local inflammation that causes a predisposition for calcification. These factors all cumulate in premature AS. Severity is commonly determined by the pressure gradient across the aortic valve. A mean gradient less than 20 mm Hg is considered mild, whereas a mean gradient greater than 40 mm Hg is considered severe.

Signs and symptoms. Most patients with bicuspid aortic valves remain asymptomatic until adulthood. Infants with severe AS suffer from feeding difficulties, poor growth, and heart failure. Supravalvular AS is much less common and is usually associated with Williams syndrome. During anesthesia, patients with supravalvular AS have a high risk of sudden death, typically from myocardial ischemia. The same is true for patients with subvalvular AS, which can be due to either a fixed stenosis (membrane, fibromuscular ridge, etc.) or dynamic left ventricular outflow tract obstruction.

The classic symptoms of patients with AS are syncope, angina, and dyspnea. In such patients, the left ventricle must generate higher than normal pressures to overcome the stenotic lesion, which is not reflected by a normal systemic blood pressure measured poststenosis. The logical consequence is concentric hypertrophy of the left ventricle, which, over time, increases oxygen requirements and decreases myocardial compliance. Consequently, left ventricle filling pressure increases and coronary perfusion pressure to the left ventricular myocardium decreases, leading to angina. Because of the high blood flow velocity and turbulent flow poststenosis, the aortic root and ascending aorta can respond with poststenotic dilation, necessitating the repair of not only the valve but also the root and perhaps the ascending aorta.

The ECG can demonstrate left ventricular hypertrophy with strain—especially during exercise. Chest x-rays show an enlarged left ventricular silhouette and potentially a prominent ascending aorta. Diagnosis is confirmed with echocardiography to evaluate the exact location of the stenosis, its severity, associated lesions or changes, and ventricular function. Rarely is cardiac catheterization and angiography needed to assess severity and associated lesions.

Management of anesthesia. See Chapter 6 and its section about aortic stenosis for details on anesthetic management.

Pulmonic stenosis. Many of the concepts for AS can be translated to pulmonary stenosis, with the main difference being that the right ventricle is much more sensitive to increases in afterload. Pulmonary stenosis is mainly valvular in origin rather than supravalvular or subvalvular. Associated lesions, especially of supravalvular pulmonic stenosis, include ASDs, VSDs, a PDA, and tetralogy of Fallot. Supravalvular pulmonic stenosis can also occur in patients with Williams syndrome (distinctive phenotype, developmental delay, hypercalcemia, and stenosis of the aorta and/or pulmonary artery). Subvalvular pulmonic stenosis is typically associated with a VSD, whereas valvular pulmonic stenosis tends to occur in isolation or sometimes in combination with a VSD. Interestingly, peak pressure gradients are frequently used for the classification of pulmonic stenosis (as opposed to mean gradients), with less than 36 mm Hg being mild and more than 64 mm Hg being considered severe.

Signs and symptoms. Symptoms depend on the severity and associated defects (e.g., cyanosis that is present in severe cases associated with a VSD). In general, patients will present with signs of right heart failure, including dyspnea, jugular venous distension, hepatomegaly, peripheral edema, and ascites. The ECG may reveal signs of right ventricular hypertrophy and strain. Echocardiography or MRI can be used to confirm and classify the type and severity of the lesion.

Management of anesthesia. Pulmonary stenosis can be treated with open surgery that requires cardiopulmonary bypass, or it can be treated percutaneously via balloon valvuloplasty. For any patient with pulmonary stenosis undergoing surgery, the anesthetic goals are to avoid increases in right ventricular oxygen demand. See Chapter 6 and its section about pulmonic stenosis for details on anesthetic management.

Coarctation of the aorta. Coarctation of the aorta consists of aortic narrowing and is often classified by its proximity to the ductus arteriosus—preductal, juxtaductal, or postductal. Depending on its location, symptoms and age at diagnosis tend to vary. The most common form, postductal coarctation, lies beyond the ductus arteriosus and is sometimes diagnosed outside the neonatal period. A preductal coarctation is located proximal to the ductus and usually manifests in the neonatal period.

Signs and symptoms. All forms of aortic coarctation share adverse outcomes common to systolic hypertension, such as congestive heart failure, aortic dissection, premature coronary artery disease, and intracerebral hemorrhage caused by aneurysm rupture.

Signs and symptoms depend not only on the severity of the coarctation but also on its location (preductal vs. postductal). In general, presenting symptoms include headache, dizziness, palpitations, and epistaxis. Individuals with postductal aortic coarctation may remain asymptomatic as infants and come to medical attention later for the workup of headaches or hypertension. A blood pressure difference between the upper (hypertensive) and lower (normotensive or hypotensive) extremities or weak and delayed femoral pulses are present. In severe cases of diminished lower extremity blood flow, lower extremity claudication can occur. Infants with preductal aortic coarctation, on the other hand, tend to become symptomatic earlier in life, as they have selective cyanosis of the lower extremity with a pink face and upper extremities. If the coarctation is not repaired at that time, the difference in blood pressure between the upper and lower extremities tends to decrease as those children develop extensive collateral blood flow involving the internal thoracic, intercostal, and subclavian arteries.

The ECG shows the classic signs of left ventricular hypertrophy, as does the chest x-ray. Chest x-ray can also reveal notching in the posterior parts of the ribs as a sign of increased collateral blood flow in the intercostal arteries. The definite diagnosis can be made with echocardiography, computed tomography (CT), or MRI, which can classify the location and severity of the stenosis. The latter two techniques can be used to quantify the degree of collateral flow.

Management of anesthesia. Coarctation ideally should be repaired in infancy or early childhood before patients develop systemic hypertension. Once hypertension develops, the risk is high that it will persist despite an adequate repair. Although coarctation can be repaired percutaneously by a balloon dilatation and stent placement, open surgical resection with an end-to-end anastomosis remains the treatment of choice in infants.

Surgical repair generally does not involve cardiopulmonary bypass, but it does require a high (proximal) aortic cross clamp. Placement of the cross clamp necessitates the management of two circulations (proximal and distal to the clamp) with very different blood pressures. Importantly, the tighter the aortic stenosis, the fewer hemodynamic perturbations arise during placement of the cross clamp. The proximal circulation (heart, head, and upper extremity) is exposed to a relatively high pressure that has the potential to cause heart failure and cerebral hemorrhage. The distal circulation (especially the gut, kidneys, spinal cord, and lower extremities) is faced with the opposite problem, profound hypotension and hypoperfusion (depending on the amount of collateral blood flow), potentially leading to gut ischemia, renal failure, or, in rare cases, paraplegia. Blood pressure should be monitored continuously above the cross clamp, which leaves only the right arm as a reliable source (blood supply to the left arm can be compromised during the repair). Blood pressure should also be monitored below the level of the cross clamp to ensure adequate perfusion via the collaterals during cross clamping and to verify the absence of a pressure gradient after the repair. Alternatively, partial circulatory bypass might be used to ensure lower body perfusion during more complex repairs.

Patients are at risk for paradoxic hypertension, which is thought to be triggered by a baroreceptor reflex, activation of the renin-angiotensin-aldosterone system, or excessive release of catecholamines. Initial treatment includes the infusion of arteriolar vasodilators. The most common nerve injury is damage to the left laryngeal nerve that leads to stridor or hoarseness. Phrenic nerve damage is less common but could result in the need for prolonged respiratory support.

Ebstein anomaly. Ebstein anomaly is rare (<1%) and produces an acyanotic lesion if it occurs as an isolated entity. However, it can be associated with other shunting lesions that in combination with right ventricular outflow tract obstruction render those patients cyanotic. Patients with Ebstein anomaly have an atrialized right ventricle, with a malformed and caudally displaced tricuspid valve. Frequently, the anterior cusp is sail-like in structure with multiple fenestrations, resulting in tricuspid insufficiency and, in rare instances, stenosis. With the tricuspid valve displaced downward, the effective right ventricle is relatively small and inefficient.

Signs and symptoms. Severity of symptoms is proportional to the degree of tricuspid valve displacement and function. Sequelae can range from congestive heart failure, syncope, and dysrhythmias to an incidental finding with no symptoms at all. If patients have an associated shunting lesion, they are at risk for paradoxic emboli and hypoxia. More severe cases are usually found in neonates, who will require surgical intervention to survive and may not be candidates for a two-ventricle repair.

The ECG can show right ventricular hypertrophy and conduction abnormalities, such as a RBBB or first-degree atrioventricular block. Some may also have signs of paroxysmal supraventricular or ventricular tachyarrhythmias, or preexcitation syndromes. Chest x-rays can show right ventricular and atrial enlargement, which might compress lung tissue. The actual right ventricular cavity, however, remains small and inefficient, as revealed by additional findings of right ventricular failure, such as a dilated azygos vein and dilation of the right atrium. In severe disease, the shape of the heart approximates a sphere. Echocardiography is used to visualize the extent of atrial dilation, tricuspid valve anatomy, and tricuspid regurgitation, as well as associated shunting lesions and their severity.

Management of anesthesia. Symptomatic treatment includes pharmacologic therapy for heart failure and arrhythmias, as well as catheter-based ablation of accessory pathways to treat excitation syndromes. Surgical repair can be quite complex. If primary repair of the lesion is not feasible, a staged procedure along the single ventricle palliation pathway might be required.

Management of anesthesia depends on the severity of right ventricular dysfunction, the functional status of the tricuspid valve, the presence of arrhythmias, and associated shunting lesions. General management strategies and anesthetic management are discussed later under "Important Management Strategies for Adults with Congenital Heart Disease."

Cyanotic Congenital Heart Disease

The major characteristic finding in patients with cyanotic heart disease is a predominantly right-to-left shunt that results in decreased pulmonary blood flow and hypoxemia. Children with cyanotic heart disease have a low likelihood of surviving into adulthood unless they receive surgical correction or palliation of the defect. Severity of hypoxemia is mainly determined by the ratio of blood flowing through the lungs to that flowing through the systemic circulation (Qp:Qs ,1). Chronic hypoxemia also results in many secondary changes, such as erythrocytosis and associated hyperviscosity syndrome (headaches, light headedness, thromboembolism). Often, patients with extremely high hematocrits are found to have abnormal coagulation studies. Other common problems in cyanotic heart disease include heart failure, pulmonary hypertension, arrhythmias, decreased lung compliance, altered response to hypoxia and hypercarbia, and renal insufficiency.

Tetralogy of Fallot

Among cyanotic congenital lesions, tetralogy of Fallot is the most common, accounting for 7% to 10% of all congenital heart lesions. The four components that comprise this lesion are (1) a

perimembranous VSD, (2) an aorta that overrides the VSD, (3) a right ventricular outflow tract obstruction, and (4) right ventricular hypertrophy (Fig. 7.4). Almost a quarter of patients will also have an ASD, sometimes referred to as pentalogy of Fallot. Associated syndromes include trisomy 21 (Down syndrome) and DiGeorge syndrome. The key determinants of tetralogy of Fallot severity are the size of the VSD and the magnitude of the right ventricular outflow tract obstruction (subvalvular, valvular, supravalvular, or involving the main pulmonary artery). The resultant pressure and volume overload lead to right ventricular hypertrophy, and the right-to-left shunt leads to hypoxia of varying degrees. Increases in systemic vascular resistance or pressure (either pharmacologically or physically [squatting]) can decrease the amount of shunt, forcing more blood through the pulmonary circulation and thereby improving oxygen saturation. The opposite is also true; systemic hypotension (e.g., with anesthesia) facilitates right-to-left blood flow and consequently hypoxia.

Signs and symptoms. Newborns with mild to moderate disease tend to become cyanotic during the first few months of life, but severe forms can cause profound cyanosis in the newborn period. Patients with mild disease might remain acyanotic and can present with heart failure later in life.

The classic presentation is a hypercyanotic spell ("tet spell"), during which profound cyanosis develops rapidly, accompanied by hyperpnea, possible loss of consciousness, stroke, seizures, or even death. Therefore hypercyanotic attacks can be very anxiety provoking for patients, parents, and caregivers.

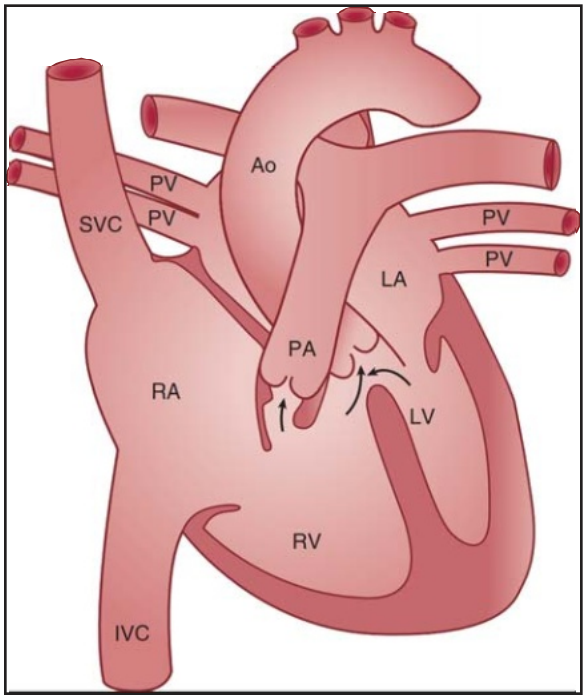


Fig. 7.4 Tetralogy of Fallot. The components associated with tetralogy of Fallot are (1) ventricular septal defect, (2) aorta (Ao) overriding the ventricular septal defect, (3) right ventricular outflow tract obstruction, and (4) right ventricular hypertrophy. IVC, Inferior vena cava; LA, left atrium; LV, left ventricle; PV, pulmonary vein; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

Generally, those attacks occur during periods of stress (exercise, feeding) or agitation (crying), but they can also occur without obvious provocation. The proposed mechanisms include spasms of the infundibular portion of the right ventricular outflow tract, likely by catecholamine release; peripheral vasodilation; and hyperventilation, which all seem to be debunked. Alternatively, they might be due to acute change in inotropy, increased systemic oxygen consumption, reduced mixed venous oxygen content, acute reduction in systemic vascular resistance, and decreased right ventricular preload associated with tachycardia. The most susceptible period appears to be 2 to 3 months of age, but they can occur any time during the first year of life, after which they occur with less frequency. Children often squat down during hypercyanotic spells, thereby increasing peripheral vascular resistance, presumably by kinking the large vessels in the groin, ameliorating the right-to-left shunt. Treatment focuses on relieving the right ventricular outflow tract obstruction and minimizing the right-to-left shunt. Preventive treatment includes the administration of a long-acting β blocker. Acute or emergent treatment entails (in escalating order) administration of 100% oxygen and positioning (bending at the hip or gentle pressure on the abdomen). Once an intravenous catheter is established, fluids should be administered. When nonpharmacologic interventions fail, administration of a systemic vasoconstrictor will reduce right-to-left shunting by increasing systemic vascular resistance. Additional steps include administration of a short-acting β blocker or a sedative (e.g., morphine) to help ameliorate spastic right ventricular outflow tract obstruction. Should these hypercyanotic spells recur frequently, a surgical intervention to provide reliable pulmonary blood flow (e.g., systemic-to-pulmonary shunt or complete surgical repair) should be considered.

Other associated symptoms could include cyanosis, hyperviscosity syndrome, and paradoxic emboli (including cerebral abscesses, seizures, and strokes), as infectious agents can more readily reach the brain via the bloodstream. Brain abscesses can manifest as headaches, emesis, fever, and lethargy and if untreated could result in seizures. These abscesses occur because the lung vasculature of children with a right-to-left shunt is bypassed, preventing filtration of small clots and infectious agents. Hence paradoxic emboli are common, and cerebrovascular accidents occur more frequently. These events cannot be explained solely by the propensity for paradoxic emboli. They also occur secondary to local thrombosis, especially in children with very high hematocrits (≥60%), and practitioners should be meticulous in preventing both dehydration and air entry into intravenous lines.

The ECG typically shows right axis deviation and right ventricular hypertrophy. Chest x-rays may show decreased pulmonary vascularity, a boot-shaped heart, an elevated right ventricular apex, and a concave pulmonary artery. The diagnosis is confirmed with echocardiography. Additional hemodynamic data collection by cardiac catheterization is rarely needed.

Management of anesthesia. Without surgical repair, only 25% of children survive to adolescence and only 3% survive to age 40. However, when the defect is repaired surgically at an early age, almost 90% of patients survive beyond 30 years of age. Complete surgical repair entails VSD closure and relief of

any right ventricular outflow tract obstruction. Efforts to preserve the pulmonary valve and its function are prioritized. In severe cases of pulmonary atresia, a Rastelli operation is also necessary, which involves placing a conduit between the right ventricle and the pulmonary artery.

When the pulmonary valve is not fully preserved, pulmonary regurgitation is expected, which over time leads to right ventricular dilation. Once dilation becomes significant, or right ventricular function is affected, surgical or transcatheter pulmonary valve replacement is indicated.

Another potential adverse event after full surgical repair is a residual shunt. A RBBB is nearly universal after full surgical repair but usually remains asymptomatic. Occasionally, patients with tetralogy of Fallot who are poor candidates for a complete surgical repair (e.g., too small or other major coexisting medical conditions) are palliated with a systemic arterial-to-pulmonary artery shunt (modified Blalock-Taussig shunt, which connects the subclavian artery to the pulmonary artery). Although the shunt provides stable pulmonary blood flow, complete repair to close the VSD and relieve right ventricular outflow tract obstruction must still be completed in the future. Alternatively, if the pulmonary valve is the area of right ventricular outflow tract obstruction, a balloon pulmonary valvuloplasty can be used to temporarily relieve the right ventricular outflow tract obstruction until the patient can undergo a complete surgical repair.

Preoperative preparation. The major preoperative considerations focus on measures that are known to decrease the incidence of hypercyanotic spells. Perioperative fasting should be kept to a minimum, as patients need to be hydrated to avoid hypotension, which favors a right-to-left shunt. Also, stressful situations and crying should be avoided, with premedications if necessary, to avoid catecholamine release. Patients on β blockers should take them the morning of surgery.

Induction and maintenance of anesthesia. There is no single best induction agent for children with tetralogy of Fallot, nor is there a single best method to maintain anesthesia that will guarantee stable hemodynamic conditions. Intravenous or inhalational techniques are acceptable, but care should be taken to choose drugs that favor pulmonary blood flow, manage the Qp:Qs ratio, and support adequate end-organ perfusion. For management strategies and anesthetic management, see "Balancing Pulmonary and Vascular Resistance (Qp:Qs)" later in the chapter.

Eisenmenger Syndrome

Eisenmenger syndrome is characterized by severe pulmonary hypertension, which develops as a result of a chronic, long-standing, left-to-right intracardiac shunt that leads to shunt reversal. Theoretically it can affect all patients with a significant left-to-right shunt, regardless of the underlying cause. Prolonged exposure of the pulmonary vasculature to volume and pressure overload leads to remodeling of the pulmonary arteries and veins. The result is a slow but steady increase in pulmonary vascular resistance that ultimately leads to a flow reversal of the left-to-right shunt, which now becomes predominantly right to left. A common cause of Eisenmenger syndrome is an unrepaired, unrestrictive VSD.

Signs and symptoms. With progressive development of a right-to-left shunt, patients become more and more hypoxic and experience decreased exercise tolerance. Enlargement of the right ventricle and atrium leads to dysrhythmias such as atrial fibrillation or flutter, which the patient may experience as palpitations. Progressive hypoxia also stimulates erythrocytosis, leading to hyperviscosity syndrome.

The ECG shows signs of right ventricular hypertrophy and strain. Echocardiography is used to delineate directionality of shunt flow, ventricular function, and estimation of right-sided pressure. Occasionally, cardiac catheterization may be used to measure pressures in the right heart and pulmonary vasculature, and quantify Qp:Qs.

Management of anesthesia. Treatments that are widely used for patients with pulmonary arterial hypertension seem to be less effective in patients with Eisenmenger syndrome. Adjunct treatment focuses on the amelioration of associated symptoms. Phlebotomy can be used to treat hyperviscosity, and oxygen administration can counteract hypoxia. The only definite treatment in selected patients is combined heart and lung transplant or a lung transplant with a surgical repair of the underlying shunting lesion. Surgical repair of the underlying defect without lung transplant is contraindicated, as this would result in right heart failure.

Management of anesthesia in patients with Eisenmenger syndrome who are undergoing noncardiac surgery reflects the management of anesthesia in patients with other forms of severe pulmonary hypertension. The general wisdom that every procedure is better done with minimally invasive laparoscopy does not necessarily apply to those patients. This approach necessitates insufflation of the abdominal cavity with carbon dioxide, which increases intraabdominal pressures and raises the $Paco_2$. As a result, hypotension (due to lower right ventricular preload), acidosis, and hypercarbia (due to increased $Paco_2$ levels) may develop. High intrathoracic pressure may become necessary to counteract the increased abdominal pressure, which is made worse when Trendelenburg positioning is required. Furthermore, the patient may experience dysrhythmias from high $Paco_2$ and atrial distension. All these effects worsen right-to-left shunting, hypoxia, and effective cardiac output. Therefore it is preferable to perform the procedure open instead of laparoscopically, while still striving for early extubation with appropriate pain control.

The anesthesiologist might consider using a neuraxial technique for either the primary anesthetic or intraoperative and postoperative analgesia. The major concern is the sudden drop in blood pressure, especially with a spinal. An epidural, however, is not necessarily contraindicated in patients with Eisenmenger syndrome; they are actually used frequently. However, one needs to be cognizant of the potential for hypotension that may worsen right-to-left shunting and hypoxemia.

By definition, pulmonary vascular resistance is fixed in these patients and cannot decrease significantly in response to changes in systemic vascular resistance. To minimize the gradient driving the right-to-left shunt, practitioners should maintain systemic vascular levels at preoperative levels or slightly above. A sudden drop in oxygen saturation without changes in ventilation can be

a first sign that systemic vascular resistance has decreased. For general management strategies and anesthetic management, see "Management of Pulmonary Hypertension" and "Balancing Pulmonary and Vascular Resistance (Qp:Qs)" later in the chapter.

Tricuspid Atresia

As the name suggests, the key feature of tricuspid atresia is the absence or permanent closure of the tricuspid valve. This closure blocks blood flow into the right ventricle, necessitating additional lesions for at least temporary survival. For example, blood flows from the right atrium to the left atrium either via a patent foramen ovale or an ASD, where it mixes with oxygenated blood. It then flows across the mitral valve into the left ventricle where a variable portion crosses a VSD into the right ventricle and the pulmonary circulation; the rest is ejected into the systemic circulation across the aortic valve. Alternatively, pulmonary blood flow can be established across a PDA or bronchial vessels. Patients with tricuspid atresia are cyanotic and have a small right ventricle, a normal or enlarged left ventricle, and decreased pulmonary blood flow. Additionally, tricuspid atresia can be subclassified according to the position of the great vessels (type I: normal relationship, type II: dextro-transposition, type III: nondextro-transposition [levo-transposition or double outlet], type IV: truncus arteriosus). Patients with normally related great arteries tend to have the obstruction at the level of the VSD, whereas patients with transposition tend to have either subvalvular or valvular stenosis.

Signs and symptoms. Severity and timing of symptoms depend on the complexity of the cumulative lesions as well as on the severity of the obstruction to pulmonary blood flow.

Approximately 50% of patients develop symptoms by 24 hours of life and 80% by the end of the first month. Decreased levels of pulmonary blood flow with a right-to-left shunt lead to cyanosis, tachypnea, and failure to thrive, all in the absence of abnormal pulses, hepatic enlargement, or overt heart failure. The subset of patients with increased pulmonary blood flow will present with minimal cyanosis, tachypnea, tachycardia, hepatomegaly, feeding difficulties, and signs of heart failure.

The ECG reveals signs of left axis deviation, left ventricular hypertrophy, and right atrial enlargement. The diagnosis is made by echocardiography, which demonstrates an absent or closed tricuspid valve, abnormal right ventricle, a VSD, and right ventricular outflow tract obstruction.

Management of anesthesia. Management of anesthesia varies slightly depending on the stage of palliation the child is undergoing. For general management strategies and anesthetic management, see "The Univentricular Heart During Different Stages of Repair" later in the chapter. Long-term survival is very good and depends in part on the anatomic origin of the systemic ventricle, with the left ventricle having a better long-term prognosis.

Transposition of the Great Arteries

Transposition of the great arteries can be divided into two separate forms: D-transposition and L-transposition, also referred to as congenitally corrected transposition of the great arteries (a misnomer).

D-transposition (dextro-transposition) is the more common form and is generally implied if someone refers to transposition of the great arteries. D-transposition results when the truncus arteriosus (the common origin of the aorta and pulmonary artery) fails to divide properly in utero (Fig. 7.5). This arrangement results in two parallel circulations, and unless there is a communication between the pulmonary circulation and the systemic circulation (e.g., ASD), it is incompatible with life.

The less common form, L-transposition (levo-transposition) results from a misdirected folding of the embryonic heart tube resulting in abnormal position of the right and left ventricles, without alteration in position of the great vessels. Systemic venous return therefore flows into the right atrium, across the mitral valve into the left ventricle (both of which are positioned on the right side), and then is ejected across the pulmonary valve into the pulmonary arteries. Pulmonary venous blood then returns to the left atrium, crosses the tricuspid valve into the right ventricle (both of which are positioned on the left side), and then is ejected across the aortic valve into the systemic circulation. Because the two circulations are in series, patients do not exhibit cyanosis and are generally asymptomatic until later in life when the systemic ventricle (the right ventricle that is positioned on the left side) starts to fail prematurely.

Signs and symptoms. Symptoms depend on the type of transposition. Children diagnosed with L-transposition are

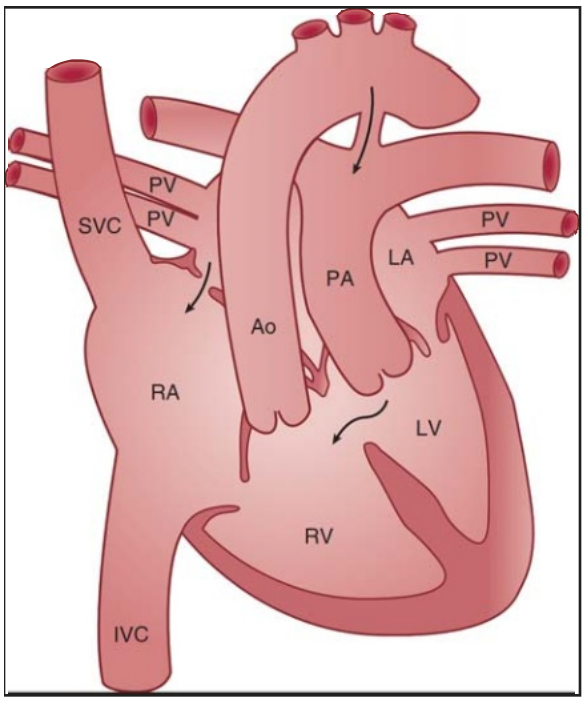


Fig. 7.5 Schematic depiction of transposition of the great arteries. The right ventricle (RV) and left ventricle (LV) are connected in parallel to each other, creating independent circulations, with the aorta (Ao) arising from the RV and the pulmonary artery (PA) arising from the LV. Survival depends on mixing of blood between the two circulations through an atrial septal defect, ventricular septal defect, or patent ductus arteriosus. IVC, Inferior vena cava; LA, left atrium; PV, pulmonary vein; RA, right atrium; SVC, superior vena cava.

generally asymptomatic. Neonates who have D-transposition of the great arteries without a mixing shunt become profoundly cyanotic within the first hours of life. Neonates with a large mixing shunt may not have significant cyanosis; however, without surgical repair they will develop heart failure.

The ECG shows right axis deviation and right ventricular hypertrophy. Fetal sonography often enables diagnosis in utero. After birth, transthoracic echocardiography is usually all that is needed prior to surgical repair. It can confirm the diagnosis as well as evaluate the degree of mixing of shunts (e.g., VSD), identify the presence of left ventricular outflow tract obstruction (present in about 5–10%), assess the suitability of the left ventricle for repair, and clarify the coronary artery arrangements. Additional cardiovascular imaging is rarely required.

Management of anesthesia. Neonates with D-transposition of the great arteries require adequate mixing of systemic venous and arterial blood, either extracardiac or intracardiac. Initially, a prostaglandin infusion can be used to maintain patency of the ductus arteriosus. However, mixing at the PDA is often insufficient, and additional mixing is required at an atrial level shunt (e.g., ASD). When mixing at the atrial level is insufficient, a balloon atrial septostomy is performed to increase the size of the atrial shunt (Rashkind procedure).

Definitive surgical correction was historically performed with either the Mustard or Senning procedure. Now surgical repair entails the arterial switch operation. Both the Mustard and Senning procedures involve the creation of an interatrial baffle to redirect blood from the vena cava to the left ventricle. In the Mustard procedure, the baffle is created with synthetic material, whereas the Senning procedure uses the patient's own tissue. These historical procedures allow systemic venous return to enter into the left heart (via the opened atrial septum), and from there it is ejected into the pulmonary arterial bed. The pulmonary venous return is directed into the right heart, from which it is ejected into the aorta. The major flaw of these operations is that the right ventricle functions as the systemic ventricle. Since the structure of the right ventricle is not meant to work for a lifetime against the systemic afterload, patients are prone to heart failure. In addition, patients have a significant risk for atrial dysrhythmias given the extensive atrial scarring that occurs. These issues are avoided with the current arterial switch operation that is now preferred. In this operation, the pulmonary artery and aorta are transected and reconnected with the right and left ventricles, respectively. Additionally, the coronary arteries are resected and reimplanted into the neoaortic root on the left side of the heart. Outcomes are generally excellent, with good long-term survival. Surgical operations for D-transposition with left ventricular outflow tract obstruction are more complex and challenging. Either the Rastelli procedure with an extracardiac right ventricular-to-pulmonary artery conduit or the Nikaidoh operation may be performed.

For general management strategies and anesthetic management, see "Balancing Pulmonary and Vascular Resistance (Qp:Qs)" later in the chapter.

Truncus Arteriosus

Patients with truncus arteriosus have a single vessel originating from the heart that gives rise to both the aorta and pulmonary artery (Fig. 7.6). This vessel overrides a large VSD and thereby both ventricles. Unoperated, prognosis is poor, with a median survival of only 6 weeks.

Signs and symptoms. Depending on the location of the pulmonary artery origins from the truncus, truncus arteriosus can be divided into different types using either the Van Praagh or the Collett and Edwards classification. According to Collett and Edwards, type I truncus arteriosus is defined by a main pulmonary artery arising from the base of the truncus. Type II truncus arteriosus is defined by the branch pulmonary arteries arising separately from the truncus in close proximity to each other (usually posterior). Type III truncus arteriosus is defined by the pulmonary arteries rising on opposite sides of the truncus, and type IV is defined by the pulmonary arteries arising from the descending aorta. All forms result in mixing of the oxygenated and deoxygenated blood and left-to-right shunting with pulmonary overcirculation. Infants can present with cyanosis, failure to thrive, and congestive heart failure.

There are no characteristic auscultatory or ECG findings in patients with truncus arteriosus. Initial diagnosis is made with echocardiography, but CT angiography is often necessary to better define vascular anatomy prior to surgical repair.

Management of anesthesia. Definite surgical correction involves closure of the VSD, disconnecting the pulmonary arteries

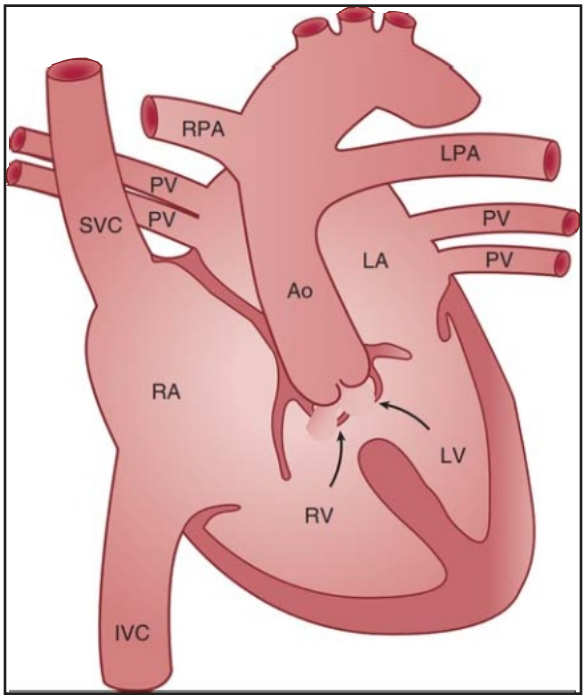


Fig. 7.6 Truncus arteriosus. In patients with truncus arteriosus, a single vessel arises from the heart, overrides the left ventricle (LV) and right ventricle (RV), and gives rise to the aorta (Ao) and pulmonary arteries. IVC, Inferior vena cava; LA, left atrium; LPA, left pulmonary artery; PV, pulmonary vein; RA, right atrium; RPA, right pulmonary artery; SVC, superior vena cava.

from the truncus, and placing a graft between the right ventricle and the pulmonary artery to provide pulmonary blood flow. The magnitude of pulmonary blood flow is the main determinant of anesthetic management. For general management strategies and anesthetic management, see "Balancing Pulmonary and Vascular Resistance (Qp:Qs)" later in the chapter.

Partial Anomalous Pulmonary Venous Return

Partial anomalous pulmonary venous return, a milder form of total anomalous pulmonary venous return (see later), occurs when one (most common) or more pulmonary veins drain into either the venous or right side of the heart instead of the left atrium. In the most common form of partial anomalous pulmonary venous return, the drainage is into the superior vena cava, resulting in a left-to-right shunt at the atrial level and consequent right heart dilation.

Only a few patients with large increases in pulmonary blood flow present with symptoms such as dyspnea on exertion and fatigue. More severe symptoms such as cyanosis and congestive heart failure are relatively rare and tend to manifest only if the Qp:Qs ratio goes beyond 1.5:1. In addition to right ventricular failure, over time patients may also present with right atrial dilation and a high arrhythmia burden. Definitive treatment requires open surgical repair to redirect pulmonary venous blood flow back to the left atrium.

Visualization of all four pulmonary veins and their drainage can be challenging with echocardiography. Sometimes CT angiography is needed to establish the diagnosis.

Total Anomalous Pulmonary Venous Return

In patients with total anomalous pulmonary venous return, all four pulmonary veins drain either separately or via a common confluence into the right atrium or the systemic venous tributaries proximal to the lungs. Most frequently (50% of cases) this connection occurs above the level of the heart (supracardiac) into the left innominate vein, which is usually associated with a left-sided superior vena cava. Cardiac connections occur in approximately 25% of cases and are characterized by either direct connections of the pulmonary veins to the right atrium or a connection of the confluence of all four pulmonary veins to the coronary sinus. Infracardiac total pulmonary venous return results when the pulmonary vein confluence connects directly to either the inferior vena cava or the portal venous system. Total anomalous venous return requires an atrial level shunt through which blood can reach the systemic arterial circulation (right-to-left shunt). Any restriction of this shunt will lead to pulmonary vascular congestion and hypoxemia.

Signs and symptoms. Most patients with total anomalous pulmonary venous return present in the neonatal period, and nearly all present by 1 year of age. However, when the anomalous veins are obstructed, patients will exhibit acute respiratory failure and hypoxemia within hours of birth. Therefore obstructed total anomalous pulmonary venous return is a surgical emergency with universal mortality if left untreated.

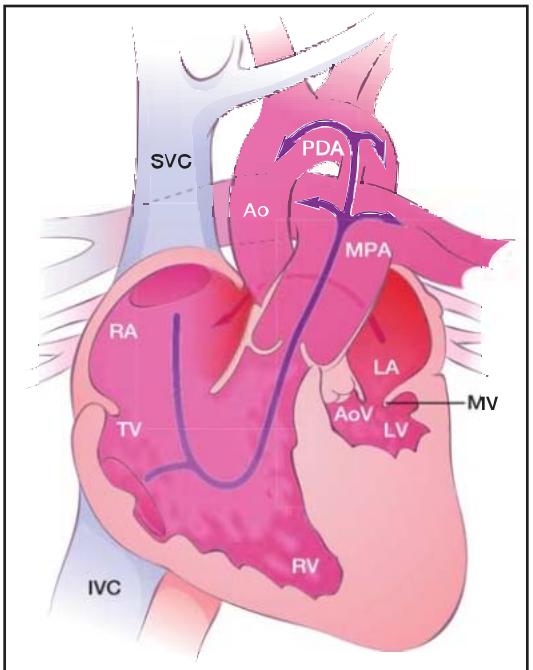
The ECG may show signs of right atrial and ventricular enlargement. When pulmonary venous obstruction is present, chest x-ray will show significant diffuse, bilateral pulmonary edema. Echocardiography is used to identify the lack of normal pulmonary venous return to the left atrium. CT angiography is often required to further delineate vascular anatomy before surgical repair.

Management of anesthesia. Definitive treatment requires emergent surgery. The common pulmonary venous confluence or the individual pulmonary veins are mobilized and reconnected to the left atrium. All associated shunting lesions (mostly ASD) are closed. This approach restores normal blood flow and eliminates volume overload and hypoxia.

These patients may be in extremis upon presentation to the operating room, as medical management often offers very little improvement. Intraoperative management involves treating systemic hypoxemia and its end-organ sequelae. Practitioners should avoid excessive fluid administration that can lead to further elevation of right atrial pressure and pulmonary edema. Quickly and safely initiating cardiopulmonary bypass to drain the right heart, reduce pulmonary arterial blood flow, and establish systemic oxygen delivery is key.

Hypoplastic Left Heart Syndrome

Hypoplastic left heart syndrome (HLHS) is the most common single-ventricle cyanotic heart lesion destined for Fontan palliation. The key pathology includes hypoplasia or atresia of each of the following: left ventricle, mitral valve, aortic valve, and aortic arch (Fig. 7.7). Therefore, in the unrepaired neonate, both systemic venous and pulmonary venous blood mix within the right



RA	Right atrium	Ao	Aorta
RV	Rigth ventricle	PDA	Patent ductus arteriosis
LA	Left atrium	TV	Tricuspid valve
LV	Left ventrticle	MV	Mitral valve
SVC	Superior vena cava	PV	Pulmonary valve
IVC	Inferior vena cava	AoV	Aortic valve
MPA	Main pulmomary artery		

Fig. 7.7 Hypoplastic left heart syndrome. (From https://www.cdc.gov/ncbddd/heartdefects/hlhs.html.)

ventricle. Pulmonary venous blood returning to the left atrium is shunted across an ASD (or a patent foramen ovale) to the right atrium and then into the right ventricle. The right ventricle then ejects the blood into the pulmonary artery. A portion of that blood is diverted to the systemic circulation through the ductus arteriosus (right-to-left shunt) while the remaining blood continues to the pulmonary vascular bed. Blood delivery to the aortic root and coronary arteries can occur by two different routes that depend on the degree of aortic hypoplasia present. Blood either travels antegrade from the left ventricle across when the aortic valve is hypoplastic or retrograde from the ductus arteriosus back down the proximal arch when the aortic valve is atretic. The ratio of blood delivered to the pulmonary or the systemic circulation depends on the resistance of the pulmonary and systemic vascular beds.

Signs and symptoms. Newborns with HLHS require patency of the ductus arteriosus to ensure systemic blood delivery. Without immediate initiation of a prostaglandin infusion after birth to maintain ductal patency, neonates will experience rapid heart failure, shock, and cardiovascular collapse. The degree of cyanosis tends to be mild but can vary with changes in pulmonary vascular resistance, ductal patency, and the degree of atrial level shunting.

Fetuses with HLHS are universally diagnosed in utero with fetal ultrasonography. The ECG demonstrates right axis deviation and right ventricular hypertrophy. A postnatal echocardiogram confirms the diagnosis and is often all that is required to identify the salient features necessary to proceed with surgical palliation.

Management of anesthesia. Initial surgical palliation (Norwood procedure) in the neonatal period requires establishment of pulmonary arterial blood flow with a shunt, augmentation of the hypoplastic aortic arch, and enlargement of the atrial septum with a septectomy. This is only the first of many surgical repairs within the single-ventricle palliation pathway, which ultimately culminates in a Fontan procedure. Consequently, management of anesthesia for patients with HLHS varies depending on the stage of palliation. For the Norwood procedure, ensuring adequate systemic vascular blood flow is of utmost importance. As pulmonary vascular resistance decreases in the first few days of life, patients tend to have a higher ratio of pulmonary blood flow to systemic blood flow (Qp:Qs .1). Therefore, while providing anesthesia, it is important that the anesthesiologist avoid things that significantly lower pulmonary vascular resistance (e.g., high inspired oxygen concentration) or significantly increase systemic vascular resistance (e.g., hypothermia). Cardiopulmonary bypass and aortic cross clamp times can be moderate in length. Temporary cessation of circulation (circulatory arrest) is also required. Therefore the immediate postoperative cardiac function may require substantial support with vasoactive medications or sometimes extracorporeal membrane oxygenation (ECMO). Furthermore, bleeding is common because of the multiple suture lines. Patients often require significant amounts of blood product resuscitation and close monitoring of hemodynamics. Manipulation of systemic and pulmonary vascular resistance to achieve appropriate systemic oxygen delivery continues in the postoperative period. The postoperative arterial oxygen saturation is expected to be 75% to 85% owing to mixing of systemic venous return and pulmonary venous return in the systemic right ventricle. It is not unusual for these patients to have extended hospital stays after surgery.

Mechanical Obstruction of the Trachea

Children with mechanical obstruction of the trachea present with stridor and upper airway obstruction. Mechanical obstruction of the trachea can be the result of an abnormal vessel impinging the trachea. Impingement can be due to a large arterial blood vessel completely encircling the trachea (double aortic arch, aberrant left pulmonary artery) or to an enlarged, dilated pulmonary artery externally compressing the trachea (e.g., in pulmonary valve atresia). If compression is at or below the level of the bronchus, patients can experience recurrent atelectasis and/or air trapping distal to the obstruction.

Double Aortic Arch

A double aortic arch is rare, but when present it is considered a complete vascular ring. This defect occurs embryologically when the paired right and left aortic arches fail to remodel into a single left-sided arch. The result is a closed circular structure that surrounds both the trachea and esophagus (Fig. 7.8). In the usual anatomy, the right aortic arch gives rise to the right subclavian and right common carotid arteries, and the left aortic arch gives rise to the left subclavian and left common carotid arteries. If these vessels exert excessive external pressure, the trachea and esophagus may become compressed. In severe cases, this causes inspiratory stridor, dysphagia, and difficulty mobilizing secretions. Diagnosis is often made during airway evaluation for respiratory complaints, and CT angiography is used to clarify vascular anatomy.

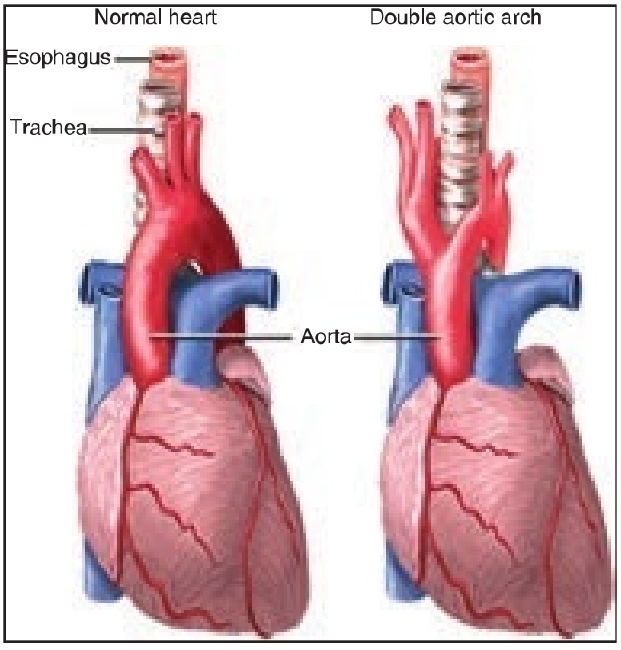


Fig. 7.8 Double aortic arch. Mechanical obstruction of the trachea secondary to a double aortic arch. (From http://www.nlm.nih.gov/medlineplus/ency/article/007316.htm.)

Treatment of choice for symptomatic children is surgical. Cardiopulmonary bypass is usually not required, and the surgery can be performed via a lateral thoracotomy or video-assisted thoracoscopy. If the patient has associated cardiac defects that require simultaneous repair (e.g., tetralogy of Fallot), median sternotomy and cardiopulmonary bypass are used. During intubation, the endotracheal tube needs to be placed distal to the tracheal compression to ensure adequate ventilation. When a thoracoscopic repair is performed, one-lung ventilation is preferred for surgical exposure; therefore either a bronchial blocker or double-lumen endotracheal tube may be necessary. Postoperative complications include chylothorax, left vocal cord injury, transient hypertension, and tracheaobronchomalacia.

Aberrant Left Pulmonary Artery

An aberrant left pulmonary artery can result in an incomplete vascular ring, sometimes referred to as a vascular sling. The left pulmonary artery arises from the proximal right pulmonary artery and runs posterior to the right main bronchus and trachea before entering the hilum of the left lung. This anatomy compresses the right side of the trachea. Patients present with respiratory symptoms such as wheezing, expiratory stridor, or difficulty clearing secretions. In contrast to a double aortic arch, an aberrant left pulmonary artery is not usually associated with esophageal obstruction. The anomaly can be associated with other cardiac defects in a third of patients (e.g., ASD, VSD, PDA, and aortic arch anomalies).

Treatment is surgical and requires cardiopulmonary bypass. The aberrant pulmonary artery is ligated and reconnected to the main pulmonary artery anterior to the trachea.

NONCARDIAC SURGERY IN THE ADULT PATIENT WITH CONGENITAL HEART DISEASE

Our understanding of CHD and care for affected patients has improved drastically over the last decades. Major strides have been made in long-term medical treatment, surgical techniques and skills, percutaneous interventions, intraoperative and perioperative care, and critical care management. These improvements have led to an increased likelihood of survival for children born with CHD. Based on data from Canada, 85% survive to adulthood, and it is now estimated that at least as many adults as children are living with CHD. For the United States that means more than 1 million adults with CHD may present not only for cardiac surgery (primary repair, revision, or conversion to a more modern operation) but for surgery that is completely unrelated to their cardiac disease. Indeed, admissions of adults with CHD for noncardiac surgery have been increasing steadily and more than doubled over the last decade. Moreover, though the age distribution of all patients with CHD was heavily skewed toward children only 30 years ago, new data show that it now almost perfectly resembles the age distribution of the general population.

Although many patients who survive into adulthood are considered cured or palliated, they do experience a high morbidity burden. The list of cardiovascular complications of long-standing CHD includes pulmonary hypertension, systemic hypertension, heart failure (especially right heart failure), cyanosis, residual shunts, arrhythmias, conduction defects, and valvular lesions (see Table 7.2). The probability of developing heart failure increases in almost all patients with CHD over their lifetime, but the magnitude depends on the type of lesion. Similarly, the cumulative incidence of any type of dysrhythmia increases steadily over time. Moreover, cardiac lesions such as valvular stenosis or regurgitation, residual shunts, outflow tract obstructions, and dysrhythmias will cause these patients to return to the cardiac operating room or electrophysiology suite for treatment of long-term sequelae.

Noncardiac, long-term complications can occur in multiple organ systems (see Table 7.2). It is helpful to categorize symptoms according to organ system and consider how the specific form of CHD can influence each. CHD-specific comorbidities occur in addition to the expected normal changes of aging. The adult with CHD therefore combines two phenotypes into one: an anatomic phenotype similar to that of a pediatric patient and a physiologic phenotype similar to that of a geriatric patient. This analogy was very nicely demonstrated in a study showing that adult patients with CHD (mean age 33) had an exercise tolerance similar to that of older patients with heart failure (mean age 59), stratified by New York Heart Association Class. In line with this finding, data from Canada suggest that adult patients with CHD do better when cared for in special centers that routinely treat patients with CHD.

Preoperative Evaluation

Evaluation of adult patients with CHD can be complex. These patients present with a wide variety of congenital lesions at different stages of repair and with different comorbidities. Patients can present with an uncorrected lesion, a partially corrected lesion, a lesion that is between repair stages, or a failed lesion repair attempt. Moreover, adult CHD is not an isolated well-described entity, but rather a multisystem disease with a broad range of severity. Consequently, no single best risk index delineates perioperative risk and stratifies the contributions of comorbidities in these patients. The American College of Cardiology and the American Heart Association (ACC/AHA) categorize severity and perioperative risk according to the type of lesion and the physiologic state of the patient. They consider low-risk patients to be those with simple disease such as a small ASD, small PDA, or isolated VSD, or those who have undergone complete ASD, VSD, or PDA repair. Moderate complex lesions include aortic coarctation, complete atrioventricular canal, Ebstein anomaly, and repaired tetralogy of Fallot, among others. Lastly, patients with great complexity are those with any form of unrepaired cyanotic heart disease, single ventricle physiology, and transposition of the great arteries, among others. In addition to this general assessment, perioperative risk increases with the patient's comorbidities and symptoms (e.g., heart failure, pulmonary hypertension, poor exercise tolerance, renal insufficiency, cyanosis, dysrhythmia). Patients usually undergo extensive workup, including multiple functional and imaging modalities. Besides the standard workup for all patients, preoperative evaluation should enable the provider to acquire a detailed knowledge of the patient's current anatomy, physiology at rest, and, importantly, a thorough understanding of changes in pulmonary and vascular resistance.

While a particular focus is placed on preoperative exercise tolerance as an indicator of cardiovascular reserve, one needs to evaluate every organ system and determine how CHD alters its function.

Premedication

The use of preoperative anxiolytics is beneficial in many adults with CHD, as they often have had multiple prior operations and hospitalizations. Some patients may have cognitive impairments, either from underlying genetic conditions (e.g., trisomy 21) or prior cerebral insults (e.g., strokes). Administration of any preoperative sedation must take into account the potential consequence that hypercarbia- or hypoxia-induced increases in pulmonary pressure can pose—especially in patients with pulmonary hypertension or shunting lesions.

Endocarditis Prophylaxis

The ACC/AHA have updated their guidelines to recommend endocarditis prophylaxis only in the highest-risk patients undergoing a high-risk procedure (see dedicated section later in this chapter). Therefore not every patient with CHD will require routine endocarditis prophylaxis.

Vascular Access

It can be challenging to obtain vascular access in adults with CHD given multiple prior cannulations. Prior cutdowns of the radial arteries, a former Blalock-Taussig shunt, or a coarctation can interfere in invasive arterial monitoring. Furthermore, the femoral or internal jugular veins can be thrombosed or scarred from prior cannulation attempts. Of note, in patients with a Glenn shunt or Fontan circulation, a central venous catheter will infuse fluids and drugs directly into the pulmonary artery. It is important to avoid catheter-associated thrombus formation as it may occlude blood flow to the lungs (pulmonary artery thrombus).

Dysrhythmia

Although most adult patients with CHD experience at least one form of dysrhythmia during their lifetime, atrial reentry tachycardia is especially prevalent. Many patients undergo electrophysiologic studies to ablate the dysrhythmia, and some may even have an implanted pacemaker or defibrillator.

Pulmonary Hypertension

Presence of pulmonary hypertension substantially increases perioperative risk. It is important to avoid medications and maneuvers that increase pulmonary artery pressures (see Table 7.5, later). Low exercise tolerance, syncope, atrial dysrhythmia, high atrial pressures, cyanosis, right ventricular dysfunction, and renal insufficiency are all predictors of poor outcomes in patients with pulmonary hypertension.

Heart Failure

The prevalence of heart failure, particularly right-sided heart failure, increases with age and is especially worrisome in patients with single ventricle physiology (e.g., HLHS). Prior to elective surgery, all patients with heart failure should be medically optimized to reduce potential morbidity.

Bleeding Diathesis

Patients with hyperviscosity syndrome from chronically elevated hematocrit often present with abnormal coagulation studies but normal bleeding times. Some may also have low levels of von Willebrand factor and vitamin K–dependent clotting factors. All patients with hyperviscosity are at increased risk for thrombosis, especially with dehydration; therefore prolonged fasting is best avoided.

Intraoperative Management

No single management strategy is applicable to all adults with CHD, and no one anesthetic technique has proven to be superior in these patients. As discussed previously, this is a multisystem disease. Management will depend on the patient's functional status, comorbidities, and specific anatomy, as well as the type and urgency of the procedure. Many patients with noncomplex CHD who are undergoing low-risk to moderate-risk surgery will do fine with standard monitoring and care. Patients with moderate or complex CHD may require invasive arterial monitoring even for seemingly minor surgery. Central venous access is infrequently used unless adequate peripheral access is unobtainable. Because interpretation of pulmonary artery catheter data can be misleading, and studies have shown that it does not provide benefit in hospital survival, practitioners are increasingly using transesophageal echocardiography (TEE) to continuously monitor these patients intraoperatively. TEE provides helpful guidance with fluid therapy and/or administration of inotropic or vasoactive medications.

Intraoperative management focuses on the optimization of oxygen delivery to all organs. Maintaining cardiac contractility (especially of the right ventricle), balancing the Qp:Qs ratio, treating dysrhythmias, and maintaining systemic blood pressure and oxygen saturation remain key components in anesthetic management (see later in this chapter).

Postoperative Management

As with preoperative and intraoperative management, decisions regarding postoperative management depend on multiple factors, including the type of procedure performed, the patient's comorbidities, and the intraoperative course. In general, providers should have a low threshold for utilizing an intensive care bed postoperatively to monitor for and quickly treat complications that may have more pronounced effects in patients with CHD than in the general population (e.g., bleeding, hypovolemia, hypotension, increasing pulmonary artery pressures, dysrhythmias, and thrombosis).

Echocardiography in Congenital Heart Disease

Few clinical tools have had as large an impact on the field of CHD as echocardiography. Recently, echocardiography has become so advanced that not only has it helped define the underlying diagnosis, but also, when used by properly trained individuals, it can elucidate specific anatomic details that previously required other more invasive imaging (e.g., cardiac catheterization). Echocardiography can show detailed anatomy of the coronary arteries, the size and directionality of intracardiac shunts, valve motion and function, ventricular function, and so much more that it provides enough information to proceed with surgical repair.

Fetal echocardiography offers a way to make an early diagnosis and provide early counseling regarding outcomes and expectations for families. Furthermore, it provides information that practitioners can use to direct clinical care. Following birth, transthoracic echocardiography is often all that is needed to proceed with surgical repair of most CHD lesions. In fact, it is becoming rare that additional invasive imaging (e.g., cardiac catheterization) is needed. However, noninvasive imaging (e.g., MRI or CT scan) may sometimes be required for more complex anatomy or to elucidate important surrounding vascular structures not visible by echocardiography.

TEE, especially in pediatric CHD, is therefore reserved for assessment of anatomy and function during cardiac surgery. Because TEE probe placement is an invasive procedure, each patient must first be assessed for contraindications. Furthermore, certain conditions in infants and children may preclude the placement of a TEE probe, as it may lead to airway compromise, distortion of the anatomy in the surgical field, or compression of surrounding vascular structures (e.g., vascular rings, aberrant subclavian artery, and total anomalous pulmonary veins).

It is becoming the standard of practice to perform a preoperative TEE during congenital heart surgery if no contraindications exist, after induction of anesthesia. The procedure should contain all the standard views of a comprehensive TEE exam. In addition, three-dimensional echocardiography can also be used to provide procedural guidance and functional assessment. These views help practitioners to confirm the preoperative diagnosis, assess myocardial function, and identify any new lesions that could not be adequately assessed by the preoperative transthoracic echocardiogram. The postoperative TEE is usually performed after the completion of surgical repair, but before the patient is separated from cardiopulmonary bypass. It is performed to assess adequacy of repair, ventricular function, volume status, and presence of air within the heart. It can also be used to assist in management decisions (e.g., inotropic support vs. volume resuscitation) after discontinuation of bypass, if a qualified provider is available. However, when interpreting the findings of the postoperative TEE, practitioners must consider the effects of anesthetics.

Imaging with echocardiography in patients with CHD demands an in-depth knowledge of congenital and acquired heart disease as well as echocardiography. At this time there is no formal certification pathway for physicians performing TEE in CHD patients, but most hospitals in which surgical repair is performed have pediatric or adult CHD-trained certified cardiologists who perform these examinations. For additional information, the American Society of Echocardiography has published guidelines and standards for performing a comprehensive TEE in pediatric and adult patients with CHD.

IMPORTANT MANAGEMENT STRATEGIES FOR ADULTS WITH CONGENITAL HEART DISEASE

Infective Endocarditis Prophylaxis

The ACC/AHA jointly updated their recommendation on endocarditis prophylaxis for patients with CHD. Using published literature, they restricted their recommendations of antibiotic use for endocarditis prevention to only patients with high risk undergoing high-risk procedures (Table 7.4).

TABLE 7.4 Patient Groups at Highest Risk for Developing Endocarditis

- History of endocarditis
- Prosthetic heart valve (prosthetic material used for valve repair)
- Status post heart transplant with valvulopathy
- Congenital heart disease-associated conditions
  - Unrepaired cyanotic congenital heart lesion (including palliative shunts and conduits)
  - Completely repaired congenital heart lesion, during the first 6 months after the procedure (if prosthetic materials or devices were used)
  - Repaired congenital heart lesion with a residual defect (at or adjacent to the site of a prosthetic patch or prosthetic device)

Endocarditis prophylaxis is advisable for patients undergoing dental procedures involving gingival tissue manipulation, manipulation of the periapical region of the teeth, or perforation of the oral mucosa. The guidelines specifically do not recommend using endocarditis prophylaxis for nondental procedures, such as colonoscopy or esophagogastroduodenoscopy, if the patient is not infected. However, it is reasonable to consider endocarditis prophylaxis in selected patients for vaginal delivery at the time of membrane rupture if patients have a prosthetic cardiac valve or prosthetic material used to repair a cardiac valve, or if they have unrepaired or palliated cyanotic CHD (including conduits).

Management of Pulmonary Hypertension

The key element to managing patients with pulmonary hypertension is lowering pulmonary resistance (Table 7.5) while supporting

TABLE 7.5 Factors That Change Pulmonary and Systemic Vascular Resistance

Decrease Pulmonary Vascular Resistance	Increase Pulmonary Vascular Resistance
100% inspired oxygen concentration	Hypoxia
Hypocarbia	Hypercarbia (e.g., hypoventilation due to premedication or sedation)
Alkalosis	Acidosis
Normothermia	Hypothermia
Low mean airway pressures or spontaneous ventilation	High mean airway pressures (positive pressure ventilation, positive end-expiratory pressure)
Avoidance of catecholamine release (avoid pain, anxiety, light anesthesia)	Catecholamine release (due to pain, anxiety, light anesthesia)
Medications (inhaled nitric oxide, prostaglandins, milrinone, etc.)	Medications (phenylephrine, all α_1 agonists, nitrous oxide, ketamine, etc.)
Increase Systemic Vascular Resistance	Decrease Systemic Vascular Resistance
Sympathetic stimulation	β_2 agonists
α_1 agonists	Neuraxial anesthesia
Hypothermia	Deep general anesthesia

right ventricular function. For a more in-depth description of the options for managing pulmonary hypertension, refer to the Chapter 9.

Balancing Pulmonary and Vascular Resistance (Qp:Qs)

The anesthetic management of patients who have shunting lesions and are undergoing noncardiac surgery varies with the severity of the lesion. Usually a component of bidirectional blood flow is present; however, the net amount of shunting in patients without Eisenmenger syndrome is left to right. Patients with minor shunting (e.g., a small ASD and a Qp:Qs ratio, 1.5:1) will likely require only minor anesthetic adjustments. Care should be taken to meticulously avoid air bubbles in all intravenous lines of all patients with a shunting lesion, as they can result in paradoxic emboli entering the systemic arterial system. With increasing degrees of left-to-right shunting and a Qp:Qs ratio greater than 1.5:1, it is increasingly important to manage and limit pulmonary blood flow to prevent heart failure secondary to volume overload.

Modifying Pulmonary and Systemic Vascular Resistance

Some congenital heart lesions (e.g., unrestrictive VSD) are very responsive to changes in the ratio of pulmonary-to-systemic vascular resistance. In general, drugs and maneuvers that increase systemic vascular resistance (hypothermia, sympathetic stimulation, or vasoconstrictive drugs) and lower pulmonary vascular resistance will promote left-to-right shunting. The same is true for drugs (e.g., nitric oxide or milrinone) and nonpharmacologic measures that decrease pulmonary vascular resistance. Examples of such measures include hyperventilation with a high inspired oxygen concentration, alkalosis, minimizing positive pressure ventilation or positive end-expiratory pressure, maintaining normothermia, and lowering catecholamine levels (deep anesthesia, avoiding pain and anxiety). These measures produce higher pulmonary blood flow (improved oxygen saturation) but also have the potential to cause heart failure. In contrast, measures that increase pulmonary vascular resistance (e.g., high levels of positive pressure ventilation, hypoxemia, nitrous oxide) or decrease systemic vascular resistance (anesthetics agents, histamine release [drugs, anaphylaxis], α blockers) will promote a decrease in left-to-right shunting (see Table 7.5).

Onset of Intravenous and Inhaled Agents

There is ongoing, but mostly academic, concern that the induction of anesthesia is altered by left-to-right shunt lesions, given the brief transit time in the pulmonary circulation. However, even in patients with highly elevated pulmonary blood flow, which could theoretically dilute intravenous anesthetic agents and cause slow transit to the brain because of recirculation, little or no clinically significant effect is seen on induction speed. Similarly, the induction speed with volatile agents is unaffected as long as cardiac output is maintained. In contrast, patients with a right-to-left shunting lesion tend to have a more rapid onset of action after intravenous drug administration. Because the drug bypasses the lungs, it gets relatively less diluted and reaches its target (i.e., brain) faster and at a higher concentration than it does in patients without a shunting lesion. The reverse is true for inhaled anesthetics, which exhibit a slower induction speed as blood concentrations rise more slowly.

Left-to-Right Shunts

Patients with increased pulmonary blood flow benefit from medications and maneuvers that maintain or avoid decreases in pulmonary artery resistance. Patients with a left-to-right flow do not typically have low oxygen saturations unless the shunt is long-standing and has resulted in significant associated pulmonary edema. These patients tolerate positive pressure ventilation and inhaled anesthetics without issue. It is important to avoid high amounts of supplemental oxygen or hyperventilation as these may decrease pulmonary artery resistance and significantly increase the amount of left-to-right flow. Similarly, it is best to minimize drugs or interventions that increase systemic vascular resistance, which can promote greater left-to-right flow (see Table 7.5).

Right-to-Left Shunts

Patients with significant right-to-left shunts will have low oxygen saturations, and conditions that increase the amount of shunting will worsen systemic oxygenation. These conditions include (1) increases in pulmonary vascular resistance, (2) increases in right ventricular outflow tract obstruction (infundibula spasm), and (3) decreases in systemic vascular resistance. In patients with a fixed right ventricular outflow tract obstruction (e.g., pulmonary valve stenosis, branch pulmonary artery stenosis), changes in pulmonary vascular resistance are less likely to modify the Qp:Qs ratio because the level of obstruction is proximal to the pulmonary arterial bed. However, changes in systemic vascular resistance can modify the Qp:Qs by encouraging more right-to-left flow across a more proximal shunt lesion (e.g., VSD). Therefore many practitioners prefer to use ketamine for intravenous induction because it maintains systemic vascular resistance and therefore prevents worsening hypoxemia from increased right-to-left shunt. Though ketamine may increase pulmonary vascular resistance, the effect is negligible. Lastly, these patients can usually be safely maintained under general anesthesia with inhaled sevoflurane as long as systemic vascular resistance is maintained.

THE UNIVENTRICULAR HEART DURING DIFFERENT STAGES OF REPAIR

Surgical Management

Surgical repair of infants with single-ventricle physiology is completed in stages to accomplish the following: (1) maintain duct patency as needed, (2) balance pulmonary-to-systemic blood flow, (3) unload the systemic ventricle, and (4) fully separate the circulations, culminating in single-ventricle palliation with Fontan completion.

The initial concern in the neonate is to determine the ratio of pulmonary-to-systemic blood flow. If antegrade pulmonary blood flow across the right ventricular outflow tract is diminished (e.g., pulmonary atresia with intact ventricular septum or severe right ventricular outflow tract obstruction), another source of pulmonary blood flow (e.g., PDA) is necessary. It is therefore

imperative to maintain duct patency with a prostaglandin infusion to ensure peripartum survival.

Thus the goal of the initial intervention is to establish a reliable source of pulmonary blood flow, either by stenting open the ductus arteriosus or by creating a surgical shunt from the systemic arterial circulation to the pulmonary arterial circulation (e.g., Blalock-Taussig shunt or central shunt). A modified Blalock-Taussig shunt is a Gor-Tex shunt that connects the right subclavian artery to a branch pulmonary artery. Creating a systemic-to-pulmonary shunt provides pulmonary blood flow from a high-pressure arterial system, which is especially important in the newborn period when the pulmonary arterial pressures are elevated. These high-pressure shunts temporarily provide stable pulmonary arterial blood flow until the infant has grown large enough for definitive surgical repair. By this time the pulmonary vascular resistance will have normalized.

Alternatively, neonates may not have an obstruction in pulmonary blood flow. In this case excessive pulmonary blood flow causes pulmonary overcirculation and symptoms of heart failure. Medical management includes using afterload reduction (e.g., an angiotensin-converting enzyme [ACE] inhibitor) and diuretics. If medical intervention is inadequate and definitive surgical repair cannot be performed safely (such as in cases of extreme prematurity), a pulmonary artery band may be placed that encircles and externally constricts the main pulmonary artery. This band restricts the amount of blood that enters the pulmonary arterial vasculature bed. Cardiopulmonary bypass is not required for this procedure.

When the aorta is hypoplastic (insufficient in size) and the patient does not have two adequately sized ventricles to support biventricular physiology, a Norwood procedure may be required in the neonatal period (Fig. 7.9). The Norwood procedure consists of an atrial septectomy to achieve maximal mixing of blood inside the heart, disconnection of the main pulmonary artery from the branch pulmonary arteries, augmentation of the small aortic arch using the main pulmonary artery, and placement of either a systemic-to-pulmonary artery shunt (e.g., modified Blalock-Taussig shunt) or a right ventricular-to-pulmonary artery conduit (Sano modification) to provide reliable pulmonary blood flow. In addition to cardiopulmonary bypass, this extensive operation requires deep hypothermia and circulatory arrest. In patients with hypoplastic left heart who undergo the Norwood procedure with Sano modification, the single systemic right ventricle ejects blood into both the systemic and pulmonary arterial circulations in parallel. Alternatively, if the Norwood operation is performed with a Blalock-Taussig shunt, the right ventricle ejects blood only into the systemic arterial circulation (via the neoaorta), and pulmonary blood flow occurs through the shunt originating from the right subclavian artery (blood flow occurs in series, not in parallel).

The child with single-ventricle physiology is allowed to grow until he or she is large enough and has low enough pulmonary vascular resistance to qualify for the next surgical stage of the palliation. Low pulmonary vascular resistance because ultimately

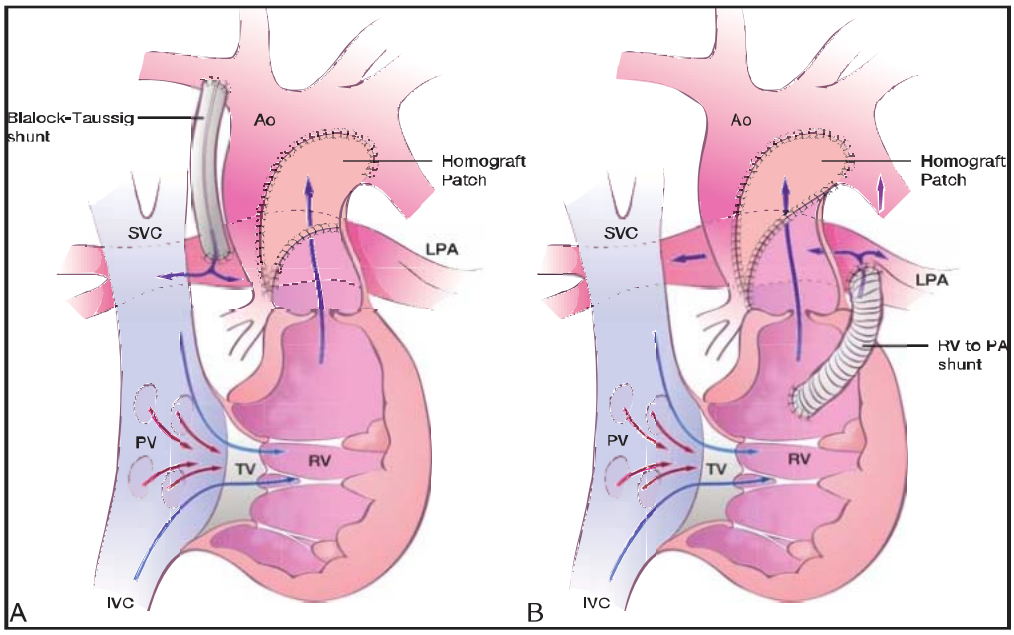


Fig. 7.9 Different stages of univentricular repair. The Norwood procedure for hypoplastic left heart syndrome. The figure shows the two variants in surgical technique according to the way in which pulmonary blood flow is established. (A) The classic procedure with a systemic pulmonary artery shunt (Blalock-Taussig). (B) Modification with a right ventricle–pulmonary artery conduit. *Ao* Aorta; *IVC* inferior vena cava; *LPA* left pulmonary artery; *PA* pulmonary artery; *PV* pulmonary valve; *RPA* right pulmonary artery; *RV* right ventricle; *SVC* superior vena cava; *TV* tricuspid valve. (From Barron DJ, Kilby MD, Davies B, et al. Hypoplastic left heart syndrome. *Lancet*. 2009;374[9689]:551–564.)

children with single-ventricle physiology will have systemic venous return that flows passively across the pulmonary bed into the systemic ventricle. The second step of the palliation (Glenn operation) occurs around the age of 4 to 6 months. It aims to improve pulmonary blood flow and reduce the volume load imposed on the right ventricle from both systemic and pulmonary venous return. In this procedure, a cavopulmonary anastomosis is created from the superior vena cava to the right pulmonary artery, and the shunt or conduit placed during the Norwood operation is removed (see Fig. 7.9). Therefore all superior systemic venous blood enters the pulmonary artery (not the right ventricle), leaving only systemic venous blood from the inferior vena cava to enter the right ventricle. Thus the Glenn operation directs approximately 30% of the cardiac output (superior vena cava return) away from the ventricle and reduces the risk of heart failure. It also allows the ventricle to remodel over time from a volume-overloaded state in which it has to provide both the full systemic and full pulmonary blood flow. After the Glenn operation the right ventricle provides the full systemic and about half of the pulmonary blood flow. It should be noted that all systemic venous blood from the inferior vena cava completely bypasses the lungs and enters the systemic circulation. Therefore systemic arterial oxygenation after the Glenn operation remains low (75–85%), as it was after the Norwood operation. After a few years, when the child has grown and the heart remodeled, the final stage of palliation, the Fontan, can be performed.

The exact timing of the Fontan operation varies among institutions, but it is generally performed between 2 and 4 years of age. Before the operation, children will undergo cardiac catheterization to ensure that pulmonary artery pressure is low and that the systemic venous-to-atrial pressure gradient (transpulmonary pressure) is adequate to allow all of the systemic venous blood to "passively" flow across the pulmonary vascular bed to the systemic ventricle. In addition, any collateral vessels that may have developed over time from chronic hypoxemia may necessitate intervention. During the Fontan operation, the pulmonary and systemic circulations are completely separated and are now aligned in series. The Fontan operation has evolved over the past several years and now is performed by creating either a lateral tunnel or, more frequently, an extracardiac conduit (see Fig. 7.9). The lateral tunnel approach has been performed for a little longer and entails creation of an intraatrial baffle (intracardiac) that shunts blood within the right atrium, from the inferior vena cava to the right pulmonary artery. When the Fontan procedure is performed with an extracardiac conduit, the conduit lies exterior to the heart and connects the inferior vena cava directly to the right pulmonary artery. In either case, the superior cavopulmonary anastomosis (Glenn operation) remains intact. Thus all systemic venous blood return flows across the pulmonary arterial bed to the left atrium and then into the systemic single ventricle where it is then ejected into the aorta and the systemic circulation. Because all systemic venous blood return now goes to the lung via the pulmonary artery, the systemic arterial oxygenation returns to normal (.92%). Furthermore, the single ventricle is no longer volume overloaded because it is receiving only pulmonary venous return and not systemic venous return. Of note, in patients with a marginal transpulmonary pressure gradient, the surgeon might elect to create a fenestration (a small connection) between the Fontan conduit (lateral tunnel or extracardiac conduit) and the right atrium. This fenestration serves as a small shunt that preserves preload to the systemic ventricle when passive pulmonary blood flow alone does not allow enough preload of the systemic ventricle. During times of increased pulmonary vascular resistance (exercise, straining), pulmonary pressure might rise high enough to restrict passive pulmonary blood flow, instead augmenting blood flow right-to-left across the fenestration. With an increase in right-to-left flow across the fenestration during such conditions, the cardiac output is preserved at the expense of temporary systemic hypoxemia.

KEY POINTS

- CHD is the most common congenital abnormality, accounting for 5 to 10 cases per 1000 live births, not including bicuspid aortic valves, which would double or even triple the incidence.
- The most prevalent congenital heart defect in children and infants is a VSD.
- Noninvasive imaging, especially echocardiography, is the cornerstone of diagnosis and classification of congenital heart lesions.
- CHD is not an isolated entity but affects many other organs, making it a multiorgan disease.
- Balancing pulmonary with systemic blood flow and supporting the right ventricle are key management features.
- Systemic and pulmonary vascular resistance can be selectively modified by changing the partial pressure of oxygen, partial pressure of carbon dioxide, pH, body temperature, and intrathoracic pressures; by controlling catecholamine release; and by administering certain medications.
- Adults with CHD outnumber children with CHD in developed countries. They can present not only for cardiac surgery but increasingly for noncardiac surgery that is completely unrelated to their congenital heart lesion. Furthermore, they present at different stages of repair or palliation and with a broad set of comorbidities (congestive heart failure, pulmonary hypertension, arrhythmias, thrombosis, bleeding diathesis, etc.) that pose a unique challenge to the anesthesiologist.
- The ACC/AHA have jointly published guidelines that limit antibiotic endocarditis prophylaxis to a select group of patients at highest risk undergoing high-risk procedures.

RESOURCES

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8

Abnormalities of Cardiac Conduction and Cardiac Rhythm

Kelley Teed Watson

OUTLINE

INTRODUCTION

The development of the modern-day electrocardiogram (ECG) started with the recognition by scientists that the electric currents regulating the heart could be detected at the surface of the skin. In the late 1800s Willem Einthoven built a machine called a string galvanometer that recorded a tracing representing the direction of cell depolarization through the heart as a series of positive and negative deflections around an isoelectric baseline. He called it an electrocardiogram. Now, over 100 years later, ECGs remain a mainstay of diagnostic cardiac evaluation.

All perioperative clinicians, whether anesthesiologists, intensivists, or pain specialists, must be proficient in recognizing normal and abnormal ECG findings. The ECG is considered the single most important clinical test to diagnose cardiac dysrhythmias, ischemia, and infarction. In preoperative risk stratification, a resting 12-lead ECG is a helpful tool to evaluate symptoms suggestive of arrhythmia or for detection of more covert problems such as silent ischemia in diabetics. Also, a preoperative ECG is a helpful baseline to determine the seriousness of ST or rhythm changes detected intraoperatively or postoperatively.

In the operating room, it is rare that we can monitor 12 leads during an anesthetic procedure. Most commonly, a 5-lead continuous ECG is used, and leads II and V_5 are monitored to assess heart rhythm, rate, and ST trending. This choice of leads has been shown to detect 80% of ischemic changes. Lead II monitors the heart in the distribution of the right ventricle and the inferior wall of the left ventricle, which is perfused by the right coronary artery (RCA). Lead V_5 represents the lateral wall

of the left ventricle, which is perfused by the left circumflex artery (Lcx).

CONDUCTION SYSTEM OF THE HEART

OVERVIEW

The human body is composed of approximately 37 trillion cells. Cellular arrangement into organ systems allows the cells to perform unique functions supporting the life and health of the body. The heart and its associated vasculature form a complex and dynamic organ system. The heart's pumping function is accomplished by the coordinated contraction of 2 to 3 billion cardiac muscle cells (myocytes) within the heart. Stimulation of the myocytes comes from electrical signals generated in specialized tracts of cardiac tissue called the myocardial conduction system. The conduction system includes the sinoatrial (SA) node, atrioventricular (AV) node, bundle of His, right and left interventricular bundles, and Purkinje fibers (Fig. 8.1). Cells of the conduction system communicate with the myocytes by various specialized ion channels such as gap junctions, sodium potassium pumps, and calcium channels.

At rest, myocytes are polarized with a resting membrane potential of −80 to −90 mV. This means that the intracellular charge is more negative in comparison to the extracellular charge. The polarized state is maintained by a specific membrane-bound sodium-potassium adenosine triphosphatase (Na^+-K^+ ATPase) that concentrates potassium intracellularly and extrudes sodium into the extracellular milieu.

Ion fluctuations in neighboring cells cause the sodium and calcium channels to open temporarily to allow positive ion entry. This alters the charge on the membrane of the myocyte from negative to positive. If the intracellular charge reaches −20 mV, an action potential (or depolarization) occurs. When an action potential occurs, the myocyte shortens (contracts). In summary, electrical stimulation from conduction system tissue causes the cell membranes of the myocytes to go from a resting (negative) polarized state to a contracted (positive) depolarized state.

A properly functioning conduction system produces a wave of depolarization resulting in perfectly coordinated contraction of the atria and ventricles (Fig. 8.2). After depolarization, myocytes are refractory to immediate electrical stimulation that might result in additional action potentials. The myocardial action potential can be broken down into five phases: phase 0, rapid depolarization by sodium influx; phase 1, rapid repolarization by potassium efflux out of the cell; phase 2, plateau from calcium (positive ions) influx starting to balance the potassium (positive ion) efflux; phase 3, continued repolarization by potassium concentration within the cell; and phase 4, the resting polarized state of the relaxed myocardial cell.

Myocyte contraction stimulated by an action potential involves thick and thin contractile myofilaments that slide past each other by forming repetitive cross bridges. The interaction of the conduction system and the contractile apparatus is termed *excitation-contraction (E-C) coupling*. The contractile process is highly calcium dependent. Calcium sources for this process come from intracellular (sarcoplasmic reticulum) and extracellular (sodium-calcium pump) sources. The E-C coupling provides a critical balance of inotropy (speed and strength of cardiac muscle contraction), a function critical to systole, and lusitropy (ability to relax and allow ventricular chamber filling), a function critical to diastole. Stroke volume is dependent on inotropy and lusitropy. A person may be affected with systolic, diastolic, or both systolic and diastolic dysfunction. Loss of inotropy leads to systolic heart failure, also termed *heart failure with reduced ejection fraction*, while loss of lusitropy

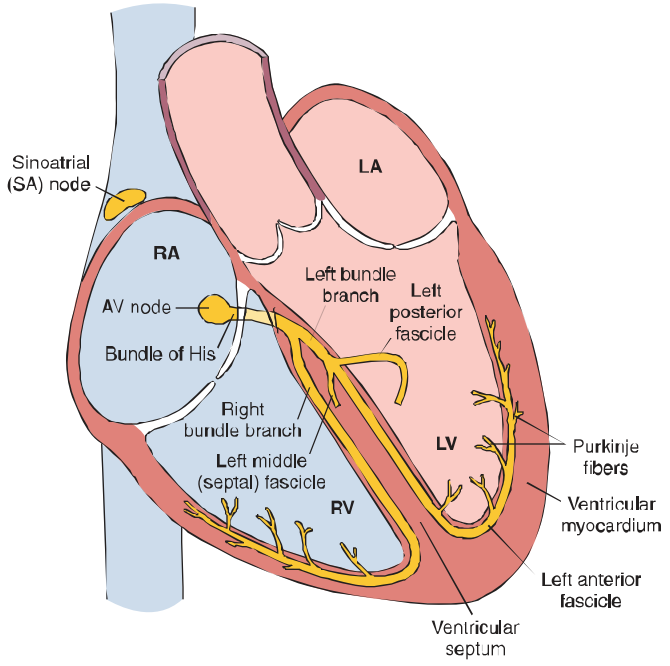

Fig 8.1 Normal conduction system.

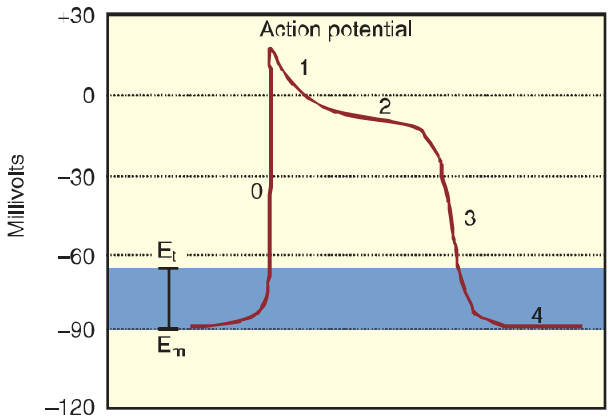

Fig. 8.2 Anatomy of the conduction system for transmission of cardiac electrical impulses. Representation of a ventricular action potential. There are five phases of the action potential beginning with phase 0, rapid depolarization by sodium influx. Phase 1 is a rapid repolarization via potassium efflux followed by phase 2 or the plateau phase. The plateau phase results from entry of calcium into the cell and potassium efflux. Phase 3 repolarization is dominated by potassium currents, which polarize the cell, and the potassium inward rectifier maintains the resting potential or phase 4.

leads to diastolic heart failure or heart failure with preserved ejection fraction.

A wide variety of physiologic states (acquired, inherited, iatrogenic) can affect E-C coupling. Certain drugs the patient may be using or abusing, medically directed or illegally, can precipitate systolic and diastolic dysfunction or ischemia particularly when combined with anesthetic agents. Some examples are street drugs such as cocaine, fentanyl, heroin, and prescription narcotic analgesics. Many of the drugs used in anesthesia temporarily alter or influence cardiac contractility, and some of the commonly used drugs for cardiac rhythm and blood pressure regulation affect the E-C coupling system. This includes cardiac glycosides, phosphodiesterase inhibitors, and angiotensin-converting inhibitors.

Digitalis, a cardiac glycoside, is thought to increase the intracellular availability of calcium by inhibiting the Na/Ca exchanger pump, which decreases the amount of Ca extruded from the cell. Phosphodiesterase type 3 inhibitors, such as milrinone, are used as inotropes in clinical medicine. They inhibit the breakdown of cyclic adenosine monophosphate (cAMP). Increasing levels of available cAMP serve to increase intracellular calcium, which increases the force of myocardial contraction. Angiotensin II is a potent vasoconstrictor that acts on the myocardium through specific receptors that over time can cause left ventricular hypertrophy (LVH) in patients with hypertension. The angiotensin receptors are stimulated by a cAMP-mediated mechanism. Angiotensin-converting enzyme (ACE) inhibiting drugs such as lisinopril block this stimulation, lower blood pressure, and help prevent LVH by a vasodilatory action.

Normally, the SA node is the primary pacemaker of the heart. The SA node is a tract of cells located at the junction of the superior vena cava and the right atrium. The impulse generated by the SA node propagates across the right and left atria, causing them to contract. After passing through the atria, the electrical impulse travels to the AV node. The AV node is located in the right atrium above the insertion of the septal leaflet of the tricuspid valve and anterior to the coronary sinus. The AV node can function as a secondary pacemaker for the heart if the SA node fails. Both the SA and AV nodes are richly innervated by the sympathetic and parasympathetic nervous systems. As such, it is influenced by endogenous hormones such as epinephrine and exogenous substances such as Γ blockers and other therapeutic drugs.

When the electrical impulse reaches the AV node, it slows down due to the long refractory period characteristic of this tissue. This so-called AV delay serves to prevent overstimulation of the ventricles in the event of abnormally rapid atrial impulses. A good example of this protective effect is seen in atrial flutter, where the atrial rate can be greater than 200 beats per minute (bpm), but due to the AV delay the impulses are conducted through to the ventricle at a 3:1 or 4:1 ratio.

After exiting the AV node, the impulse passes between the fibrous AV rings of the tricuspid and mitral valves and continues down the proximal ventricular conduction system within the interventricular septum. This part of the conduction system, the bundle of His, splits into right and left portions called bundle branches. The right and left bundle branches terminate as an interlacing network of small fibers called the His-Purkinje system. As the impulse travels through the bundle branches, the first portion of the ventricles to depolarize is the septum. It is followed by depolarization of the apex and most of the ventricular free walls. The last area to be depolarized is the superior portion of the left ventricular free wall and the right ventricular outflow tract.

While the sinus node portion of the conduction system is responsible for being the dominant pacemaker of the heart, any myocyte can generate an action potential and become an ectopic pacemaker in certain circumstances. The location of the group of cells acting as the dominant pacemaker affects the resultant heart rate and waveform morphology. In general, the further away from the SA node the dominant pacemaker is, the slower the heart rate generated.

The average rate of impulse generation by the SA node is 60 to 100 bpm. If the AV node takes over as the dominant pacemaker due to SA node dysfunction, then the so-called nodal or junctional rhythm generates an average rate of 40 to 60 bpm. Impulses below the AV node such as ventricular cells generate an extremely slow heart rate in the range of 30 to 45 bpm in the absence of a faster sinus or AV node dominant rhythm.

Interruptions or abnormalities in the blood supply to the heart can significantly impair the conduction system. The RCA supplies the SA and AV nodes in 60% to 85% of people. The remaining population get blood supply to these major pacemakers from the left circumflex coronary. This explains why patients suffering from an inferior myocardial infarction (MI; occlusion of the RCA) often present with conduction disturbances such as bradyarrhythmia or heart block as slower ectopic foci take over rate dominance due to the ischemic insult and dysfunction of the SA and AV nodes. Prompt restoration of blood flow to the ischemic tissue can correct the bradyarrhythmia, but temporary transcutaneous or transvenous pacing may be necessary in the interim.

PHYSIOLOGIC ACTIONS REPRESENTED IN THE ECG

As clinicians we rely on measurable data from tests and personal observations to guide our therapeutics. The ECG is one of the most important diagnostic tests to corroborate and define clinical signs and symptoms of rhythm disturbances and ischemic heart disease. The ECG machine apparatus processes, filters, and translates weak electrical signals detected on the skin surface into a tracing. For clinical use, it can be a continuous active trace as used in intensive care units (ICUs) or the operating room, or a single snapshot of cardiac rate rhythm captured in a resting 12-lead ECG.

The ECG components that we examine, the PQRST complex, reflect physiologic actions within the heart (Fig. 8.3). The P wave coincides with spread of action potentials across the right and left atria, causing them to contract. The PR interval is normally 120 to 200 ms. Existence of a P wave on ECG indicates that the impulse was generated by the SA node. Electrical impulse movement through the bundle branches coincides with the isoelectric PR interval on the ECG tracing. After the electrical impulse exits the AV node and travels through the bundle

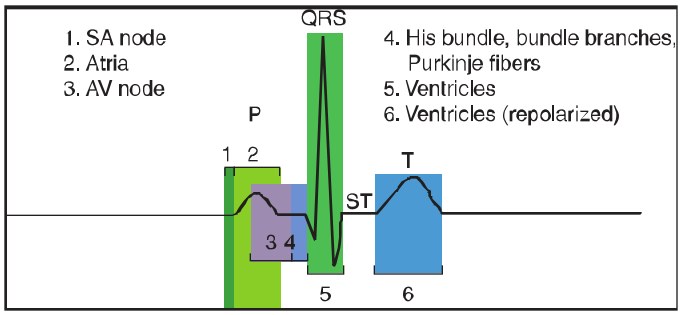

Fig. 8.3 Physiologic actions represented in the electrocardiogram (ECG). Relation between cardiac depolarization, ventricular repolarization, and appearance of the normal ECG, including P wave, QRS complex, ST segment, and T wave. The PR interval can be prolonged by disease from the atria to the Purkinje fibers (steps 2–4). The sinoatrial (SA) node is not seen on the surface ECG due to its small mass; its activity is inferred from the P wave, which reflects atrial activation. *AV*, Atrioventricular. (Data from Arnsdorf MA. Electrophysiology of the heart. *Electrocardiography II: Applied Theory, Part 1*. Bethesda, MD: American Physiological Society; 1978.)

branches, the first portion of the ventricles to depolarize is the septum. This causes a minor ECG deflection called the Q wave. It is followed by depolarization of the apex and the bulk of the ventricular free walls, as reflected in the R wave of the ECG. The last area to be depolarized is the superior portion of the left ventricular free wall and the right ventricular outflow tract. Depending on the bulk of the left ventricular free wall, this vector may show up as a negative deflection, the S wave. The interval from the Q wave through the R wave to the end of the S wave is called the QRS complex. Normal QRS duration varies depending on age and gender. Abnormal intraventricular conduction is suggested by a QRS complex that exceeds 110 ms in adults. The portion of the ECG between the S and T waves (ST segment) is normally isoelectric and represents the time between ventricular depolarization and the start of ventricular repolarization.

ST segments that are not isoelectric can indicate ischemia, electrolyte abnormalities, or other pathologic states. Acute ST segment changes trending down (ST depression) or up (ST elevation) should be considered myocardial ischemia until proven otherwise. The pattern of ECG leads reflecting the ST changes gives a clinical indication of which area of myocardium is ischemic or damaged. Inferior wall ischemia will show up in leads II, III, and aVF. Anterior ischemia is often seen in the precordial leads V_1 through V_6. Left ventricular septal ischemia is seen in V_1 to V_3 and lateral wall abnormalities in V_4 to V_6.

Other causes of ST-segment elevation considered in a differential of acute ST elevation include acute inflammatory states (myocarditis and pericarditis), hyperkalemia, acute myocarditis, nonischemic vasospasm, LVH, ventricular aneurysms, cardiac tumors, hypothermia (Osborne waves), and early repolarization (ER).

ER is a notching or slurring at the terminal part of the QRS complex giving the appearance of ST elevation. Most literature defines ER as being present on the ECG when there is J-point elevation of 0.1 mV or greater in two adjacent leads with either a slurred or notched morphology. Patients with early repolarization are more often young, athletic, with black ancestry, and male. Early repolarization on ECG has been thought to represent exercise-induced interventricular septal thickening although there are studies suggesting an increased risk of arrhythmia, particularly idiopathic ventricular fibrillation, in these patients.

Hyperkalemia may have peaked T waves, PR interval and QRS duration increases, atrial standstill, ST elevation in V_1 to V_2, or sine wave. Osborne waves are characteristically seen in hypothermia (typically body temperature < 34°C and appear as a J-point elevation in the precordial leads).

ST-segment depression is often seen in LVH (LV strain), with certain cardioactive drugs (digoxin), and hypokalemia. Digitalis toxicity may lead to both tachyarrhythmia and bradyarrhythmia. Hypokalemia may cause ST-segment depression, decrease in T-wave amplitude or T-wave inversion, increase in U-wave amplitude, merging of the T and U waves, increase in P-wave size and duration, PR interval prolongation, and widening of the QRS complex.

Ventricular repolarization is represented by the T wave. After the T wave there is another isoelectric period until the depolarization process begins again. The T-wave deflection should be in the same direction as the QRS complex and should not exceed 5 mm in amplitude in standard limb leads or 15 mm in precordial leads. T waves should be upright in all leads except aVR and V_1.

The QT interval is the time from the start of the Q wave to the end of the T wave. It represents the time taken for full ventricular depolarization and repolarization. The QT shortens at faster heart rates and lengthens at slower heart rates. Normal values for the QT interval should be corrected for the heart rate (QTc) because the QT interval varies inversely with heart rate. Typically, women have longer QT intervals than men do. This difference is more pronounced at slower heart rates.

The prolongation of repolarization in LQTS results in a dispersion of refractory periods throughout the myocardium. This abnormality in repolarization allows afterdepolarizations to trigger premature ventricular contractions (PVCs). These PVCs can degenerate into a form of pulseless ventricular tachycardia called torsades de pointes (TdP). TdP, also called polymorphic ventricular tachycardia, is a distinct form of reentrant ventricular tachycardia initiated by a PVC in the setting of abnormal ventricular repolarization (prolongation of the QT interval). TdP is a lethal arrhythmia characterized by a twisting of the peaks or rotation around the ECG baseline. In other words, there is a constantly changing cycle length, axis, and morphology of the QRS complexes around the isoelectric baseline during TdP (see Fig. 8.7, later). This dysrhythmia may be repetitive, episodic, or sustained and may degenerate into ventricular fibrillation.

Long QT syndrome can be congenital or acquired and predisposes the affected patient to TdP. The incidence of congenital and acquired prolonged QT syndromes is higher in women. The strongest predictor of the risk of syncope or sudden death

in patients with congenital prolonged QT syndrome is a QTc exceeding 500 ms. A preoperative ECG to rule out long QT syndrome (LQTS) is useful in a patient with a history of unexplained syncope, a family history of sudden death, and prior to initiating treatment with a drug that has potential to prolong the QT interval.

Common drugs that might be encountered in the perioperative period that are associated with QT prolongation include propofol; chloral hydrate; Γ_2 agonists (albuterol); methadone; antiarrhythmic drugs; antiemetics such as ondansetron and granisetron; many antipsychotics such as chlorpromazine, serotonin reuptake inhibitors, trazodone, fluroquinolone, and macrolide antibiotics; HIV antiretrovirals; cocaine; herbs such as licorice extract; and toxic exposure to organophosphate insecticides. Isoflurane and sevoflurane have both been shown to prolong the QTc in otherwise healthy children and adults. However, there is insufficient information to favor one volatile anesthetic over another.

Preoperative treatment of LQTS includes correction of electrolyte abnormalities, particularly magnesium or potassium, and discontinuation of drugs associated with QT prolongation if possible. These patients are often on $\Box$ blockers for PVC suppression. Cardiac pacing is also a treatment option in LQTS because TdP is often preceded by bradycardia. Pacing is usually employed in combination with $\bar{}$-blocker therapy. Implantable cardioverter-defibrillators (ICDs) with pacing capability have emerged as lifesaving therapy for patients with recurrent symptoms and recalcitrant TdP despite PVC suppression therapy with _ blockers. Temporary or permanent pacing at a higher backup rate than usual can prevent the bradycardia that precedes TdP and abort the arrhythmia. In addition, left cervicothoracic sympathetic ganglionectomy may reduce dysrhythmogenic syncope in patients with congenital LQTS who cannot take L blockers or have recurrent syncope despite ICD and $\exists$-blocker therapy.

Short QT syndrome (SQTS) is an inherited electrical disease of the heart associated with paroxysmal atrial fibrillation, ventricular tachycardia, ventricular fibrillation, syncope, and sudden cardiac death (SCD). In contrast to long QT syndrome, ion channel defects associated with SQTS lead to abnormal shortening of repolarization, predisposing affected individuals to a risk of atrial and ventricular arrhythmias. The corrected QT interval (QTc) in this syndrome is 0.30 seconds or less. SQTS, first reported in 2000, is a rare inherited disorder that affects the movement of ions through channels within the cell membrane associated with marked shortened QT intervals and an increased risk of SCD in individuals with a structurally normal heart.

CARDIAC CONDUCTION DISTURBANCES

An intact cardiac conduction system normally ensures conduction of each sinus node impulse from the atria to the ventricles. Inherited abnormalities of the conduction system, certain drugs, iatrogenic trauma, and disease processes can disrupt normal conduction and result in heart block. The classification of conduction block is by the site of disruption and the degree of blockade.

Acute and chronic ischemia account for about 40% of cases of AV block. New heart block in the setting of acute MI occurs on the order of 10% to 20%. The most common conduction disturbances associated with ischemia and acute MI are left bundle branch block (LBBB) and right bundle branch block (RBBB) with left anterior fascicular block (LAFB). In this situation, restoration of blood flow can improve or correct the conduction block. Chronic AV blockade present prior to an ischemic episode is not usually reversible with reperfusion.

Cardiomyopathies, including hypertrophic obstructive cardiomyopathy and infiltrative processes such as amyloidosis, sarcoidosis, and cardiac tumors, can contribute to the development of heart block. Inflammation of the heart tissue from infections or autoimmune diseases, such as rheumatic fever, Lyme disease, thyroid disorders, neuromuscular degenerative diseases, diphtheria, viruses, systemic lupus erythematosus, dermatomyositis toxoplasmosis, bacterial endocarditis, and syphilis can contribute to myocarditis associated with heart block. Congenital heart defects with associated structural abnormalities such as atrial septal defect (ASD) and ventricular septal defect (VSD) can also cause heart block. Physiologic states associated with hyperkalemia such as end-stage renal disease with potassium greater than 6.0 mEq/L can also precipitate AV block.

Any procedure with the potential to cause edema, impingement, or interruption of the tissues that surround the conduction system can precipitate periprocedural episodes of AV block. Surgeries such as aortic or mitral valve replacement, transcatheter procedures, and catheter ablations have AV block as a known risk. Transcatheter aortic valve implantation (TAVI) risk of AV block is 2% to 8%; transcatheter closure of patent foramen ovale (PFO), ASD and VSD, and catheter ablations for arrhythmia (supraventricular tachycardia, atrial fibrillation, or aberrant pathways as with Wolff-Parkinson-White syndrome) AV block risk is approximately 1%. Septal ablation for hypertrophic obstructive cardiomyopathy (HOCM), a procedure where alcohol is injected into the septal branch of the left anterior descending artery to cause septal shrinkage and relief of left ventricular outflow obstruction, has a high incidence of AV block at 8% to 10%. In all these situations, the block may be a transient or permanent conduction abnormality requiring temporary pacemaker support or a permanent pacemaker implantation.

Quite a few medications can cause AV block particularly in patients with underlying conduction system disease. The list of drugs includes _ blockers, calcium channel blockers (especially verapamil and diltiazem), digoxin, amiodarone, procainamide, and quinidine, to name a few. In most cases, the resulting AV block is at least partially reversible following withdrawal of the offending medication(s).

First-Degree Atrioventricular Heart Block

A delay in passage of the cardiac impulse through the AV node resulting in a PR interval of greater than 200 ms is called first-degree AV block. A normal PR interval is 120 to 200 ms. Higher

heart rates tend to slightly shorten the PR interval. This condition only impacts the PR interval, so the corresponding QRS complex is of normal duration.

The PR interval measures the speed of conduction between the atria and the ventricles. It is the time it takes for atrial depolarization, conduction through the AV node, His bundle, bundle branches, and terminal Purkinje fibers. The conduction delay resulting in a first-degree heart block is most frequently in the AV node but may also be in the His-Purkinje system. In first-degree heart block, every P wave has a corresponding QRS; all other types of heart block present with some dyssynchrony or absence of QRS following a P wave.

Patients with first-degree heart block are usually asymptomatic and seldom need treatment for this condition. First-degree AV block can be found in patients with and without structural heart disease. This type of conduction disturbance occurs in males twice as often as in females. Most commonly it is seen in highly conditioned athletes or in patients taking medications that slow conduction through the AV node such as digoxin, □ blockers, and calcium channel blockers. It can be associated with pathologic states such as ischemia, infiltrative diseases, muscular dystrophies, myocarditis, Lev disease, and Lenègre disease. Lev disease is a calcification of the aortic and mitral rings adjacent to the conduction system in patients over 70 years of age. Lenègre disease a progressive, fibrosis/sclerosis of the conduction system in younger (age ⌜ 60 years) individuals.

Should first-degree heart block develop during clinical care, identification of drugs or situations that increase vagal tone or decrease AV conduction should be sought. The clinical evaluation for any heart block that develops during an anesthetic should include evaluation and treatment of ischemia and electrolyte abnormalities and ensuring adequate oxygenation and blood pressure. Digoxin levels should be checked before surgery, and serum potassium should be maintained at normal levels. Usually removing the offending vagal stimulation or drug is all that is needed to restore normal conduction in these patients. Atropine, a centrally acting vagolytic medication, can be employed to increase heart rate and speed conduction of cardiac impulses through the AV node if necessary.

Second-Degree Atrioventricular Heart Block

Second-degree AV block can be suspected when a P wave is present without a corresponding QRS complex. There are two types of second-degree heart block: Mobitz type I (Wenckebach) and Mobitz type II. Mobitz type I is characterized by a sequence of progressive prolongation of the PR interval until a QRS is dropped. It is thought to occur because each successive depolarization produces a prolongation of the refractory period of the AV node. This process continues until an atrial impulse reaches the AV node during its absolute refractory period and conduction of that impulse is blocked completely. A pause allows the AV node to recover, and then the process resumes. This type of block is often transient, asymptomatic, and rarely progresses to third-degree heart block since secondary pacemakers in the AV node usually take over pacing duties and maintain adequate cardiac output.

Mobitz type I block can be the result of myocardial ischemia or infarction, myocardial fibrosis or calcification, or infiltrative or inflammatory diseases of the myocardium, or it can occur after cardiothoracic surgery. It can also be associated with the use of certain drugs such as calcium channel blockers, _ blockers, digoxin, and sympatholytic drugs. Mobitz type I block does not usually require treatment unless the decreased ventricular rate results in signs of hemodynamic compromise. Symptomatic patients may be treated with atropine as needed. If atropine is unsuccessful, pacing may be indicated.

Mobitz type II heart block is characterized by a sudden and complete interruption of conduction with loss of the QRS following the P wave. Patients are usually symptomatic, with palpitations and near-syncope being common complaints. Mobitz type II block is considered more serious and the conduction interruption is usually at a point below the AV node in the bundle of His or in a bundle branch. This type of second-degree heart block is much more likely to be associated with permanent damage to the conduction system and is more likely to progress to third-degree heart block.

Treatment of a Mobitz type I or II second-degree heart block that develops during an anesthetic depends on the ventricular response and the patient's symptoms. In the presence of an acceptable ventricular rate and an adequate cardiac output, no acute treatment is needed. All safety parameters should be checked and maximized ensuring adequate oxygenation, hemodynamic parameters, and blood chemistries. Plans should be for pacemaker support if the block should progress or the patient becomes unstable. Temporizing treatment for Mobitz type II block includes transcutaneous or transvenous cardiac pacing until a permanent pacemaker is in place. Atropine is unlikely to improve bradycardia in this situation, but an isoproterenol infusion acting as a so-called chemical pacemaker may be helpful as a temporizing measure prior to pacemaker placement.

Third-Degree Atrioventricular Heart Block

Third-degree AV heart block, also known as complete heart block, is complete interruption of AV conduction and is characterized by AV dissociation. There is no conduction of cardiac impulses from the atria to the ventricles. Third-degree heart block can manifest as a slow escape rhythm insufficient to sustain an acceptable cardiac output. Continued activity of the ventricles is due to impulses from an ectopic pacemaker distal to the site of the conduction block. If the conduction block is near the AV node, the heart rate is usually 45 to 55 bpm and the QRS complex is narrow. When the conduction block is below the AV node (infranodal), the heart rate is usually 30 to 40 bpm and the QRS complex is wide.

Third-degree heart block is usually symptomatic with the bradycardia induced reduction in cardiac output contributing to congestive heart failure (CHF) with symptoms such as weakness and dyspnea. Onset of third-degree AV block in an awake patient may be signaled by near syncope or syncope. Syncope attributed to third-degree heart block is called an Adams-Stokes attack. The most common cause of third-degree AV block in adults is fibrotic degeneration of the distal conduction system associated with aging (Lenègre disease).

In anesthetized patients, third-degree heart block can be due to cardiac ischemia, metabolic or electrolyte abnormalities,

infection or inflammation near the conduction system, reperfusion injury, or stunned myocardium after cardiac surgery. Treatment of third-degree AV block occurring during anesthesia consists of transcutaneous or transvenous cardiac pacing. An intravenous (IV) isoproterenol infusion may also be helpful in maintaining an acceptable heart rate by acting as a chemical pacemaker. Caution must be exercised when administering antidysrhythmic drugs to patients with third-degree AV block before permanent pacemaker placement. Such drugs may suppress the only remaining functioning ectopic pacemaker responsible for maintaining the heart rate. Preoperative placement of a transvenous pacemaker or the availability of transcutaneous cardiac pacing is necessary before an anesthetic is administered for insertion of a permanent cardiac pacemaker.

In patients with isolated chronic RBBB, the progression to complete AV block is rare. Patients with bifascicular block (RBBB and left anterior or posterior fascicular block) or complete LBBB have a 6% incidence of progression to complete heart block. Approximately 8% of patients with acute inferior wall MI develop complete heart block. It is usually transient, although it may last for several days. Development of new bifascicular block plus first-degree AV block is associated with a very high risk (40%) of progression to complete heart block. ECG evidence of alternating bundle branch blocks, even if asymptomatic, is a sign of advanced conduction system disease and is an indication for permanent pacing.

INTRAVENTRICULAR CONDUCTION DISTURBANCES

Intraventricular conduction disturbances are abnormalities in conduction occurring past the AV node involving the His-Purkinje system of the myocardium. Two major branches emerge from the singular bundle of His, the left and the right bundle branches. The LBB divides into two fascicles: the left anterior superior fascicle and the left posterior inferior fascicle. The RBB is a relatively thin bundle of fibers that courses down the right ventricle and then branches late in its course near the right ventricular apex. The right and left bundle branches terminate in an interlacing network of small fibers (i.e., His-Purkinje system).

Normal, rapid conduction of the depolarization signal results in near simultaneous contraction of the left and right ventricles, which optimizes the myocardial pump function. Intraventricular conduction disturbances can be due to structural changes or disease processes, acquired or inherited, affecting the ventricular myocardium. The wide range of causes includes necrosis, fibrosis, calcification, infiltrative lesions, or impaired vascular supply. This subset of disorders includes incomplete and complete RBBB, LAFB, left posterior fascicular block (LPFB), and complete LBBB. These abnormalities change the shape and/or duration of the QRS complex. They may be fixed and present at all heart rates, or they may be intermittent and occur only with tachycardia or bradycardia.

Right Bundle Branch Block

The left and right ventricles should depolarize virtually simultaneously. When the RBB is interrupted (complete RBBB), electrical stimuli from the AV node conducts to the bundle of His and down the LBB. In the absence of conduction down the right bundle, the left ventricle depolarizes first while the right ventricle polarized later, causing the characteristic ECG findings. RBBB is recognized by a widened QRS complex ($\geq$ 120 ms in adults) and a rSR′ configuration in leads V_1 and V_2. There is also a deep S wave ($\geq$40 ms) in leads I and V_6. Some patients exhibit an incomplete RBBB where the QRS is prolonged between 110 and 120 ms, and the other criteria for RBBB is fulfilled. Interpretation of ST segments for diagnosis of ischemia and MI in the presence of RBBB is not altered. By contrast, the presence of a LBBB renders the ST segments of the ECG difficult to interpret and unreliable for diagnosis of ischemia and MI.

The RBB receives most of its blood supply from septal branches of the left anterior descending coronary artery. In most patients, it also receives some collateral supply from either the right or circumflex coronary systems depending on the dominance of the coronary system. Most of the population has a right dominant (coronary) system. Because of its superficial position as it courses down the interventricular septum and its less robust size, the right bundle is vulnerable to stretch as might occur with increased right heart pressures seen in acute situations such as pulmonary embolism, pulmonary edema, and chronic conditions such as pulmonary hypertension, chronic obstructive pulmonary disease (COPD)/emphysema/pulmonary fibrosis, and left-sided conditions transmitting pressure back to the right side such as mitral insufficiency and diastolic or systolic heart failure.

The incidence of RBBB typically increases with age, with up to 11.3% of people by age 80. It has an occurrence of between 1% and 2% in patients with no known structural or ischemic heart disease. In the absence of structural or functional heart disease, it is of no clinical significance in the perioperative period. With aging, the occurrence of RBBB is a representation of an idiopathic slowly progressive degenerative disease of the conduction system (Lev or Lenègre disease) in the absence of other causative factors. Isolated RBBB has no significant association with cardiac disease, ischemic heart disease, or cardiac risk factors.

A patient with RBBB is usually asymptomatic, and it is frequently discovered incidentally on ECG. On cardiac auscultation, the patient may have a split-second heart sound. In terms of prognosis, the conduction delay from RBBB rarely progresses to advanced AV block. Generally, the isolated presence of a RBBB does not require further evaluation or treatment. In patients without significant heart disease, RBBB has no additional risk. In patients with cardiovascular disease, including ischemia, infarction, inflammation (myocarditis), cardiomyopathies, or congenital heart disease, RBBB is an independent risk factor for all-cause mortality. In the setting of heart failure with a low ventricular ejection fraction in combination with RBBB, cardiac resynchronization therapy (CRT) is indicated.

RBBB is more common than LBBB. RBBB can exist in combination with block of either fascicle of the left bundle. Block of one of the two fascicles of the left bundle is called hemiblock. Although hemiblock is a form of intraventricular heart block, the duration of the QRS complex is normal or only minimally

prolonged. RBBB in association with block of the left anterior fascicle, called left anterior hemiblock, is seen in 1% of all adults. RBBB with block of the left posterior fascicle, left posterior fascicular block, is called left posterior hemiblock and occurs much less frequently and is associated with a 1% to 2% risk of progression to third-degree heart block. The term *bifascicular block* is used when RBBB exists with either LAFB or LPFB.

Perioperative assessment and treatment of RBBB or RBBB with left anterior hemiblock consists of observation and awareness of drugs or clinical factors that may contribute to conduction disturbances. If contributing factors can safely be eliminated, this should be done. As with all anesthetics, maintenance of adequate blood pressure, arterial oxygenation, and normal serum electrolyte concentrations should be a priority to minimize potential compromise to the remaining fascicle due to ischemia, arrhythmia, or ventricular dysfunction. Regardless of the anesthetic technique chosen, there is no evidence to prefer one technique over the other if the abovementioned concerns are met. Surgery performed with either general or regional anesthesia does not predispose patients with preexisting bifascicular heart block to develop third-degree heart block. Preparation for care of patients with bifascicular block should include availability of pacing capability with staff trained in this technique if possible. Pacing in this situation can be instituted by transcutaneous or transvenous pacing should it be needed. Prophylactic placement of a temporary or permanent cardiac pacemaker is not necessary.

Brugada syndrome, an autosomal dominant genetic disorder with variable expression, has an ECG resembling RBBB. The majority of affected individuals are middle-aged males of Asian descent, with the highest prevalence in Southeast Asia. There is also increased incidence of Brugada syndrome in patients with schizophrenia. The ECG in these patients includes a pseudo-RBBB and persistent ST-segment elevation in leads V_1 to V_2. These patients have an increased risk of ventricular tachyarrhythmias and SCD.

Left Bundle Branch Block

The left bundle component of the bundle of His is composed of two components: the left anterior fascicle and the left posterior fascicle. A complete LBBB is recognized as a QRS complex of longer than 120 ms in duration in the absence of Q waves in leads I, V_5, and V_6, and a broad notched or slurred R wave in leads I, aVL, V_5, and V_6. The S and T waves are usually opposite in direction to the QRS. The appearance of LBBB on ECG is often an indication of serious heart disease (e.g., hypertension, coronary artery disease, aortic valve disease, cardiomyopathy). Isolated LBBB is often asymptomatic, and some patients do not exhibit LBBB until a critical heart rate is achieved.

The left and right bundles both receive blood supply from branches of the left anterior descending coronary artery (LAD). The LBB is more richly perfused than the RBB. Ischemia or infarction involving the LAD can affect the left or right bundle. The left posterior fascicle is usually spared because it receives additional blood supply from the posterior descending coronary artery, a branch of the right coronary artery. This is due to the redundant blood supply to the LBB and the fact that it branches early and widely into anterior and posterior fascicles during its course down the left ventricular septum.

This redundant blood supply to the LBB explains why complete disruption of the LBB, as indicated by LBBB on ECG, usually indicates more extensive cardiac disease or damage than RBBB.

As mentioned earlier, if one of the two fascicles of the LBB fails to conduct for whatever reason, this is called a hemiblock (HB). Block of the left anterior fascicle (LAHB) is the most common hemiblock. Left posterior hemiblock (LPHB) is uncommon because the posterior fascicle of the LBB is larger and better perfused than the anterior fascicle.

Development of LBBB during anesthesia should be taken seriously and may be a sign of myocardial ischemia. Taking care to treat hypertensive or tachycardic episodes, maximize oxygenation, and treat electrolyte abnormalities should be instituted immediately. ST-segment and T-wave changes (repolarization abnormalities) in the presence of LBBB cannot be relied on to diagnose ischemia as they are already abnormal due to the bundle branch block pattern. Additionally, a narrow complex tachycardia such as SVT may look like ventricular tachycardia (wide complex tachycardia) in a patient with LBBB because the QRS is widened from the LBBB. Another common perioperative scenario that can be mistaken for LBBB is ventricular pacing and biventricular pacing. Ventricular pacing electrodes pace from the right ventricle and result in a QRS that is typically widened. The presence of pacing spikes on ECG can help differentiate a V-paced patient from an ECG widened due to LBBB.

If a patient has a complete LBBB, special care needs to be taken when undergoing a right heart catheterization or other procedures that introduce a wire or catheter into the right ventricle such as placement of a pulmonary artery catheter or even a central line where the guidewire may pass into the right ventricle. The superficial course of the right bundle makes it vulnerable to disruption by trauma or inflammation. In these situations there is an increased risk of complete (third-degree) heart block due to the increased risk of catheter-induced RBBB in the setting of complete LBBB. RBBB (usually transient) occurs in approximately 2% to 5% of patients undergoing insertion of a pulmonary artery catheter.

CARDIAC RESYNCHRONIZATION THERAPY

Any delays in conduction, particularly of the lateral wall of the left ventricle (as in LBBB), cause dyssynchrony between the ventricles and impaired efficiency. This can lead to heart failure secondary to decreased left ventricular function and elevated left heart pressures. CRT with biventricular pacing has been used in patients with chronic heart failure with reduced ejection fraction and bundle branch block to improve ventricular function, symptoms, and survival. CRT is now a mainstay of treatment in patients who have left ventricular dysfunction (ejection fraction $\bar{}$35%), QRS prolongation ($\bar{}$120 ms), and moderate to severe heart failure symptoms (New York Heart Association [NYHA] functional class III or IV) while receiving optimal medical therapy. CRT with or without a defibrillator component has been shown to reduce hospitalizations and all-cause mortality in these patients. Since being approved by the

US Food and Drug Administration (FDA) in 1985, there are more than 3 million Americans living with a pacemaker and over 300,000 living with an ICD with pacing capacity. There is continual work to improve cardiac implantable electronic device (CIED) technology with the most current developments in leadless pacemakers and subcutaneous ICDs.

Some CIEDs are only pacers and others pace and defibrillate. The three standard components of a CRT pacer/defibrillator are a right atrial lead and right and left ventricular leads. Pacing of the left ventricle is most frequently achieved by transvenous placement of an electrode into the coronary sinus. CRT is usually an adjunct to medical optimization. The evidence of benefit is greatest in patients with LBBB and a QRS duration greater than 150 ms. The three leads are tuned to simulate a normal functioning His-Purkinje complex. By adjusting the timing of each lead, AV synchrony is optimized. The goal is to restore normal coordination of contraction of the right and left sides of the heart. For defibrillation capability, a specialized right ventricular lead with a built-in shocking coil is implanted with a larger pulse generator to power this functionality. In addition to internal defibrillation, an ICD can deliver antitachycardia or antibradycardia pacing and synchronized cardioversion. Detailed diagnostic data concerning intracardiac electrograms and dysrhythmia event markers are stored in the memory of the device and are downloaded for analysis during device checks.

There is a standard defibrillator coding system to delineate its functionality. The first letter is the chamber shocked (*O,* none; *A,* atrium; *V,* ventricle; *D,* dual). The second letter indicates the antitachycardia pacing chamber (*O,* none; *A,* atrium; *V,* ventricle; *D,* dual). The third position indicates the tachycardia detection mechanism (*E,* electrogram; *H,* hemodynamic). The fourth position denotes the antibradycardia pacing chamber (*O,* none; *A,* atrium; *V,* ventricle; *D,* dual).

The pulse generator is usually implanted in the left pectoral region to maximize the defibrillation vector. Right-sided implantation is avoided if possible because it significantly increases the defibrillation threshold, which can result in premature battery depletion. If the device detects ventricular fibrillation, the capacitor charges, then a secondary algorithm confirms the rhythm prior to shock delivery. During the confirmatory process, which lasts approximately 10 to 15 seconds, the patient may experience presyncope or syncope prior to defibrillation. This process prevents inappropriate shocks in response to self-terminating events or spurious signals. There are also diagnostic recording devices called loop recorders or insertable cardiac monitors that monitor and record rhythm but deliver no therapy. They function as a leadless Holter monitor to record rhythm data to aid in evaluation of patients suspected to have conduction system disease or paroxysmal arrythmia.

Anesthesia for Insertion of ICDs

Preparation of a patient for ICD placement is the same as that for pacemaker insertion. Some of these procedures are done under general anesthesia because of the increased risks associated with repeated defibrillation during threshold testing. The nature and severity of the patient's coexisting medical conditions dictate the extent of monitoring and the necessary clinical preparations.

SURGERY IN PATIENTS WITH CARDIAC IMPLANTABLE ELECTRONIC DEVICES

The presence of any type of CIED—whether an artificial cardiac pacemaker or ICD for any indication; whether pacing, cardioversion, defibrillation, or resynchronization—in a patient scheduled for surgery unrelated to the device introduces special considerations for preoperative evaluation and subsequent management of anesthesia to ensure patient safety and preservation of proper device function. These CIED recommendations apply to all forms of anesthetic care, from conscious sedation and monitored anesthesia care to regional and general anesthesia; there are no clear data regarding the effect of anesthetic technique on CIED function.

Preoperative Evaluation

A patient with a preexisting CIED coming for surgery has at least one of three underlying cardiac problems: sustained or intermittent bradydysrhythmia, tachydysrhythmia, and/or heart failure. Bradydysrhythmias require pacing and may involve a single or dual lead depending on the function of the AV node. Tachydysrhythmias and heart failure usually require pacing and cardioversion/defibrillation capability using a pacemaker/defibrillator. Pacing the ventricle at a rate slightly faster than the tachycardia or overdrive pacing (short bursts of rapid pacing) can terminate ventricular tachycardia. Regardless of the indication for the device, any patient with a CIED requiring anesthetic care must undergo a detailed systematic preoperative evaluation. This preoperative evaluation should include identification of the brand and type of device, the clinical indication for the device, degree of dependence on the device, and assessment of device function. A patient who is compliant with regular device follow-up will have these parameters followed regularly as part of routine device checks that are performed at least once a year. In the absence of this documentation, clinical signs indicating that a patient is CIED dependent include a history of bradycardia symptoms, a history of AV node ablation, and an ECG showing a majority of paced beats.

All implanted cardiac devices are designed to detect and respond to low-amplitude electrical signals. Extraneous signals produced by external electric or magnetic fields can influence the function of CIEDs. These signals are known as electromagnetic interference (EMI). EMI can be any strong external electrical or magnetic force in close proximity to a CIED. EMI signals enter device circuits primarily through the leads. Other factors influencing the susceptibility of a device to EMI include field strength, patient body mass, and the proximity and orientation of the implanted electronic device to the EMI field. Perioperative EMI may cause damage to the pulse generator or leads (circuitry), damage to the tissue around the device (burns, thermal changes affecting impedance), failure of the device to pace or defibrillate, and inappropriate pacing or defibrillation. The current return pad (grounding pad) of the electrocautery system should be placed so that the current path does not cross the chest or CIED system.

The grounding electrode should be as far as possible from the pulse generator to minimize detection of the cautery current by the pulse generator.

The most common CIED-related problem encountered in the perioperative period is interference with device function resulting from EMI. Use of monopolar electrocautery and the EMI it generates remains the principal intraoperative concern in patients with CIEDs. The cautery device generating the EMI field need not actually touch the patient to adversely affect the CIED. Use of coagulation settings in monopolar electrocautery uses a higher voltage and causes more EMI problems than use of nonblended cutting settings. The cautery tool and return pad should be positioned so the current pathway does not pass near the CIED pulse generator or leads. It is recommended to avoid cautery of tissue near the pulse generator and leads if possible. It is beneficial to keep the electrocautery current as low as possible and to apply electrocautery in short bursts, especially if current is being applied close to the pulse generator. Use of bipolar electrocautery or the ultrasonic harmonic scalpel is associated with lower rates of EMI on the pulse generator and leads. Even with the utmost caution, problems can arise.

Monitoring of the patient with a CIED should always follow the American Society of Anesthesiologists (ASA) standards and should include continuous ECG monitoring and continuous monitoring of a peripheral pulse. This can be done with a pulse oximeter, manual palpation of a pulse, auscultation of heart sounds, or intraarterial catheterization. Verification of the presence of a pulse is necessary to confirm continued cardiac activity in the event of disruption of the ECG signal by EMI. Skeletal muscle contractions and fasciculation from succinylcholine could inhibit a normally functioning cardiac pacemaker by misinterpretation of the myopotentials for intrinsic R waves. Clinical experience suggests that succinylcholine is usually a safe drug for use in patients with cardiac pacemakers and that if myopotential inhibition does occur, it is generally transient.

Preoperative interrogation of loop recorder devices should be done as long as it does not delay urgent or emergent care. The presence of the loop recorder poses no threat to the patient as it does not deliver any therapy to the heart, but all data may be lost if it is exposed to EMI.

No special laboratory testing or radiographs are needed for CIED patients undergoing surgery unless otherwise clinically indicated. At times, a chest radiograph can be useful to evaluate the location and external condition of pacemaker electrodes. Most current CIEDs have an x-ray code that can be used to identify the manufacturer of the device. If the patient is known to have a biventricular pacemaker, a chest radiograph to confirm the position of the coronary sinus lead is helpful when insertion of a central line or pulmonary artery catheter is planned. There have been reports of coronary sinus and endocardial lead dislodgement in association with central venous catheterization; however, the danger of dislodgement is minimal after the first month postinsertion.

There are no known CIED concerns involving exposure to plain x-rays, ultrasonography, fluoroscopy, mammography, or electroconvulsive therapy (ECT). However, there are reports of EMI associated with electrocautery, radiofrequency ablation, magnetic resonance imaging (MRI), radiation therapy, and lithotripsy. MRI scanning of patients with CIEDs is controversial and is generally regarded as contraindicated. However, 50% to 75% of patients with cardiac devices will likely need to undergo MRI at some point in their lifetime, so this is becoming an important concern. There is insufficient evidence at present to standardize management of the patient with a CIED needing MRI scanning. If MRI must be performed, care should be coordinated among the ordering physician, radiologist, and pacemaker specialist or cardiologist.

Management of EMI associated with radiofrequency ablation includes keeping the radiofrequency current path, which runs from the electrode tip to the current return pad, as far away from the pulse generator as possible. Some suggest keeping the ablation electrode at least 5 cm away from the pacer leads. Recommendations for patients undergoing lithotripsy include keeping the focus of the lithotripsy beam away from the pulse generator. If the lithotripsy triggers on the R wave, it may be necessary to disable atrial pacing before the procedure. There is insufficient evidence to standardize care for CIED patients needing radiation therapy. It is preferable to keep the device out of the radiation field. Most manufacturers recommend verification of appropriate pulse generator function at the completion of radiation therapy. No clinical studies have reported EMI or permanent CIED malfunction in association with electroconvulsive therapy, but care should be coordinated with a cardiologist. The device should be interrogated and the antitachycardia functions suspended. ECT can be associated with considerable swings in blood pressure, heart rate, and vigorous skeletal muscle contraction from the seizure activity, so backup external defibrillator and temporary pacing capability is recommended. In pacemaker-dependent patients, programming to asynchronous mode is recommended, so there is no pacing inhibition due to the myopotentials produced by the seizure.

Temporary pacing and defibrillation equipment should be immediately available before, during, and after procedures in CIED patients. It has been suggested that before performing defibrillation or cardioversion in a patient with an ICD in a magnet-disabled treatment mode, all sources of EMI be eliminated and the magnet be removed to reactivate the antitachycardia capabilities of the device. The patient can then be observed for appropriate CIED function. If emergency defibrillation is necessary in a patient with a CIED (permanent cardiac pacemaker or ICD that is turned off), an effort should be made to keep the defibrillation current away from the pulse generator and lead system. The recommended position of the electrode pads is the anterior-posterior position. An acute increase in pacing threshold and loss of capture by the CIED may follow external defibrillation. If this occurs, transcutaneous cardiac pacing or temporary transvenous pacing may be required.

Cardiac rate and rhythm should be monitored throughout the immediate postoperative period, including during transport from the anesthetizing location to the recovery area. Backup cardioversion-defibrillation and pacing equipment should be immediately available. Postoperative management of the patient with a CIED consists of interrogating the device and restoring appropriate baseline settings, including antitachycardia therapy

in patients with defibrillators. This should be done as soon as possible after the procedure, either in the postanesthesia care unit or ICU.

Postoperative CIED checks may not be needed if surgery did not include use of EMI-generating devices, no electronic preoperative device reprogramming was done, no blood transfusions were administered, and no intraoperative problems were identified that related to CIED function. Remote device checks have facilitated preprocedural and postprocedural interrogation of CIEDs, particularly in clinical situations where there is no immediate availability of a qualified device interrogator.

CARDIAC DYSRHYTHMIA OVERVIEW

Cardiac rhythms that have abnormalities in rate, interval length, or conduction path are referred to as dysrhythmias. Intraoperative arrythmias occur in approximately 11% of general anesthetics. Patients with cardiac disease are more likely to have serious dysrhythmias. The most common intraoperative arrhythmias are sinus tachycardia and sinus bradycardia. There are three basic causes of dysrhythmia in the anesthetized patient: patient physiology and existing abnormalities, stimulation or iatrogenic factors from the procedure, and effects of the anesthetic itself. Most of these arrythmias are insignificant and transient. Some arrhythmias may only require observation and others immediate intervention. During a surgical procedure, it is the anesthesiologist's responsibility to make our surgical colleagues aware of the untoward effects their action may be having on the anesthetized patient, such as vagal stimulation causing bradycardia and hypotension during intraperitoneal insufflation or gut traction. Expert knowledge of the interaction of patient physiologic states, drug therapy, and the effect of surgical procedures is why anesthesiologists are known as patient safety advocates.

Sinus dysrhythmia is a normal variant encountered in patients who exhibit normal sinus rhythm with a normal sinus rate ($\sqsubset$ 60 bpm and $\sqsupset$ 100 bpm), normal PR interval, normal QRS length, and normal ST intervals but an irregular RR interval length. This variation in the RR interval is usually due to a physiologic phenomenon known as the Bainbridge reflex, which accelerates the heart rate when intrathoracic pressure is increased during inspiration and slows the heart rate when the intrathoracic pressure decreases during expiration. Sinus dysrhythmia carries no increased risk of deterioration into a dangerous rhythm. It is seen frequently in children and young people and tends to decrease with age.

MECHANISMS OF TACHYDYSRHYTHMIAS

A cardiac rhythm greater than 100 bpm is considered a tachydysrhythmia. A tachydysrhythmia can be initiated from a pacemaker source above or below the bundle of His. Tachydysrhythmias originating in tissue above the bundle of His are SVTs, which usually have a narrow QRS complex. Narrow complex tachycardias include sinus tachycardia, atrial flutter, atrial fibrillation, junctional tachycardia, paroxysmal atrial tachycardia, and accessory pathway–mediated reentrant tachycardias.

Tachydysrhythmias generated from below the AV node have a wide QRS complex. Wide complex tachycardias include ventricular tachycardia, SVT with an intraventricular conduction defect or bundle branch block, SVT with aberrant conduction, SVT with wide QRS due to a metabolic or electrolyte disorder, and SVT with conduction over a preexcitation (accessory) pathway.

In addition to the location of origin of the arrhythmia, we must consider the mechanism by which the impulse is accelerated beyond the usual pacemaker control of the sinus node. Tachydysrhythmias can result from three mechanisms: (1) increased automaticity in normal conduction tissue or in an ectopic focus, (2) reentry of electrical potentials through abnormal pathways, and (3) triggering of abnormal cardiac potentials due to afterdepolarizations.

Increased Automaticity

A sustained rhythm resulting from accelerated firing of a pacemaker other than the SA node is called an ectopic rhythm. Dysrhythmias resulting from an ectopic focus often have a gradual onset and termination. Automaticity is not confined to secondary pacemakers within the conduction system; virtually any myocardial cell can exhibit automaticity under certain circumstances and is therefore capable of initiating cardiac depolarization. The fastest pacemaker in the heart is normally the SA node. The SA node spontaneously discharges at a rate of 60 to 100 bpm. The sinus node can be accelerated or overridden by ectopic pacemakers due to increased endogenous catecholamines, disease states, or iatrogenic drug effects.

The automaticity of cardiac tissue changes when the slope of phase 4 depolarization shifts or the resting membrane potential changes. Sympathetic stimulation causes an increase in heart rate by increasing the slope of phase 4 of the action potential and by decreasing the resting membrane potential. Conversely, parasympathetic stimulation results in a decrease in the slope of phase 4 depolarization and an increase in resting membrane potential to slow the heart rate (see Fig. 8.2).

Reentry Pathways

Reentry pathways account for most premature beats and tachydysrhythmias. Pharmacologic or physiologic events may alter the balance between conduction velocities and refractory periods of the dual pathways, resulting in the initiation or termination of reentrant dysrhythmias. Reentrant dysrhythmias tend to be paroxysmal with abrupt onset and termination.

Reentry or triggered dysrhythmias require two pathways over which cardiac impulses can be conducted at different velocities (Fig. 8.4) In a reentry circuit there is anterograde (forward) conduction over the slower normal conduction pathway and retrograde (backward) conduction over a faster accessory pathway.

Triggering by Afterdepolarizations

Afterdepolarizations are oscillations in membrane potential that occur during or after repolarization. Normally these membrane oscillations dissipate; however, under certain circumstances they can trigger a complete depolarization. Once

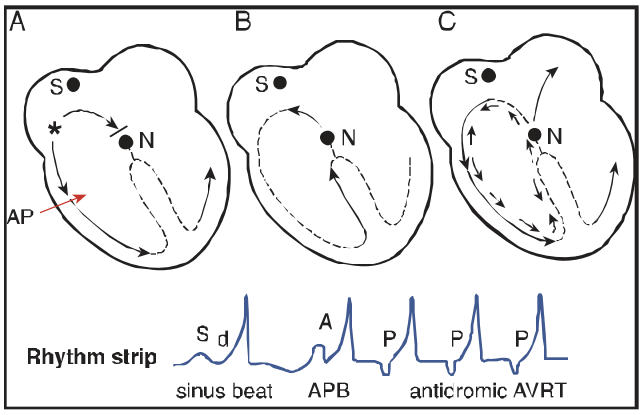

Fig. 8.4 The essential requirement for initiation of reentry excitation is a unilateral block that prevents uniform antegrade propagation of the initial cardiac impulse. Under appropriate conditions, this same cardiac impulse can traverse the area of blockade in a retrograde direction and become a reentrant cardiac impulse. (Adapted from Akhtar M. Management of ventricular tachyarrhythmias. *JAMA*. 1982;247:671–674.)

triggered, the process may become self-sustaining and result in a dysrhythmia. Triggered dysrhythmias associated with early afterdepolarizations are enhanced by a slow heart rate and are treated by accelerating the heart rate with positive chronotropic drugs or pacing. Conversely, triggered dysrhythmias associated with delayed afterdepolarizations are enhanced by fast heart rates and can be suppressed with drugs that lower the heart rate.

SUPRAVENTRICULAR DYSRHYTHMIAS

Sinus Tachycardia

Normal sinus rhythm in a patient at rest is under the control of the sinus node, which fires at a rate of 60 to 100 bpm. When sinus rhythm exceeds 100 bpm, it is considered sinus tachycardia. The ECG shows a normal P wave before every QRS complex. The PR interval is normal unless a coexisting conduction block exists. Sinus tachycardia is caused by acceleration of SA node discharge due to either sympathetic stimulation or parasympathetic suppression. Typically, it is a nonparoxysmal increase in heart rate that speeds up and slows down gradually. It is the most common supraventricular dysrhythmia seen during anesthesia in the operating room. Reasons for sinus tachycardia range from simple to complex. Sinus tachycardia without hemodynamic instability is not life threatening. Sinus tachycardia is usually well tolerated in young healthy patients. It can occur in an awake patient as part of the normal physiologic response to stimuli (e.g., fear, pain, anxiety) or as a pharmacologic response to medications such as atropine, ephedrine, or other vasopressors. Intake of stimulant substances such as caffeine or cocaine may also cause sinus tachycardia. Other potential intraoperative causes include sympathetic stimulation, pain, vagolytic drug administration, hypovolemia, light anesthesia, hypoxia, hypercarbia, heart failure, cardiac ischemia, fever, and infection. The likelihood of sinus tachycardia is reduced by avoidance of sympathomimetic agents/vagolytic drugs, ensuring adequate anesthetic depth, maintenance of euvolemia, correction of hypercarbia, avoidance of hypoxemia, antibiotic treatment of suspected infection, use of the lowest effective dose of inotropic support for heart failure (many inotropes increase heart rate), and prompt treatment of myocardial ischemia (Table 8.1).

In patients with ischemic heart disease, diastolic dysfunction, or CHF, the heart rate increase above normal sinus rhythm can lead to significant clinical deterioration because of increased oxygen demand, increased wall stress, and a decrease in coronary perfusion. Treatment may include IV administration of a β blocker to lower the heart rate and decrease myocardial oxygen demand. However, β blockers must be used with caution in patients susceptible to bronchospasm and in patients with impaired cardiac function. Patients with a low ejection fraction may be dependent on elevated heart rate to maintain adequate cardiac output. A decrease in heart rate in the setting of a fixed reduced stroke volume may cause an abrupt and dangerous decrease in blood pressure.

Premature Atrial Beats

Premature atrial contractions (PACs) are early (premature) ectopic beats. They appear as a P wave with a QRS complex earlier than expected given the preceding two sinus beats. The P wave of the PAC originates from an ectopic focus in the atria. The PR interval is variable. Most often, the corresponding QRS

TABLE 8.1 Perioperative Causes of Sinus Tachycardia

Physiologic Increase in Sympathetic Tone
Pain
Anxiety or fear
Light anesthesia
Hypovolemia or anemia
Arterial hypoxemia
Hypotension
Hypoglycemia
Fever or infection

Pathologic Increase in Sympathetic Tone
Myocardial ischemia or infarction
Congestive heart failure
Pulmonary embolus
Hyperthyroidism
Pericarditis
Pericardial tamponade
Malignant hyperthermia
Ethanol withdrawal

Drug-Induced Increase in Heart Rate
Atropine or glycopyrrolate
Sympathomimetic drugs
Caffeine
Nicotine
Cocaine or amphetamines

complex is narrow because activation of the ventricles following the ectopic P wave occurs through the normal conduction pathway. PACs with aberrant conduction of atrial impulses can occur, resulting in a widened QRS complex that may resemble a PVC. There is typically a slight pause after a PAC before the next sinus beat.

Symptoms of PACs in an awake patient are much like symptoms of PVCs and include an awareness of a fluttering in the chest or a heavy or prominent heartbeat. PACs are common in patients of all ages, with or without heart disease. They often occur at rest and become less frequent with exercise. Emotional stress, alcohol, stimulant substances such as caffeine, nicotine, and cocaine can increase the prevalence of PACs. Patients with chronic lung disease, ischemic heart disease, and hyperthyroidism and digitalis toxicity often experience PACs.

PACs are usually hemodynamically insignificant and do not require therapy unless they are associated with initiation of a tachydysrhythmia. If they are implicated in the generation of a tachydysrhythmia, PACs can be suppressed with calcium channel blockers or _ blockers.

Paroxysmal Supraventricular Tachycardia

Paroxysmal supraventricular tachycardia (PSVT) is a tachydysrhythmia (average heart rate, 150–250 bpm) initiated and sustained by tissue at or above the AV node. Unlike sinus tachycardia, PSVT usually begins and ends abruptly. Common symptoms in an awake patient experiencing PSVT include lightheadedness, dizziness, fatigue, chest discomfort, and dyspnea. Up to 15% of patients with PSVT may experience syncope. PSVT often occurs in individuals without structural heart disease.

The prevalence of SVT in the general population is 2.29 cases per 1000 persons. When adjusted by age and sex in the US population, the incidence of PSVT is estimated to be 36 per 100,000 persons per year. There are approximately 89,000 new cases per year and 570,000 persons with PSVT. Women have twice the risk of men of developing PSVT. Individuals over age 65 years have over five times the risk of younger persons of developing PSVT.

The relative frequency of tachycardia mediated by an accessory pathway decreases with age. The incidence of manifest preexcitation or WPW pattern on ECG tracings in the general population is 0.1% to 0.3%. However, not all patients with manifest ventricular preexcitation develop PSVT. Other mechanisms for PSVT include enhanced automaticity of secondary pacemaker cells and triggered impulse initiation by afterdepolarizations.

Strategies for clinical care of a patient with a history of PSVT should include avoiding factors known to increase ectopy, such as increased sympathetic tone, electrolyte imbalances, and acid-base disturbances. Because PSVT is paroxysmal, monitoring of vital signs to detect any progression to hemodynamic instability and verbal reassurance (if the patient is awake) is usually all that is needed until an episode of PSVT terminates. If the patient is in hemodynamically stable condition, the initial treatment of PSVT can consist of vagal maneuvers such as carotid sinus massage or a Valsalva maneuver. Termination by a vagal maneuver suggests reentry as the causative mechanism. If conservative treatment is not effective, pharmacologic treatment directed at blocking AV nodal conduction is indicated. The most common agents to treat PSVT are adenosine, calcium channel blockers, and L blockers (Fig. 8.5).

Adenosine has an advantage over other IV drugs used to treat PSVT; it has a very rapid onset (15–30 s) and very brief duration of action (10 s). Most AV nodal reentry tachycardia (AVNRT) episodes can be terminated by a single dose of adenosine. Multifocal atrial tachycardia (MAT), atrial flutter, and atrial fibrillation do not respond to adenosine. Heart transplant recipients require a reduction in adenosine dosage because of denervation hypersensitivity. Conversely, methylxanthines such as theophylline act as adenosine receptor antagonists, so a higher dose of adenosine will likely be needed to produce a therapeutic effect.

IV administration of calcium channel blocking drugs such as verapamil and diltiazem can also be useful for terminating PSVT. These drugs have a longer duration of action than adenosine. Side effects, including peripheral vasodilation and negative inotropy, can contribute to an undesirable degree of hypotension. Intravenous _ blockers can be used to control or convert PSVT. Digoxin is not clinically useful in acute control of PSVT secondary to the characteristic delayed peak effect and a narrow therapeutic window. Electrical cardioversion is indicated for PSVT unresponsive to drug therapy or PSVT associated with hemodynamic instability. Long-term medical treatment of patients with repeated episodes of PSVT includes calcium channel blockers, digoxin, and/or ¯ blockers. Radiofrequency catheter ablation may be used in patients with recurrent or recalcitrant AVNRT.

Wolff-Parkinson-White Syndrome

WPW syndrome is an inherited disorder characterized by reentrant tachycardias. The incidence of manifest preexcitation or WPW pattern on ECG tracings in the general population is 0.1% to 0.3%. However, not all patients with ECG signs of ventricular preexcitation develop PSVT. There is a bimodal age distribution in initial symptoms, with the first peak in early childhood, then a second in young adulthood. Some women experience their initial manifestation of WPW syndrome during pregnancy. Other patients may have the first manifestation of WPW syndrome during the perioperative period. The incidence of SCD in patients with WPW syndrome is 0.15% to 0.39% per patient-year, but it is very unusual for sudden death to be the initial manifestation of WPW syndrome. The relative frequency of tachycardia mediated by an accessory pathway decreases with age.

The diagnosis of WPW syndrome is reserved for conditions characterized by both preexcitation and tachydysrhythmia. Ventricular preexcitation causes an earlier than normal deflection of the QRS complex called a delta wave. These preexcitation ECG changes are a form of conduction block. The ECG criteria in adults are PR interval less than 120 ms, slurring of the initial portion of the QRS (delta wave), QRS longer than 120 ms in adults, and secondary ST-segment and T-wave changes. The incidence of SCD in patients with WPW syndrome is 0.15% to 0.39% per patient-year, but it is very unusual for sudden death to be the initial manifestation of WPW syndrome. WPW is more common in patients with Ebstein

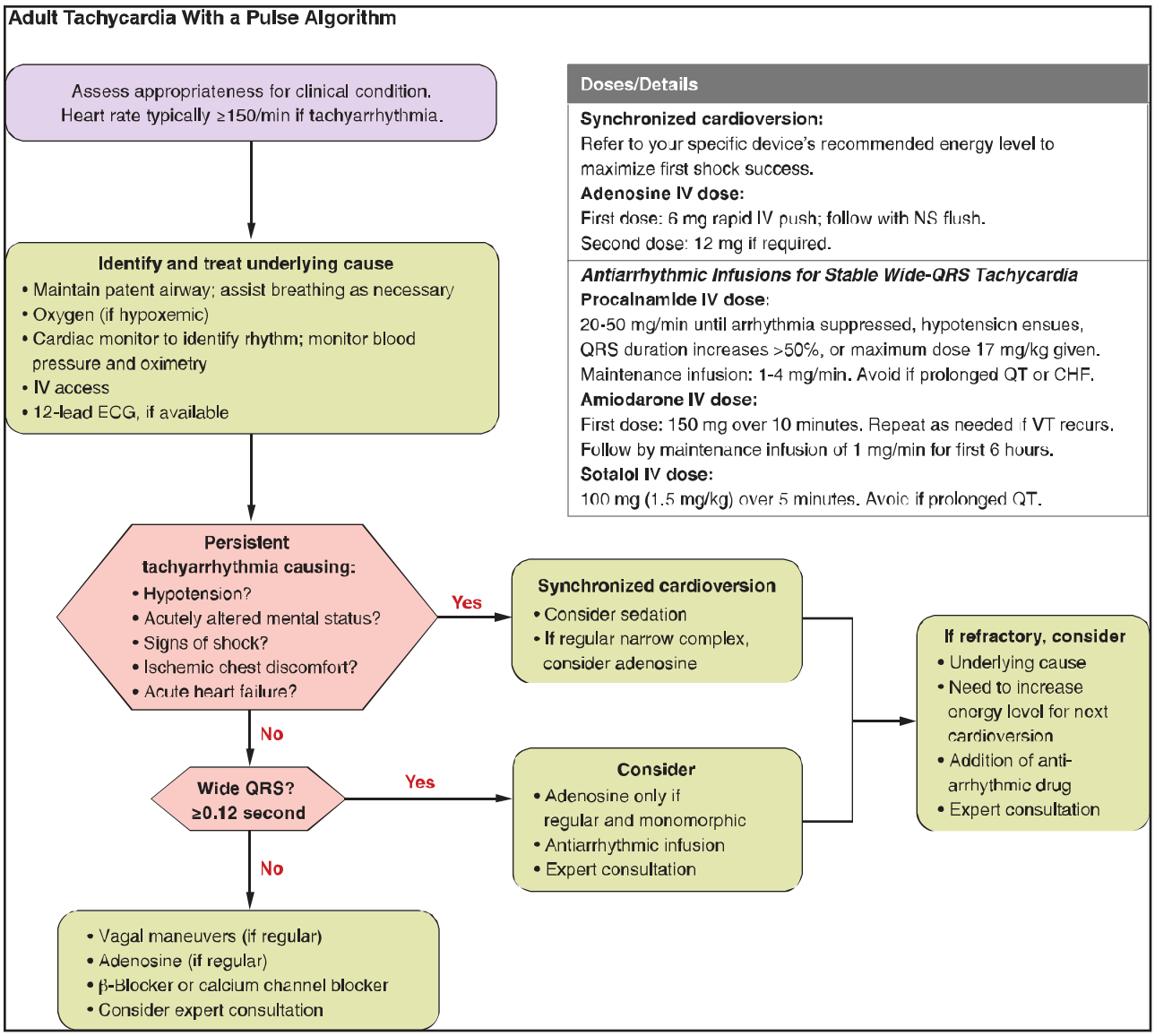

Fig. 8.5 Algorithm for treatment of adult tachycardia (with pulse). *CHF,* Congestive heart failure; *ECG,* electrocardiogram; *IV,* intravenous; *NS,* normal saline; *VT,* ventricular tachycardia. (Page 79, Figure 30. Adult Tachycardia With a Pulse algorithm. Reprinted with permission Advanced Cardiovascular Life Support Provider Manual ©2020 American Heart Association, Inc.)

malformation of the tricuspid valve, hypertrophic cardiomyopathy, and transposition of the great vessels. Paroxysmal palpitations with or without dizziness, syncope, dyspnea, or angina pectoris are common during the tachydysrhythmias associated with this syndrome.

AVNRT is the most common tachydysrhythmia seen in patients with WPW syndrome. It accounts for 95% of the dysrhythmias seen with this syndrome. This tachydysrhythmia is usually triggered by a PAC. AVNRT is classified as either orthodromic (narrow QRS complex) or antidromic (wide QRS complex). Orthodromic AVNRT is much more common (90–95% of cases) and has a narrow QRS complex because the cardiac impulse is conducted from the atrium through the normal AV node–His-Purkinje system. These impulses return from the ventricle to the atrium using the accessory pathway. Treatment of orthodromic AVNRT in conscious patients in stable condition should begin with vagal maneuvers such as carotid sinus massage or a Valsalva maneuver. If vagal maneuvers are unsuccessful, adenosine, verapamil, β blockers, or amiodarone may be used as clinically appropriate.

In the less common antidromic form of AVNRT, the cardiac impulse is conducted from the atrium to the ventricle through the accessory pathway and returns from the ventricles to the atria via the normal AV node. The wide QRS complex seen in antidromic AVNRT makes it difficult to distinguish this dysrhythmia from ventricular tachycardia. Treatment of antidromic AVNRT is intended to block conduction of the cardiac impulse along the accessory pathway. Drugs used to treat orthodromic AVNRT (e.g., adenosine, calcium channel blockers, β blockers, lidocaine, digoxin) are contraindicated in antidromic AVNRT as they may increase conduction along the accessory pathway and produce a marked increase in ventricular rate.

Patients with known WPW syndrome coming for surgery should continue to receive their antidysrhythmic medications. It

is helpful to know whether the patient is being treated for orthodromic or antidromic AVNRT prior to undergoing anesthetic care. The goal during management of anesthesia is to avoid excess sympathetic stimulation (pain, anxiety, or hypovolemia) and drugs that may enhance anterograde conduction of cardiac impulses through an accessory pathway (digoxin, verapamil if they have antidromic AVNRT). Appropriate antidysrhythmic drugs for treatment and equipment for electrical cardioversion-defibrillation must be immediately available.

Treatment of antidromic AVNRT in WPW patients with stable vital signs includes IV administration of procainamide 10 mg/kg infused at a rate not to exceed 50 mg/min. Procainamide slows conduction of cardiac impulses along the accessory pathway and may slow the ventricular response and terminate the wide-complex tachydysrhythmia. Electrical cardioversion is indicated if the ventricular response cannot be controlled by drug therapy.

Atrial fibrillation and atrial flutter are uncommon in WPW syndrome but are potentially lethal because they can result in very rapid heart rates and deteriorate into ventricular fibrillation. The mechanism responsible is anterograde conduction from the atria to the ventricles through the accessory pathway. There is no mechanism along an accessory pathway to slow the conduction speed. The result is extremely rapid ventricular rates that often degenerate into ventricular fibrillation and death. Atrial fibrillation in the setting of WPW syndrome can be treated with IV procainamide; however, electrical cardioversion is preferred in the presence of hemodynamic instability. Verapamil and digoxin are contraindicated in this situation because they accelerate conduction through the accessory pathway. Long-term management of tachydysrhythmias in patients with WPW syndrome usually involves radiofrequency catheter ablation of the accessory pathway.

Radiofrequency catheter ablation refers to a procedure in which an intracardiac electrode catheter is inserted percutaneously under local anesthesia through a large vein (femoral, subclavian, internal jugular, or cephalic). This electrode is then used to produce small, well-demarcated areas of thermal injury that destroy the myocardial tissue responsible for initiation or maintenance of dysrhythmias. The procedure is curative in 95% of patients and has a low complication rate. Antidysrhythmic drugs may be used as adjuvant therapy.

Multifocal Atrial Tachycardia

MAT is a form of SVT that demonstrates the presence of multiple ectopic atrial pacemakers (Fig. 8.6). The ECG shows P waves with three or more different morphologies, and the PR intervals vary. This rhythm is frequently confused with atrial fibrillation, but unlike it, the rate is not excessively rapid, and each QRS has an associated P wave. The atrial rhythm is usually between 100 and 180 bpm.

MAT is most commonly seen in patients experiencing an acute exacerbation of chronic lung disease. It can also be associated with methylxanthine (theophylline and caffeine) toxicity, CHF, sepsis, metabolic derangements, and electrolyte abnormalities. Treatment of the underlying pulmonary decompensation with supplemental oxygen and bronchodilators with improvement in arterial oxygenation decreases the activity of the ectopic foci that cause MAT. Preoperative optimization of pulmonary function and arterial oxygenation is the main goal in management of these patients. Intraoperatively, avoidance of medications or procedures that could worsen the pulmonary status (such as ¯ blockers) and avoidance of hypoxemia are recommended.

Magnesium sulfate 2 g IV over 1 hour followed by 1 to 2 g IV per hour by infusion has shown some success in decreasing atrial ectopy and converting MAT to sinus rhythm. Verapamil 5 to 10 mg IV over 5 to 10 minutes slows the ventricular rate and will convert to sinus rhythm in some patients. Likewise, ⊥ blockers such as esmolol or metoprolol can decrease the ventricular rate but at the risk of provoking bronchospasm in susceptible patients. Pharmacologic treatment of MAT has limited success and is considered secondary to improvement in oxygenation. Theophylline can also exacerbate this condition. Cardioversion has no effect on the multiple sites of ectopy that produce this dysrhythmia.

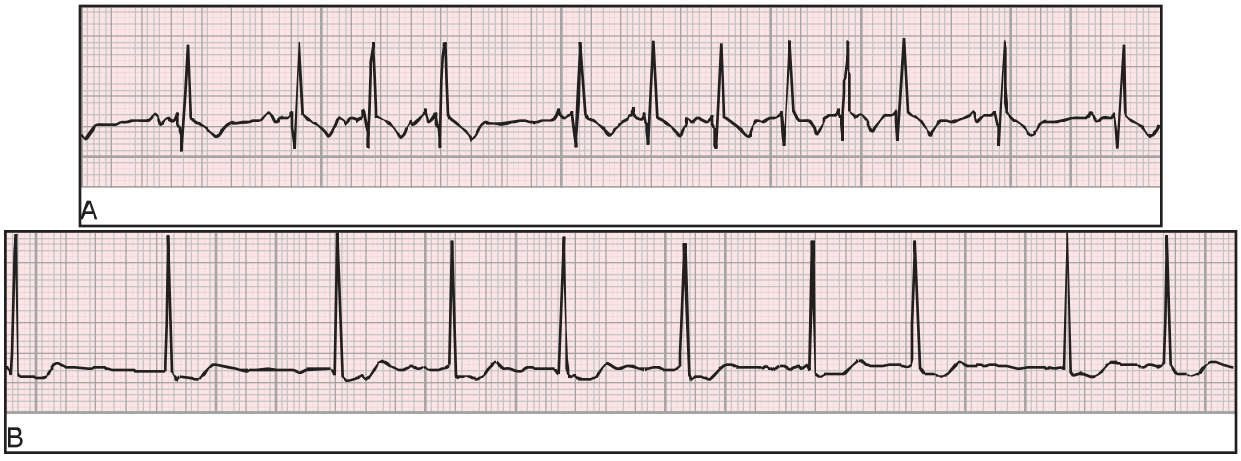

Fig. 8.6 Comparison of the electrocardiogram (ECG) appearance of multifocal atrial tachycardia (A) and atrial fibrillation (B). Both rhythms are irregular. However, note several distinct P-wave morphologies and varying PR intervals with multifocal atrial tachycardia. There are no distinct P waves with atrial fibrillation.

Atrial Fibrillation

Atrial fibrillation is the most common sustained cardiac dysrhythmia in the general population. In 2005 there were about 3 million Americans with the condition. This number is expected to triple by 2050. The incidence of atrial fibrillation increases with age: It is present in 1% of individuals younger than 60 years and increases to 12% of patients aged 70 to 84 years. A third of patients with atrial fibrillation are older than 80 years. For whites, the lifetime risk for developing atrial fibrillation after age 40 is 26% for men and 23% for women. Blacks tend to have more risk factors for developing atrial fibrillation but a lower incidence of occurrence. Atrial fibrillation is the most common postoperative tachydysrhythmia and often occurs early in the postoperative period (first 2–4 days), especially in elderly patients following cardiothoracic surgery.

Atrial fibrillation is a type of supraventricular dysrhythmia characterized on ECG by chaotic atrial activity with no discernible P waves and irregular RR intervals (see Fig. 8.6). The resulting heart rate can be normal or rapid depending on the status of the conduction system and the use of drugs that affect AV conduction. Atrial fibrillation may be seen in a patient with no associated symptoms; however, most patients are symptomatic. The most common complaint is fatigue. Other common signs and symptoms are generalized weakness, palpitations, hypotension, syncope, angina pectoris, shortness of breath, orthopnea, and hypotension.

Atrial fibrillation occurs with structural heart changes such as left atrial dilation and/or electrophysiologic abnormalities that promote abnormal impulse generation or propagation. The causes of these abnormalities are diverse but include medical issues and comorbidities commonly encountered in the anesthetic patient such as obesity, diabetes, sleep apnea, anemia, arthritis, chronic kidney disease, hyperlipidemia, hypertension, recreational drug use, hyperthyroidism, CHF, rheumatic heart disease (especially mitral valve disease), ischemic heart disease, COPD, binge alcohol intake (holiday heart syndrome), pericarditis, pulmonary embolus, and ASD.

If new-onset atrial fibrillation occurs prior to induction of anesthesia, surgery should be postponed—if possible, until the ventricular rate is controlled or sinus rhythm is achieved. Although atrial fibrillation is a common chronic medical problem, a large proportion of patients with new-onset type experience spontaneous conversion to sinus rhythm within 24 to 48 hours. After conversion to sinus rhythm, blockers are often useful in preventing recurrent episodes and reducing symptoms should subsequent episodes occur. Treating coexisting factors such as uncontrolled blood pressure, COPD, or ischemic heart disease can eliminate atrial fibrillation permanently.

In the operating room or other acute settings, amiodarone is a good choice for chemical cardioversion and rate control. The efficacy of IV amiodarone in producing chemical cardioversion ranges from 34% to 69% for a bolus dose of the drug and 55% to 95% when the bolus is followed by a continuous drug infusion. Amiodarone also suppresses atrial ectopy and thus recurrent atrial fibrillation and improves the success rate of electrical cardioversion. It is the preferred drug for patients with significant heart disease, including ischemic heart disease, left ventricular hypertrophy, left ventricular dysfunction, and heart failure. In patients with atrial fibrillation and a known or suspected accessory pathway and preexcitation, procainamide or amiodarone are first-line agents. Adverse effects of short-term amiodarone administration include bradycardia, hypotension, and phlebitis at the site of administration. Potential long-term side effects include visual disturbances, thyroid dysfunction, pulmonary toxicity, and skin discoloration.

Electrical cardioversion is the most effective method for converting atrial fibrillation to normal sinus rhythm and is indicated in patients with coexisting symptoms of heart failure, angina pectoris, or hemodynamic instability. If vital signs are stable, the primary goal should be rate control with a blocker or calcium channel blocker if there are no clinical contraindications such as suspected accessory pathways or preexcitation. Digoxin can be useful to control ventricular rate in appropriate patients but is not effective for conversion of atrial fibrillation to sinus rhythm. In the acute setting, the usefulness of digoxin is limited because its peak therapeutic effects are delayed by several hours. Side effects associated with digitalis therapy are dose related and most commonly include AV block and ventricular ectopy.

Patients with chronic atrial fibrillation are usually treated with anticoagulants. The loss of coordinated atrial contraction promotes stasis of blood within the left atrium and can lead to formation of atrial thrombi. As a result, atrial fibrillation is associated with a fivefold increase in the risk of embolic stroke, a threefold increase in the risk of heart failure, and a twofold increase in the risk of dementia and death.

Regimens for prophylaxis against perioperative stroke in patients with nonvalvular atrial fibrillation are determined by risk stratification for stroke based on stratification systems such as $CHADS_2$ or CHA_2DS_2-VAS. These stratification tools are composed of weighted scores for patient comorbidities such as CHF, hypertension, age older than 75 years, diabetes mellitus, previous embolic event (stroke or transient ischemic attack), sex, and evidence of vascular disease.

Long-term anticoagulation for atrial fibrillation is most often accomplished with warfarin, a vitamin K antagonist with a narrow therapeutic window that necessitates frequent monitoring and measurement of its clinical effect. Warfarin drug levels can be affected by numerous foods and medications. Newer drugs for stroke prevention due to nonvalvular atrial fibrillation include dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis). They inhibit other portions of the coagulation cascade. Their principal benefit is that they do not require monitoring of drug effect.

Patients intolerant to medications may be candidates for radiocatheter ablation treatment to achieve and maintain sinus rhythm. If the patient is undergoing cardiac surgery for other indications, a surgical Maze procedure with pulmonary vein isolation and left atrial appendage exclusion may be done to convert atrial fibrillation and eliminate a site of blood stasis in the heart.

Patients coming for elective surgery who are taking anticoagulants typically have their anticoagulant stopped for 3 to 7 days before surgery, depending on the pharmacokinetics of the particular drug. The goal is normal coagulation on the day of surgery.

IV standard heparin or low-molecular-weight heparin such as Lovenox are used most often for this perioperative prophylaxis. They can be administered as needed to bridge before an operation in a high-risk individual coming off a longer acting anticoagulant such as Coumadin and then as a postoperative anticoagulant bridge until long-term anticoagulation is reestablished.

Patients having urgent or emergent surgery present a dilemma. The effects of warfarin can be reversed by administration of vitamin K, fresh frozen plasma, and/or 4-factor prothrombin complex concentrate to facilitate production and replacement of the clotting factors suppressed by warfarin. Until recently there were no antidotes for reversal of the anticoagulation effects of the other anticoagulants such as dabigatran, rivaroxaban, and apixaban. In 2015 the FDA approved a reversal agent for dabigatran called Praxbind (idarucizumab), which is a monoclonal antibody fragment that binds to dabigatran and reverses its clinical effects within minutes to a few hours. As such, it is very useful for emergency surgery or urgent procedures and in life-threatening bleeding due to dabigatran. Its effects appear to last 12 to 24 hours. Apixaban and rivaroxaban, which inhibit factor X, can be treated with andexanet, which is a recombinant inactive form of factor Xa that binds and sequesters the factor Xa anticoagulant. More studies and clinical experience will be needed to clarify the safety profile in these new reversal drugs.

Atrial Flutter

Atrial flutter is characterized by an organized atrial rhythm with an atrial rate of 250 to 350 bpm with varying degrees of AV block. The rapid P waves create a sawtooth appearance on ECG called flutter waves. Flutter waves are particularly noticeable in leads II, III, aVF, and V_1. The flutter waves are not separated by an isoelectric baseline. The ventricular rate may be regular or irregular depending on the rate of conduction. Most commonly, patients have 2:1 AV conduction; an atrial rate of 300 bpm with 2:1 conduction, for example, results in a ventricular rate of 150 bpm. Atrial flutter frequently occurs in association with other dysrhythmias such as atrial fibrillation. It occurs in approximately 30% of patients with atrial fibrillation and may be associated with more intense symptoms than atrial fibrillation because of the more rapid ventricular response. About 60% of patients experience atrial flutter in association with an acute exacerbation of a chronic condition such as pulmonary disease, acute MI, ethanol intoxication, thyrotoxicosis, or after cardiothoracic surgery. In many instances, treatment of the underlying disease process restores sinus rhythm.

Ventricular response rates as high as 180 bpm can occur in patients with normal AV node function. Extremely rapid ventricular responses in excess of 180 bpm can be seen in patients with accessory AV nodal bypass tracts. In this situation the QRS complex is often wide, and the ECG can resemble ventricular tachycardia or ventricular fibrillation.

If atrial flutter is hemodynamically significant, the treatment is cardioversion. Often less than 50 J (monophasic) is adequate to convert the rhythm to sinus. If the patient is hemodynamically stable, overdrive pacing using transesophageal or atrial electrodes may be helpful to convert atrial flutter to sinus rhythm. Patients with atrial flutter lasting longer than 48 hours should receive anticoagulant therapy.

Pharmacologic control of the ventricular response and conversion to sinus rhythm can be challenging in patients with atrial flutter. Ventricular rate control should be the initial goal of therapy. This is done to prevent deterioration in AV conduction from 2:1 to 1:1, which would represent a doubling of the heart rate. Such an increase in heart rate can cause severe hemodynamic instability. If there is 1:1 conduction with a ventricular rate of 300 bpm or faster, reentry is the most likely mechanism, and procainamide administration should be considered. Drug therapy for ventricular rate control includes amiodarone, diltiazem, and verapamil. All these drugs are helpful in controlling the ventricular rate, but none of them is likely to convert atrial flutter to sinus rhythm.

If atrial flutter occurs before induction of anesthesia, surgery should be postponed if possible until control of the dysrhythmia has been achieved. Management of atrial flutter occurring during anesthesia or surgery depends on the hemodynamic stability of the patient. If the atrial flutter is hemodynamically significant, treatment requires cardioversion. Synchronized cardioversion starting at 50 J (monophasic) is indicated. Pharmacologic control of the ventricular response with IV amiodarone, diltiazem, or verapamil may be attempted if vital signs are stable. The choice of drug depends on the coexisting medical conditions of the patient.

VENTRICULAR DYSRHYTHMIAS

Ventricular Ectopy (Premature Ventricular Beats)

Ventricular dysrhythmias occur in 70% to 80% of persons older than age 60 and are often asymptomatic. Premature ventricular beats (i.e., PVCs) can arise from single (unifocal) or multiple (multifocal) foci located below the AV node. Characteristic ECG findings include a premature and wide QRS complex (≥0.12 s), with no preceding P-wave, ST-segment, and T-wave deflections opposite the QRS deflection, and a compensatory pause before the next sinus beat. The clinical significance of ventricular ectopy depends on whether a patient is symptomatic and whether there is coexisting structural heart disease. The incidence of PVCs in a healthy population ranges from 0.5% in those younger than 20 years to 2.2% in those older than 50.

In the absence of structural heart disease, asymptomatic ventricular ectopy is benign with no demonstrable risk of sudden death. Benign PVCs occur at rest and disappear with exercise; however, PVCs that increase in frequency during exercise may be an indication of underlying heart disease. Ventricular ectopy can occur as short episodes with spontaneous termination or as a sustained pattern. Two or three PVCs—called a couplet or triplet, respectively—separated by one or more regular sinus beats is called bigeminy or trigeminy. The occurrence of more than three consecutive PVCs is considered ventricular tachycardia. Ventricular tachycardia that spontaneously terminates is termed *nonsustained ventricular tachycardia* (NSVT). The number of PVCs a patient is experiencing is termed the *PVC burden*. A low burden of PVCs is considered less than 2% to 3% of beats on a 24 or 48 Holter or other event monitor.

When patients experience several PVCs in a row, have a high burden of PVCs, or have runs of NSVT, symptoms range from dizziness, lightheadedness, presyncope, or syncope. Physiologically, the symptoms are a function of decreased blood pressure during PVCs or runs of NSVT due to the reduction in cardiac output from the ventricular beats.

Asymptomatic patients are not likely to be on suppressive therapy with β blockers, calcium channel blockers, or other antiarrhythmics unless they have underlying heart disease such as heart failure, hypertension, coronary artery disease, or cardiomyopathy. Treating the underlying heart disease will often reduce the incidence of PVCs. Patients with symptomatic PVCs are often managed on ectopy suppression therapy with β blockers, which not only suppress ventricular ectopy and other ventricular dysrhythmias but also reduce the risk of SCD in patients with heart diseases, including heart failure.

The most common symptoms in patients experiencing ventricular ectopy are palpitations or a heavy or prominent heartbeat. Palpitations elicit this feeling because the stroke volume of the sinus beat following a PVC is usually larger than volume of blood ejected in a regular sinus beat. The stroke volume during a PVC is smaller than that ejected during a normal sinus beat because of the lack of the atrial contribution to ventricular filling during the PVC. After the PVC, there is a compensatory pause before the P wave of the next sinus beat. Ejection of that extra volume can cause the feeling of a prominent heartbeat or palpitation in some patients. If an untreated symptomatic patient is identified in the preoperative anesthetic assessment for an elective procedure, postponement for immediate cardiology evaluation and treatment is recommended.

PVCs are frequently observed during anesthesia. During an anesthetic, new onset of PVCs, frequent unifocal PVCs, and multifocal PVCs are cause for concern and should be investigated. The differential for intraoperative PVCs should be considered, and any factors that can be improved should be addressed to prevent escalation of the PVCs to ventricular tachycardia or ventricular fibrillation. Common causes of PVCs encountered in the surgical population include acidosis, electrolyte imbalances (e.g., hypokalemia, hypomagnesemia), use of prodysrhythmic drugs, arterial hypoxemia, myocardial ischemia or infarction, valvular heart disease, cardiomyopathy, direct mechanical irritation from thoracic and/or cardiac surgery, intracardiac or intrathoracic catheters, drugs prolonging the QT interval, and digitalis toxicity. Preoperative consumption of excessive caffeine, alcohol, and cocaine use can also cause PVCs (Table 8.2).

PVCs can be dangerous in two specific clinical scenarios. One is when they occur during the middle third of the T wave which is a relative refractory period in the cardiac action potential. This may initiate sustained ventricular tachycardia or ventricular fibrillation, and is referred to as R on T phenomenon. This phenomenon is called R-on-T phenomenon. LQTS is another clinical situation where patients are at risk for ventricular dysrhythmias.

There are two types of LQTS: congenital and acquired. Iatrogenic acquired LQTS is far more common than the inherited forms of LQTS. Perioperative conditions increasing the risk of LQTS include sinus node dysfunction or second- or third-degree AV block with a QTc greater than 440 ms. Other causes include common electrolyte abnormalities such as hypokalemia, hypomagnesemia, and hypocalcemia. Hypothermia, myocardial ischemia, starvation, hypothyroidism, anorexia nervosa, raised intracranial pressure, and certain drugs can also contribute to iatrogenic LQTS.

TABLE 8.2 Conditions and Factors Associated With Development of Ventricular Premature Beats

Normal heart
Arterial hypoxemia
Myocardial ischemia
Myocardial infarction
Myocarditis
Sympathetic nervous system activation
Hypokalemia
Hypomagnesemia
Digitalis toxicity
Caffeine
Cocaine
Alcohol
Mechanical irritation (central venous or pulmonary artery catheter)

Drugs used in surgical and critical care that are associated with QT prolongation include propofol, chloral hydrate, β_2 agonists (albuterol), methadone, antiarrhythmic drugs, and antiemetics such as ondansetron and granisetron. Isoflurane and sevoflurane have both been shown to prolong the QTc in otherwise healthy children and adults. However, there is insufficient information to favor one volatile anesthetic over another.

Other drugs associated with prolonged QT such as various antipsychotics (chlorpromazine), serotonin reuptake inhibitors (Zoloft, fluoxetine), trazodone, fluoroquinolone and macrolide antibiotics, HIV antiretrovirals, cocaine, herbs such as licorice extract, and toxic exposure to organophosphate insecticides can contribute to prolonged QT and must be kept in mind when deciding to use a perioperative drug that may have additive QT prolongation.

A baseline ECG to document the QT interval is important prior to initiating treatment with a drug that has potential to prolong the QT interval. QTc is prolonged if it exceeds 440 ms in men or 460 ms in women. This prolongation of repolarization allows afterdepolarizations to trigger PVCs. These PVCs can degenerate into a form of pulseless ventricular tachycardia (i.e., TdP). Patients with QTc over 500 ms are at particularly high risk of TdP (aka polymorphic ventricular tachycardia), a distinct form of reentrant ventricular tachycardia initiated by a PVC or bradycardia in the setting of abnormal ventricular repolarization. (Fig. 8.7). The incidence of TdP is higher in women.

There are several genetic syndromes that manifest a long QT interval. At least 17 gene mutations have been identified thus far

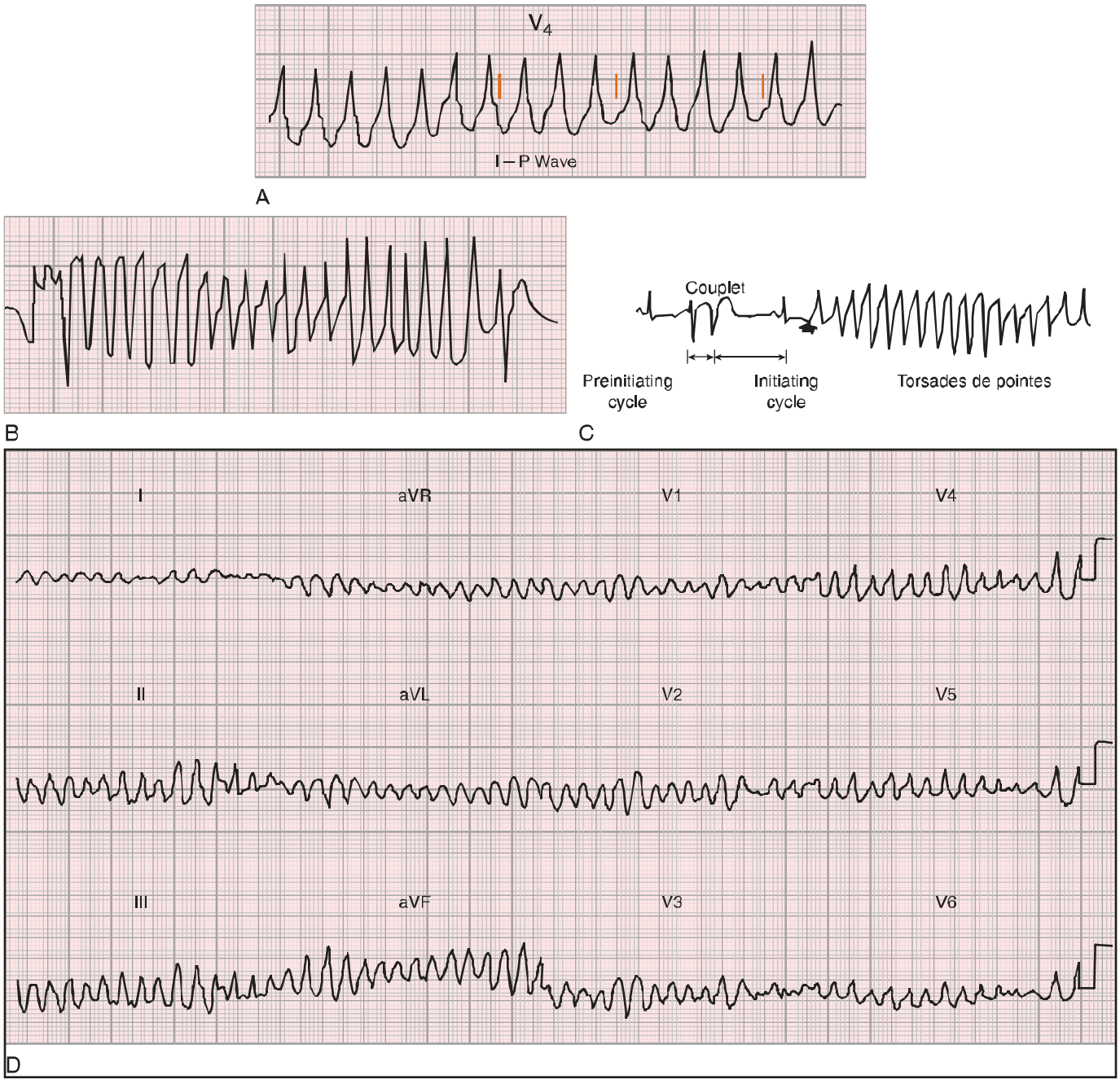

Fig. 8.7 Comparison of the electrocardiogram (ECG) appearance of monomorphic ventricular tachycardia, polymorphic ventricular tachycardia (torsades de pointes), and ventricular fibrillation.

in patients with congenital LQTS. Arrhythmogenic syncope followed by seizures and sudden cardiac arrest brought on by stress, emotion, exercise, or other sympathetic stimulation are often the presenting symptoms in these patients. The most common inherited form of prolonged QT syndrome is Romano-Ward syndrome. This autosomal dominant disorder with purely cardiac manifestations does not involve other organ systems. It usually presents in late childhood. Jervell and Lange-Nielsen syndrome is an autosomal recessive disorder with associated congenital deafness. These patients tend to have clinical manifestations early in life, and cardiac event occurred in over 80% of patient with more than one of four patients experiencing SCD. Timothy syndrome is extremely rare and seen in infants with syndactyly of the hands and feet and accompanying structural cardiac defects such as patent ductus arteriosus.

Preoperative treatment of LQTS includes correction of electrolyte abnormalities, particularly magnesium or potassium, and discontinuation of drugs associated with QT prolongation if possible. These patients are often on ectopy suppression with a βblocker. Cardiac pacing is also a treatment option in LQTS as it

allows control over the heart rate and avoidance of the bradycardia that frequently preceded the onset of TdP. ICDs with pacing capability have emerged as lifesaving therapy for patients with recurrent symptoms and recalcitrant TdP resistant to chemical suppression. In addition, left cervicothoracic sympathetic ganglionectomy may assist in reducing dysrhythmogenic syncope in patients with congenital LQTS who cannot take ∃ blockers or have recurrent syncope despite ICD and ⊏ blocker therapy.

In patients with congenital LQTS, it is particularly important to avoid abrupt increases in sympathetic stimulation associated with preoperative anxiety and noxious stimulation intraoperatively, acute hypokalemia due to iatrogenic hyperventilation, and administration of drugs known to prolong the QTc. Standard therapy for these patients includes ⊥ blockade and cardiac pacing. Cardiac events and mortality in congenital LQTS patients have been reduced from 50% to less than 5% over 10 years with ⊥-blocker therapy. Consideration should be given to establishing ⊾ blockade before induction in patients believed to be at particular risk. A defibrillator should be available because the likelihood of perioperative ventricular fibrillation is increased.

Ventricular Tachycardia

During administration of an anesthetic, if a patient exhibits six or more PVCs per minute or repetitive or multifocal forms of ventricular ectopy, there is an increased risk of development of a life-threatening dysrhythmia. Defibrillation may be needed if the rhythm deteriorates into pulseless ventricular tachycardia or ventricular fibrillation. Identification, treatment, and elimination of as many causative factors as possible should be the highest priority. Amiodarone, lidocaine, and other antidysrhythmics are indicated only if PVCs progress to ventricular tachycardia or are frequent enough to cause hemodynamic instability. Many antidysrhythmic drugs, such as sotalol, have prodysrhythmic effects and/or prolong the QT interval and can increase the propensity for dysrhythmias.

Ventricular tachycardia (also called monomorphic ventricular tachycardia) is present when three or more consecutive ventricular premature beats occur at a heart rate of more than 100 bpm lasting more than 30 seconds. The rhythm is regular with wide QRS complexes and no discernible P waves (see Fig. 8.7).

VT can occur as a nonsustained paroxysmal rhythm or as a sustained rhythm. NSVT is ventricular tachycardia lasting less than 30 seconds. A wide-complex SVT can be difficult to distinguish from ventricular tachycardia, especially if there is aberrant conduction or if the patient has RBBB or LBBB causing a widened QRS. A wide QRS tachycardia should be presumed to be ventricular tachycardia if the diagnosis is unclear. Direct current (DC) cardioversion is recommended if at any point a patient with sustained monomorphic ventricular tachycardia develops hemodynamic instability.

Sustained ventricular tachycardia has a regular rhythm of 100 to 200 bpm. The ratio of P waves to QRS has no fixed relationship because there is atrioventricular dissociation. Although some patients can maintain a pulse with this rhythm, it can easily degenerate into a pulseless rhythm and should be considered life threatening and requires immediate treatment. Treatment of ventricular tachycardia includes amiodarone and cardioversion. If the rhythm degrades to ventricular fibrillation, the uncoordinated electrical state produces a rhythm with no discernable QRS and no pulse. Immediate cardiopulmonary resuscitation (CPR) and defibrillation are needed.

In the perioperative environment, mechanical ventilation, drug therapy, insertion of central catheters, and other interventions can be iatrogenic causes of ventricular dysrhythmias. Ventricular tachycardia is common after an acute MI and in the presence of inflammatory or infectious diseases of the heart. It is also associated with digitalis toxicity. The occurrence of paroxysmal nonsustained ventricular tachycardia during anesthesia should prompt an investigation into potential causes and correction of any reversible factors. Timely termination of ventricular tachycardia is desirable even if it is well tolerated. IV amiodarone is the first-line drug for patients with stable ventricular tacycardia. It is the most effective agent for suppressing the condition in post-MI and CHF patients. Procainamide and other class 1c drugs can be used, but there is an increase in arrhythmic sudden death and total cardiovascular mortality in patients treated with 1c drugs used for ventricular ectopy suppression post MI or with lowered ejection fraction. Close monitoring of the blood pressure and cardiovascular status is necessary because this drug can cause hypotension.

Lidocaine is effective if the ventricular tachycardia is related to myocardial ischemia. Transvenous catheter pacing for termination of ventricular tachycardia can be useful in patients with sustained VT refractory to cardioversion or recurrent on antidysrhythmic therapy. Calcium channel blockers should never be used to terminate a wide QRS complex tachycardia of unknown origin, especially in patients with a history of myocardial dysfunction.

Patients with symptomatic or unstable monomorphic or polymorphic ventricular tachycardia should undergo cardioversion immediately. Pulseless ventricular tachycardia of any kind requires defibrillation. Cardioversion can begin at an output of 100 J (monophasic) and increase in increments of 50 to 100 J as necessary. In addition to electrical therapy and drug treatment, endotracheal intubation and evaluation and correction of acid-base and electrolyte disturbances should be undertaken as clinically appropriate. If vital signs are stable but the ventricular tachycardia is persistent or recurrent after cardioversion, administration of amiodarone 150 mg over 10 minutes is necessary. Dosing of amiodarone may be repeated as needed to a maximum total dose of 2.2 g in 24 hours. Alternative drugs include procainamide, sotalol, and lidocaine. Sotalol is effective in suppressing ventricular dysrhythmias but has significant prodysrhythmic effects and has not been shown to improve long-term survival.

Reversible factors contributing to cardiac arrest should be managed by advanced cardiac life support (ACLS), including treatment of hypoxia, electrolyte disturbances, mechanical factors, and volume depletion. The prognosis for patients with ventricular tachycardia depends on the presence or absence of structural heart disease. The risk of sudden death in patients with structurally normal hearts experiencing ventricular dysrhythmias is low. In pregnancy, women with unstable ventricular

tachycardia or fibrillation should be cardioverted or defibrillated. Long-term treatment with a _ blocker or calcium channel blocker can suppress ventricular tachycardia and prevent recurrence. _1-selective blockers, amiodarone, or both in combination with an ICD may be considered. Pregnant women with LQTS with symptoms should be on □ blockers unless contraindicated. Ventricular tachycardia in the absence of structural heart disease may be due to elevated catecholamine levels. □ blockers are particularly effective in this circumstance. If ventricular tachycardia presents in the last 6 weeks of pregnancy or in the postpartum period, the possibility of postpartum cardiomyopathy should be considered.

Catheter ablation of the causative ectopic pathway or implantation of a pacemaker/defibrillator are options for long-term treatment of drug-refractory ventricular tachycardia. ICD therapy, compared with conventional antidysrhythmic therapy, has been associated with reductions in mortality ranging from 23% to 55% depending on the study, and this is attributed to a reduction in SCD from ventricular dysrhythmias. In certain circumstances, coronary revascularization may improve survival from malignant ventricular dysrhythmias, especially in patients with left main and proximal left anterior descending coronary artery disease.

Ventricular Fibrillation

Ventricular fibrillation is a rapid, grossly irregular ventricular rhythm with marked variability in QRS cycle length, morphology, and amplitude (see Fig. 8.7). It is incompatible with life because no stroke volume is generated by this rhythm. A pulse or blood pressure never accompanies ventricular fibrillation. Ventricular tachycardia often precedes the onset of ventricular fibrillation, which during anesthesia is a critical event. CPR must be initiated immediately. Without defibrillation, cardiac output, coronary blood flow, and cerebral blood flow are extremely low even with ideally performed external cardiac compressions. Ventricular fibrillation is the most common cause of SCD. Most victims have underlying ischemic heart disease. Patients with acute coronary ischemia receiving □ blockers, ACE inhibitors, or statins have ventricular tachycardia and fibrillation less often than those not receiving these drugs. Also, the incidence of ventricular fibrillation occurring with acute MI has decreased due to increased □ blocker use and early revascularization.

Electrical defibrillation is the only effective method to convert ventricular fibrillation to a viable rhythm. Defibrillation involves delivery of a high-energy electric current throughout the heart to depolarize all myocardial cells at once. Ideally a single intrinsic pacemaker focus will then restore myocardial synchrony. The single most important factor affecting survival in patients experiencing ventricular fibrillation is time to defibrillation. Survival is best if defibrillation occurs within 3 to 5 minutes of cardiac arrest. When ventricular fibrillation is refractory to electrical treatment, IV administration of epinephrine 1 mg or amiodarone 150 to 300 mg may improve the response to electrical defibrillation. Adjunctive therapy with amiodarone, lidocaine, or magnesium may be indicated. The gold standard for long-term treatment of recurrent episodic ventricular tachycardia or fibrillation is implantation of a permanent automatic cardioverter-defibrillator, with adjuvant drug therapy if needed as a second-line treatment.

In any pulseless arrest, contributing factors must be sought and treated. The differential diagnosis includes hypoxia, hypovolemia, acidosis, hypokalemia, hyperkalemia, hypomagnesemia, hypoglycemia, hypothermia, drug or environmental toxins, cardiac tamponade, tension pneumothorax, coronary ischemia, pulmonary embolism, and hemorrhage. Standardized ACLS algorithms (Fig. 8.8) should be followed for electrical, pharmacologic, and adjunctive therapy.

MECHANISMS OF BRADYDYSRHYTHMIAS

Bradycardia is defined as a heart rate less than 60 bpm (see Table 8.3). If the SA or AV node does not fire, other slower pacemaker cells may take over primary intrinsic pacemaker function. There is normally a pause in electrical activity before a secondary slower pacemaker begins to fire. Each group of potential pacemaker cells has an intrinsic rate. Cells near the AV node, called junctional pacemakers, fire at 40 to 60 bpm. Ventricular cells below the AV node can act as an ectopic pacemaker's heart rate resulting from these myocytes in the range of 30 to 45 bpm. An ectopic rhythm generated from the ventricular myocytes will not have a P wave in proper association with the QRS. It can have random P waves not associated with a QRS as in third-degree heart block.

Sinus Bradycardia

The ECG during sinus bradycardia demonstrates a regular rhythm with a normal-appearing P wave before each QRS complex and a heart rate less than 60 bpm. Sinus bradycardia is due to decreased sympathetic stimulation or increased parasympathetic stimulation, as in deep relaxation, sleep, performance of a Valsalva maneuver, carotid sinus massage, gut traction, and vomiting. Noncardiac causes of sinus bradycardia include hyperkalemia, increased intracranial pressure, hypothyroidism, and hypothermia (Table 8.3).

Sinus bradycardia may be asymptomatic or symptomatic. In asymptomatic patients, no treatment is required. There is no set heart rate that is too low for a patient; however, most patients will not feel well with heart rates of 35 bpm or less. In the care of patients undergoing surgery with a high likelihood of vagal stimulation careful administration of a vagolytic such as glycopyrrolate or atropine can be used to increase the heart rate and mitigate the excess vagal tone. The degree of heart rate increase is unpredictable with administration of either of these drugs so careful consideration of the goal of such an action should be examined. A small dose of atropine (□0.5 mg) may even lower the heart rate further, setting up potential hemodynamic deterioration. If the patient is hemodynamically stable and comfortable with a heart rate below 60, it may be prudent just to monitor and treat only if symptoms or unstable vital signs occur.

In symptomatic patients, any potential contributing factors such as excess vagal tone or drugs should be eliminated. If the patient is experiencing chest pain or syncope, immediate transcutaneous or transvenous pacing is indicated. Atropine 0.5 mg

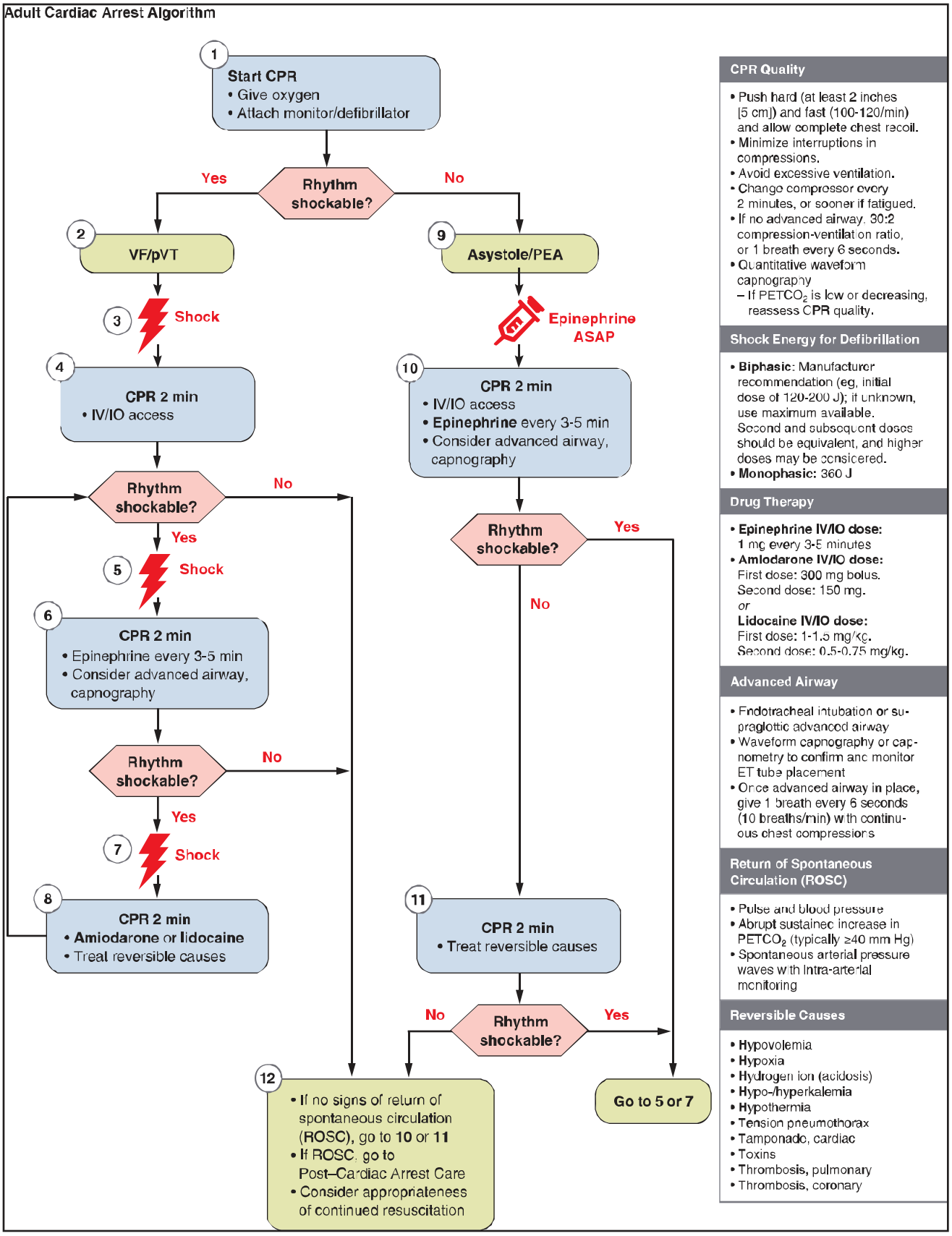

Fig. 8.8 Algorithm for treatment of adult cardiac arrest. *CPR,* Cardiopulmonary resuscitation; *ET,* endotracheal; *IV/IO,* intravenous/intraosseous; *PEA,* pulseless electrical activity; $PETCO_2$, extrapolated end-tidal carbon dioxide pressure; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia. (Page S374, Figure 3. Adult Cardiac Arrest algorithm. Reprinted with permission Circulation.2020;142:S366-S468. ©2020 American Heart Association, Inc.)

TABLE 8.3 Perioperative Causes of Sinus Bradycardia

- Vagal stimulation
  - Oculocardiac reflex: traction on eye muscles
  - Celiac plexus stimulation: traction on the mesentery
  - Laryngoscopy
  - Abdominal insufflation
  - Nausea
  - Pain
  - Electroconvulsive therapy
- Drugs
  - β blockers
  - Calcium channel blockers
  - Opioids (fentanyl, sufentanil)
  - Succinylcholine
- Hypothermia
- Hypothyroidism
- Athletic heart syndrome
- Sinoatrial nodal disease or ischemia

IV every 3 to 5 minutes (to a maximum 3 mg) may be given to increase heart rate but should not delay initiation of pacing. If cardiac pacing is not immediately available, isoproterenol infusion may be used as a chemical pacemaker until cardiac pacing is available. Isoproterenol is a second-line drug in the treatment of symptomatic bradycardia unresponsive to atropine. The recommended dosage is 2 to 10 μg/min by continuous infusion titrated to heart rate effect. Because of its direct action on β receptors, isoproterenol is useful to treat symptomatic bradycardia in heart transplant recipients. An initial IV dosage of 1 μg/min is titrated slowly upward until the desired effect is achieved.

If it is suspected that the bradycardia is due to β-blocker or calcium channel blocker overdose, glucagon may be an effective treatment. Suggested dosing of glucagon is 50 to 70 μg/kg (3–5 mg in a 70-kg patient) every 3 to 5 minutes until clinical response is achieved or a total dose of 10 mg is reached. To maintain clinical effect a continuous infusion at 2 to 10 mg/h should be maintained. Glucagon increases cAMP levels, which in turn augments myocardial contractility, heart rate, and AV conduction through a calcium-mediated mechanism.

Bradycardia during neuraxial blockade is a special circumstance that deserves additional consideration. It can occur in patients of any age and any ASA physical status class. The incidence of profound bradycardia and cardiac arrest during neuraxial anesthesia is approximately 1.5 per 10,000 cases. By contrast, cardiac arrest during general anesthesia occurs at a rate of 5.5 per 10,000 cases.

Bradycardia or asystole may develop suddenly (within seconds or minutes) in a patient with a previously normal or even increased heart rate, or the heart rate slowing may be progressive. Bradycardia can occur at any time during neuraxial blockade but most often occurs approximately 1 hour after anesthetic administration. The bradycardia risk is independent of whether they have received sedative or hypnotic drugs. This risk of bradycardia extends into the postoperative period after the sensory and motor blockade receded. Oxygen saturation is usually normal before the onset of bradycardia. Approximately half of patients who experience cardiac arrest around the time of neuraxial anesthesia complain of shortness of breath, nausea, restlessness, lightheadedness, or tingling of the fingers and manifest deterioration in mental status before the arrest.

Bradydysrhythmias associated with spinal or epidural anesthesia should be treated aggressively. Bradycardia can occur despite prophylactic therapy with atropine and/or IV fluids. Recalcitrant bradycardia necessitates transcutaneous or transvenous pacing. Secondary factors such as hypovolemia, opioid administration, sedation, hypercarbia, concurrent medical illnesses, and long-term use of medications that slow the heart rate can contribute to the development of bradycardia. In the clinical setting of severe bradycardia, preparation should be made for management of asystole, which is treated with CPR. Pharmacologic management should follow ACLS protocols and include treatment with atropine and epinephrine as appropriate.

The exact mechanism responsible for this phenomenon of bradycardia and asystole during spinal and epidural anesthesia is not known. One proposed mechanism is termed the *Bezold-Jarisch response*. This is a paradoxic reflex-induced bradycardia resulting from decreased venous return and activation of vagal reflex arcs mediated by baroreceptors and stretch receptors. Another possible mechanism is the unopposed parasympathetic nervous system activity that results from the anesthetic-induced sympathectomy. This sympathectomy may include blockade of T_1 to T_4 cardiac accelerator fibers originating from thoracic sympathetic ganglia. This blockade alters the balance of autonomic nervous system input to the heart and leads to relatively unopposed parasympathetic influences on the SA node and AV node causing the decrease in heart rate.

Junctional Rhythm

Junctional or nodal rhythms occur when the tissue around the AV node becomes the dominant pacemaker of the heart. It is often an escape rhythm because of depressed sinus node function, SA node block, or delayed conduction in the AV node. Junctional pacemakers usually generate a rhythm with a rate of 40 to 60 bpm. Junctional rhythms have variable relationship with a P wave. It may appear absent (buried within the QRS complex), the P wave may precede the QRS complex (with a shortened PR interval), or it may follow the QRS complex. Junctional rhythms are not uncommon during general anesthesia using halogenated vapor anesthetics and, in this setting, require no treatment. Junctional rhythm can be associated with many different disorders. Myocarditis, myocardial ischemia, or digitalis toxicity can all increase automaticity of junctional tissue. Even in the setting of acute MI, junctional rhythms are usually considered benign and require no treatment. Certain patients will have myocardial ischemia, heart failure, or hypotension during junctional rhythm and may require vasopressor support. Atropine at a dose of 0.5 mg IV (repeatable every 3-5 minutes up to a total dose of 3 mg) can be used to treat a slow junctional rhythm if it becomes hemodynamically significant.

If the junctional rhythm has an accelerated rate, it is called a junctional tachycardia or accelerated nodal (junctional)

rhythm. Junctional tachycardia is a narrow-complex tachycardia at a rate usually less than 120 bpm. Junctional rhythms can cause AV dyssynchrony and loss of atrial kick, resulting in symptoms such as fatigue, generalized weakness, angina pectoris, impaired cardiac output, CHF, pulmonary edema, and hypotension.

TREATMENT OF CARDIAC DYSRHYTHMIAS

Antidysrhythmic Drugs

The first line of defense in treating dysrhythmias should be avoidance of drugs or clinical events known to exacerbate the arrhythmia. The majority of antidysrhythmic drugs work by one of three mechanisms: (1) suppressing automaticity in pacemaker cells by decreasing the slope of phase 4 depolarization, (2) prolonging the effective refractory period to eliminate reentry circuits, or (3) facilitating impulse conduction along normal conduction pathways to prevent conduction over a reentrant pathway. Some antidysrhythmic drugs increased PR interval or prolong QRS duration on the ECG. This is the reason why a baseline ECG to document ECG intervals prior to initiating antidysrhythmic drug therapy is particularly important.

Adenosine

Adenosine is a nucleoside and the drug of choice for pharmacologic termination of AVNRT and AV reentry tachycardia (AVRT). It slows the SA and AV nodal conduction and can interrupt the reentry circuit that requires AV nodal conduction. Adenosine has an extremely short half-life (< 5 s) owing to rapid active transport of the drug into red blood cells and endothelial cells, where it is metabolized.

The dose used peripherally is adenosine 6 mg injected rapidly over 1 to 2 seconds and flushed quickly through the IV tubing with saline. If the initial dose is not effective a second dose of 12 mg can be given. Peripheral dosing beyond 12 mg is not recommended. If a central line is being used, a reduced dose of 3 mg can be effective. Several drugs influence the clinical effectiveness of adenosine. Caffeine and theophylline antagonize the actions of adenosine, while dipyridamole and carbamazepine increase the potency of adenosine. Heart transplant patients are uniquely sensitive to adenosine. A transplanted sinus node demonstrates a three- to fourfold increased response to adenosine, and the duration of sinus node slowing in the denervated atria is three- to fivefold longer than a normal patient. Administration of adenosine is contraindicated in patients with sick sinus syndrome and second- or third-degree heart block unless the patient has a functioning cardiac pacemaker.

Common side effects of adenosine in the awake patient include facial flushing, dyspnea, and chest pressure. Generally these effects are transient, lasting less than 60 seconds. Less common side effects include nausea, lightheadedness, headache, sweating, palpitations, hypotension, and blurred vision.

Atropine

Atropine sulfate is a vagolytic drug that is a competitive antagonist at muscarinic cholinergic receptor sites. It is used to increase heart rate and blood pressure. Potential adverse side effects of atropine administration include tachycardia, sedation (especially in the elderly), urinary retention, and increased intraocular pressure in patients with closed-angle glaucoma.

Atropine is recommended in the treatment of symptomatic bradycardia as a temporizing measure while awaiting initiation of transcutaneous or transvenous pacing. The recommended dose is 0.5 mg IV every 3 to 5 minutes as needed to a maximum total dose of 3 mg. Doses of less than 0.5 mg in adults can worsen bradycardia. Heart rate effects appear within seconds of administration and last 15 to 30 minutes. Atropine is not effective in patients who have undergone cardiac transplantation.

Amiodarone

Amiodarone is a class 3 antidysrhythmic structurally similar to thyroxine and procainamide. It acts on sodium, potassium, and calcium channels to produce ⊥- and ⊥-blocking effects that result in prolongation of the refractory period in myocardial cells. Amiodarone is useful in controlling ventricular rate in patients with atrial fibrillation. It is also indicated for treatment of ventricular fibrillation and pulseless ventricular tachycardia unresponsive to defibrillation, CPR, and vasopressors. In this situation, amiodarone improves the likelihood of successful defibrillation. The dose recommended for cardiac arrest unresponsive to CPR, defibrillation, and vasopressor therapy is an initial dose of 300 mg IV. It can be followed by a second dose of 150 mg IV.

Amiodarone is metabolized in the liver and slows the metabolism and increases the blood levels of other drugs metabolized by the liver, such as warfarin, digoxin, diltiazem, quinidine, procainamide, disopyramide, and propafenone.

⊐-adrenergic Blockers

⊐ blockers counteract the effects of circulating catecholamines and decrease heart rate and blood pressure. These cardioprotective effects are particularly important in patients with acute coronary syndromes. ⊓ blockers are indicated in patients with preserved left ventricular function who require ventricular rate control in atrial fibrillation, atrial flutter, and narrow-complex tachycardias originating at or above the AV node.

Side effects of ⊓ blockade include bradycardia, AV conduction delays, and hypotension. Contraindications to ⊢blocker therapy include second- or third-degree heart block, hypotension, severe CHF, and reactive airway disease. ⊥blockers should not be used in the treatment of atrial fibrillation or flutter associated with WPW syndrome since either may decrease conduction through the AV node and speed conduction through the accessory bypass tract, resulting in an increased ventricular response.

Calcium Channel Blockers

Calcium channel blockers (e.g., verapamil, diltiazem) inhibit the influx of extracellular calcium across myocardial and vascular smooth muscle cell membranes. They inhibit vascular smooth muscle contraction and cause vasodilation in coronary and other

peripheral vascular beds. Calcium channel blockers are contraindicated in patients with an accessory bypass tract, such as those with WPW syndrome since they can accelerate conduction through the accessory tract and thereby increase the ventricular rate to dangerously high levels. Calcium channel blockers have negative inotropic properties and should be avoided in patients with left ventricular dysfunction. If they are administered to patients already receiving □ blockers, additive effects can result in iatrogenic second- or third-degree heart block.

Verapamil is indicated for the treatment of narrow-complex tachycardia (i.e., SVT) in patients in whom vagal maneuvers and adenosine therapy have failed. It is also indicated for ventricular rate control with atrial flutter or fibrillation. Verapamil slows conduction and increases the refractoriness of the AV node and is useful in controlling ventricular rate in patients with atrial tachydysrhythmias and in terminating reentrant dysrhythmias. Diltiazem has a similar mechanism of action and similar clinical indications as verapamil. However, diltiazem has less negative inotropic effect and causes less peripheral vasodilation than verapamil. The degree of AV node inhibition is similar for both drugs.

Verapamil can prolong the PR interval and is not effective in treating tachycardias originating below the AV node. The initial dose of verapamil is typically 2.5 to 5 mg IV over 2 minutes. This can be repeated if needed to a maximum total dose of 0.15 mg/kg. Hemodynamic effects peak in 5 minutes and persist for 20 to 30 minutes. The recommended dose for diltiazem is 0.25 mg/kg IV over 2 minutes. This can be repeated if needed. Successful dysrhythmia treatment can be followed by a maintenance infusion at 5 to 15 mg/h.

Digoxin

Digoxin is a cardiac glycoside used for the treatment of CHF and atrial fibrillation. Digoxin inhibits the myocardial cell membrane Na -K ATPase pump. Useful pharmacologic effects include positive inotropy, slowing of conduction through the AV node, and lengthening of the refractory period of the AV node.

The inotropic effects of digoxin are due to an increase in intracellular calcium that allows for greater activation of contractile proteins. In addition to having positive inotropic effects, digoxin also increases phase 4 depolarization and shortens the action potential. This decreases conduction velocity through the AV node and prolongs the AV nodal refractory period.

Digoxin is effective in controlling the ventricular rate in AF, although it does not convert AF to sinus rhythm. Onset of therapeutic effect after IV administration of digoxin occurs in 5 to 30 minutes, with the peak effect at 2 to 6 hours after injection. Digoxin has a narrow therapeutic index, especially in the presence of hypokalemia.

High serum digoxin levels can cause a variety of symptoms and signs, including life-threatening dysrhythmias. Coexisting disease states that can contribute to digitalis toxicity include hypothyroidism, hypokalemia, and renal dysfunction. A digoxin-specific antibody is available for treatment of significant digitalis toxicity.

Vasopressin

Vasopressin is a potent peripheral vasoconstrictor that works independently of _- or _-adrenergic mechanisms. It is an endogenous antidiuretic hormone that in high concentrations produces direct peripheral vasoconstriction by activating smooth muscle vasopressin (V_1) receptors. Prior ACLS guidelines listed epinephrine and vasopressin as recommended interchangeably to treat cardiac arrest. However, the most recent ACLS guidelines no longer support the use of vasopressin in cardiac arrest. However, vasopressin therapy may be useful in maintaining systemic vascular resistance in patients who have severe sepsis or acidosis or have undergone cardiopulmonary bypass when other drug treatments have failed.

Dopamine

Dopamine is a precursor to the catecholamines norepinephrine and epinephrine and is present in nerve terminals and the adrenal medulla. It has direct dose-related effects on _, _, and dopaminergic receptors. At low doses (3–5 _g/kg/min), dopamine increases renal, mesenteric, coronary, and cerebral blood flow through the activation of dopaminergic receptors. At moderate doses (5–7 Lg/kg/min), L effects predominate, producing an increase in heart rate, contractility, and cardiac output with a decrease in systemic vascular resistance. At high doses (□ 10 □g/kg/min), □-receptor stimulation causes peripheral vasoconstriction and a reduction in renal blood flow.

Dopamine is a second-line drug for the treatment of symptomatic bradycardia unresponsive to atropine. In this clinical scenario it should be considered a temporizing measure while awaiting initiation of transcutaneous or transvenous pacing. The dose is 2 to 20 lg/kg/min titrated to the heart rate response. Caution must be exercised if infusion is through a peripheral IV line because skin necrosis can result from extravasation at the injection site.

Epinephrine

Epinephrine is a catecholamine produced by the adrenal medulla. Epinephrine is a potent mast cell stabilizer and bronchodilator and is useful in the treatment of severe bronchospasm and anaphylactic reactions. It is also a potent inotrope, chronotrope, and vasopressor. Increased contractility and heart rate occur at all dosages, but the effect on systemic vascular resistance is dose dependent. At low dosages (10–100 ¯g/min) the systemic vascular resistance may decrease or stay the same, but at high dosages (Γ 100 ¯g/min) the systemic vascular resistance increases.

Epinephrine is indicated in the treatment of cardiac arrest because of its -adrenergic vasoconstrictor properties. The effects of epinephrine can be beneficial during CPR by increasing coronary and cerebral perfusion. There is a higher likelihood of return to spontaneous circulation in patients treated with epinephrine during cardiac arrest from ventricular fibrillation, pulseless electrical activity, or asystole. The suggested dose is 1 mg IV every 3 to 5 minutes during adult cardiac arrest. Occasionally, larger doses may be needed to treat cardiac arrest resulting from □-blocker or calcium channel blocker overdose. Epinephrine is a second-line drug in the treatment of symptomatic bradycardia unresponsive to

atropine. The recommended dosage is an infusion of 2 to 10 ¯g/min titrated to heart rate response. Like atropine, it should be considered a temporizing measure while awaiting initiation of transcutaneous or transvenous pacing.

Epinephrine should be given through central venous catheters if at all possible because extravasation from a peripheral IV line can cause tissue necrosis. Epinephrine can also be administered by the intratracheal route. The dose for intratracheal use is 2 to 2.5 mg diluted in 5 to 10 mL of sterile water (which provides better drug absorption than saline). Other drugs that may be given intratracheally include lidocaine, atropine, naloxone, and vasopressin.

Isoproterenol

Isoproterenol is a potent bronchodilator and sympathomimetic structurally similar to epinephrine. Functionally it has potent ¬$_1$ and ¬$_2$ agonist actions but lacks any ¯-adrenergic properties. The actions of isoproterenol are mediated intracellularly by cAMP. Stimulation of $_1$ receptors produces positive inotropic and chronotropic effects. Isoproterenol increases myocardial excitability and automaticity, which potentially favors dysrhythmias.

Isoproterenol administration causes the systolic blood pressure to increase and the diastolic blood pressure to decrease. This is attributed to drug-induced peripheral vasodilation. This vasodilatory effect does increase coronary blood flow, but the increased oxygen demand resulting from a higher heart rate outweighs the potential benefit of any increase in myocardial blood flow. Isoproterenol is a second-line drug in the treatment of symptomatic bradycardia unresponsive to atropine. The recommended dosage is 2 to 10 ¬g/min by continuous infusion titrated to heart rate effect. Because of its direct action on ¬ receptors, isoproterenol is useful to treat symptomatic bradycardia in heart transplant recipients. An initial IV dosage of 1 g/min is titrated slowly upward until the desired effect is achieved.

Lidocaine

Lidocaine is an amide local anesthetic commonly employed in regional anesthetic nerve blockade. However, the same sodium channel blocking effects that make it a good local anesthetic also make it a useful antidysrhythmic drug when administered intravenously. Lidocaine may be used in the treatment of cardiac arrest associated with ventricular fibrillation or pulseless ventricular fibrillation if amiodarone is not available. The recommended dose is 1 to 1.5 mg/kg IV. If ventricular fibrillation or pulseless ventricular tachycardia persists, half this dose can be repeated at 5- to 10-minute intervals to a maximum total dose of 3 mg/kg. Lidocaine is rapidly redistributed out of the plasma and myocardium, so multiple loading doses may be needed to achieve therapeutic blood levels. Clinical duration of action is 15 to 30 minutes after a loading dose. To sustain therapeutic effect, lidocaine must be administered by continuous infusion. The recommended infusion dose is 1 to 4 mg/min.

Lidocaine undergoes extensive first-pass hepatic metabolism, so clinical conditions that result in decreased hepatic blood flow (e.g., general anesthesia, CHF, liver disease, advanced age) can result in higher-than-normal blood levels. Certain drugs such as cimetidine can also cause an increase in the plasma concentration of lidocaine.

Therapeutic doses of lidocaine have minimal negative inotropic effects. When administered in combination with other antidysrhythmic drugs, lidocaine can cause some myocardial depression or sinus node dysfunction. During lidocaine therapy, monitoring of mental status is desirable because the first signs of lidocaine toxicity are usually central nervous system symptoms such as tinnitus, drowsiness, dysarthria, or confusion. At higher blood levels, signs of central nervous system depression such as sedation and respiratory depression predominate and may be accompanied by seizures.

Magnesium

Magnesium functions in the body as a cofactor in the control of sodium and potassium transport. The use of magnesium sulfate to treat polymorphic ventricular tachycardia associated with QT prolongation (TdP) is considered an off-label use. There are a few observational studies supporting the use of magnesium in the termination of TdP ventricular tachycardia associated with QT prolongation, and there is no evidence that magnesium is effective in treating ventricular tachycardia associated with a normal QT interval. In ventricular fibrillation or pulseless ventricular tachycardia associated with TdP, magnesium can be given in a dose of 1 to 2 g over 5 minutes. If a pulse is present, the same dose can be administered but more slowly. It may be followed by a continuous infusion of 0.5 to 1 g/hr.

Procainamide

Procainamide is an antidysrhythmic drug that slows conduction, decreases automaticity, and increases the refractoriness of myocardial cells. It can be used in patients with preserved ventricular function to treat the following conditions: VT with a pulse, atrial flutter or fibrillation, atrial fibrillation in WPW syndrome, and SVT resistant to adenosine and vagal maneuvers.

Procainamide can be administered at a rate of 50 mg/min IV until the dysrhythmia is suppressed, significant hypotension occurs, or the duration of the QRS complex is prolonged by 50%. The duration of action after a bolus dose is 2 to 4 hours. Procainamide must be used with caution in patients with QT prolongation and in combination with other drugs that prolong the QT interval. To maintain therapeutic effect, procainamide can be given as a maintenance infusion at a rate of 1 to 4 mg/min. Dosage should be reduced in renal failure.

Sotalol

Sotalol is a nonselective blocker. It prolongs the duration of the action potential and increases the refractoriness of cardiac cells. Sotalol can be used in the treatment of ventricular tachycardia and atrial fibrillation or flutter in patients with WPW syndrome. The dose is 1.5 mg/kg IV over 5 minutes. Potential side effects include bradycardia, hypotension, and QT prolongation.

Twenty Percent Lipid Emulsion

Infusion of 20% lipid emulsion is used in the clinical scenario of bupivacaine or other local anesthetic overdose. The first reported case of its use in an adult human to successfully treat a

bupivacaine-related cardiac arrest was in 2006. Since then, with accumulation of more data and experience, so-called lipid rescue has become a widely accepted treatment. The overall incidence of LAST (defined as occurrence of cardiac arrest, seizure, and/or administration of lipid emulsion on the day of surgery) was 1.8 per 1000. The suggested initial dose is 1.5 mL/kg over 1 minute while chest compressions and related ACLS maneuvers are continued. The dose can be repeated every 3 to 5 minutes to a maximum of 12 mL/kg. After conversion to sinus rhythm, a maintenance infusion of 0.25 mL/kg/min is suggested until hemodynamic recovery occurs.

Transcutaneous Pacing

Transcutaneous pacing is an effective temporizing measure to treat bradydysrhythmias until a transvenous pacemaker can be placed or a more permanent mode of cardiac pacing can be implemented. If transcutaneous pacing is needed, pacer/defibrillator electrodes are placed on the chest and back, and electrical impulses are delivered through the chest wall to pace the heart. The device is impractical for long-term use because of the high current required, the skin irritation caused by the delivery pads, and significant patient discomfort during pacing.

Electrical Cardioversion

Electrical cardioversion is the delivery of an electrical discharge synchronized to the R wave of the ECG. The purpose of cardioversion is to reset the electrical pathways of the heart by delivering a single overriding burst of electricity on the R wave of the ECG. The cardioversion is coordinated with the R wave on the ECG so that the stimulus is not delivered during the relative refractory period during the T wave. This is to avoid R-on-T phenomenon, which can produce ventricular tachycardia or fibrillation. The electrical discharge or shock is transmitted through two chest electrodes configured as handheld paddles or adhesive pads on the chest in the anterior and apical positions or in the anterior and posterior positions.

Synchronized cardioversion is used to treat acute unstable SVTs such as PSVT, atrial flutter, and atrial fibrillation and to convert chronic stable rate-controlled atrial flutter or fibrillation to sinus rhythm. Cardioversion can also be used to treat monomorphic ventricular tachycardia with a pulse. Cardioversion is only useful if there is an R wave on ECG to synchronize the shock. Without an organized rhythm and therefore no R wave, defibrillation (unsynchronized shock) is necessary to depolarize the entire myocardium at once in the hope that a normal pacemaker will take over and restore a functional rhythm.

Digitalis-induced dysrhythmias are refractory to cardioversion, and attempts at cardioversion in this situation could trigger more serious ventricular dysrhythmias. Digitalis-induced dysrhythmias should be treated by correction of acid-base status and electrolyte abnormalities, and administration of digitalis-binding antibody if needed.

Defibrillation

In contrast to cardioversion, electrical defibrillation is a nonsynchronized shock used to correct dysrhythmias with no R wave (defined QRS complex). The single most important factor determining survival after cardiac arrest due to ventricular fibrillation is the time between arrest and the first defibrillation attempt. In witnessed cardiac arrest due to ventricular fibrillation, patients who undergo defibrillation within the first 3 minutes have a survival rate of 74%.

Modern defibrillators are classified according to the type of waveform delivered and may be monophasic or biphasic. The first-generation defibrillators were monophasic. Most modern defibrillators are biphasic devices. Neither type of defibrillator has been shown to be more successful in terminating pulseless rhythms or improving survival. A current dose of 360 J is indicated for transthoracic defibrillation using a monophasic defibrillator. Biphasic defibrillators deliver lower currents (120–200 J) than monophasic devices. The optimal energy dose delivered by a biphasic defibrillator is not standardized; the manufacturer of each device has suggestions specific to its equipment. In the absence of a generally recommended dose, 200 J should be used.

The electric current delivered encounters some increase in impedance from air spaces within the lung tissue in the current path. Therefore the defibrillator current should be delivered when the lungs are deflated (i.e., during exhalation) if possible.

The position of the paddles or pads is the same as for cardioversion. Defibrillation-cardioversion electrodes should not be placed directly over pacemakers or ICD pulse generators. Delivery of a high current near a pacemaker or ICD can cause the device to malfunction and can block and/or divert the current path and result in suboptimal current delivery to the myocardium. All permanently implanted cardiac devices should be evaluated after defibrillation or cardioversion to ensure proper function.

Radiofrequency Catheter Ablation

Radiofrequency catheter ablation refers to a procedure in which an intracardiac electrode catheter is inserted percutaneously under local anesthesia through a large vein (femoral, subclavian, internal jugular, or cephalic). This electrode is then used to produce small, well-demarcated areas of thermal injury that destroy the myocardial tissue responsible for initiation or maintenance of dysrhythmias. Cardiac dysrhythmias amenable to radiofrequency catheter ablation include reentrant supraventricular dysrhythmias and some ventricular dysrhythmias. Radiofrequency catheter ablation is usually considered after pharmacologic therapy has failed or has not been well tolerated. The procedure is typically performed under conscious sedation with routine monitoring.

CARDIAC IMPLANTED ELECTRONIC DEVICES

CIEDs are implanted cardiac rhythm management devices. CIEDs include permanent pacemakers, ICDs, and cardiac resynchronization devices. Although not specified in the name, all ICDs include pacing and shock therapies for the management of bradydysrhythmia and tachydysrhythmia.

All implanted cardiac devices are designed to detect and respond to low-amplitude electrical signals. Extraneous signals

(i.e., EMI) produced by external electric or magnetic fields can influence the function of CIEDs. There are no known CIED concerns involving exposure to plain x-rays, ultrasonography, fluoroscopy, mammography, or ECT. However, there are reports of EMI associated with electrocautery, radiofrequency ablation, MRI, radiation therapy, and lithotripsy.

EMI can be any strong external electrical or magnetic force in close proximity to a CIED. EMI signals enter device circuits primarily through the leads. Unipolar systems are more prone to EMI because there is a larger separation between the positive and negative poles. In a bipolar lead system there are two separate electrodes (positive and negative) in the same chamber in very close proximity to each other, so the distance the current travels to complete the circuit is very small, and hence there is very little chance that extraneous signals will intrude into or affect the lead circuit (Fig. 8.9).

Other factors influencing the susceptibility of a device to EMI include field strength, patient body mass, and the proximity and orientation of the implanted electronic device to the EMI field. Potential effects of EMI depend on the pacing mode and the lead(s) involved but range from cessation of pacing to inappropriate triggering of pacemaker activity. Improved shielding of pacemakers and use of mostly bipolar lead systems has eliminated many problems related to EMI.

Permanently Implanted Cardiac Pacemakers

Bradycardia associated with symptoms such as syncope, dizziness, and chest pain; inability to increase the heart rate adequately during exercise; or a heart rate of less than 40 bpm in the absence of physical conditioning or sleep is considered abnormal. The prevalence of sinus node dysfunction may be as high as 1 in 600 patients older than 65 years. Many patients with sick sinus syndrome are asymptomatic; others experience syncope or palpitations. Episodes of SVT may be interspersed with periods of bradycardia. This accounts for another common name for sinus node dysfunction: tachycardia-bradycardia (tachy-brady) syndrome. In patients with ischemic heart disease, periods of bradycardia may contribute to the development of CHF, whereas periods of tachycardia can contribute to the development of hypertension and angina pectoris. The rate of progression to second- or third-degree AV block in patients with sick sinus syndrome is approximately 1% to 5% per year. Sick sinus syndrome with symptomatic bradycardia is the most common reason for insertion of a permanent cardiac pacemaker.

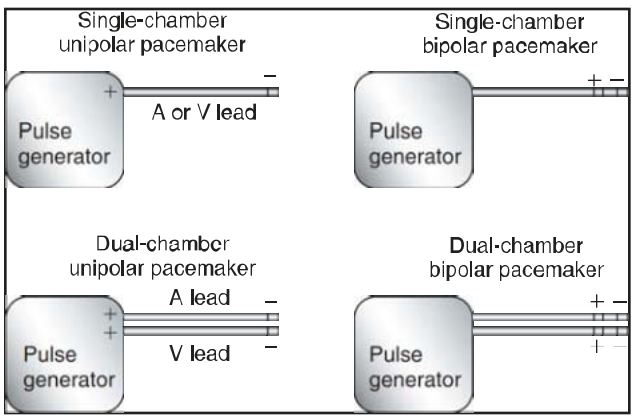

Fig. 8.9 Unipolar and bipolar lead systems. *A*, Atrial; *V*, ventricular. (From Stone ME, Apinis A. Current perioperative management of the patient with a cardiac rhythm management device. *Semin Cardiothorac Vasc Anesth.* 2009;13:32.)

Permanently implanted cardiac pacemakers are CIEDs composed of a pulse generator, one or more sensing and pacing electrodes (usually located in the right atrium and right ventricle), and a battery power source. Electrical impulses originating in the pulse generator are transmitted through specialized leads to excite endocardial cells and produce a propagating wave of depolarization in the myocardium. The pulse generator is powered by a small lithium-iodide battery. The lithium-iodide batteries used in pulse generators can last up to 10 years, but battery depletion requires surgical replacement of the entire pulse generator. The pulse generator for endocardial leads is usually implanted in a subcutaneous pocket below the clavicle.

Endocardial leads can be unipolar or bipolar. In a unipolar pacing system there is one electrode that is an active lead. Current flows from the negative pole (active lead) to stimulate the heart and then returns to the positive pole (the casing of the pulse generator). The current returns to the positive pole by traveling through myocardium to complete the circuit.

Pacing Modes

A five-letter generic code is used to describe the various characteristics of cardiac pacemakers. The first letter denotes the cardiac chamber(s) being paced (*A*, atrium; *V*, ventricle; *D*, dual chamber). The second letter denotes the cardiac chamber(s) in which electrical activity is being sensed or detected (*O*, none; *A*, atrium; *V*, ventricle; *D*, dual). The third letter indicates the response to sensed signals (*O*, none; *I*, inhibition; *T*, triggering; *D*, dual—inhibition and triggering). The fourth letter, *R*, denotes activation of rate response features, and the fifth position denotes the chamber(s) in which multisite pacing is delivered. The most common pacing modes are AAI, VVI, and DDD.

Asynchronous pacing. Asynchronous pacing is the simplest form of pacing. It can be AOO, VOO, or DOO. In this mode, the lead(s) fire at a fixed rate regardless of the patient's underlying rhythm. This pacing mode can be used safely in patients with no intrinsic ventricular activity because there is no risk of the R-on-T phenomenon. Asynchronous pacing could compete with a patient's intrinsic rhythm, and the continuous pacing activity decreases battery life and necessitates more frequent battery/pulse generator replacement.

Single-chamber pacing. The choice of pacing mode depends on the primary indication for the artificial pacemaker. Single-chamber pacemakers can be atrial or ventricular. If the patient has SA node disease and no evidence of disease in the AV node or bundle of His, an atrial pacemaker (AAI) can be placed. Use of atrial pacing modes requires a functioning AV node, and then AAI pacing can maintain AV synchrony. However, it has been estimated that approximately 8% of patients with SA node dysfunction will progress to AV node dysfunction within 3 years.

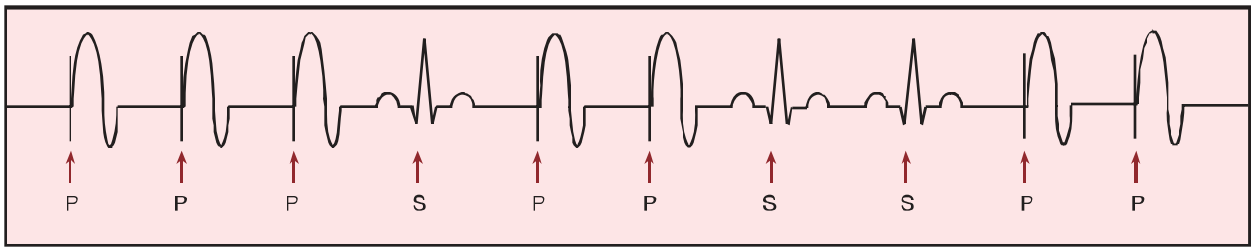

Fig. 8.10 Electrocardiogram (ECG) evidence of pacemaker function with a VVI (ventricular pacing, ventricular sensing, inhibition) pacemaker. *P*, Paced beat; *S*, sensed beat. (From Aller M. Pacemakers and implantable cardioverter defibrillators. *Anaesthesia* 2006;61:885.)

Individuals experiencing episodes of symptomatic bradycardia caused by SA node or AV node disease may benefit from placement of a single-chamber ventricular (VVI) pacemaker. This mode of pacing senses the native R wave, and if it is present, pacemaker discharge is inhibited (Fig. 8.10). It is often used in patients with complete heart block with chronic atrial flutter or fibrillation and in patients with long ventricular pauses. A factor to consider in the patient with a single-chamber ventricular pacemaker is the potential for pacemaker syndrome.

Pacemaker syndrome is a constellation of symptoms caused by the loss of AV synchrony. Symptoms include syncope, weakness, lethargy, cough, orthopnea, paroxysmal nocturnal dyspnea, hypotension, and pulmonary edema. DDD pacing can be used to alleviate symptoms of pacemaker syndrome by restoring AV synchrony.

Dual-chamber pacing. Cardiac pacing is the only long-term treatment for symptomatic bradycardia, regardless of cause. Disease of the AV node or His bundle, or ongoing drug treatment to slow AV nodal conduction, requires a dual-chamber (DDD or DDI) system. Disorders such as neurogenic syncope (resulting from carotid sinus hypersensitivity), vasovagal syncope, and hypertrophic cardiomyopathy can also be successfully treated with a dual-chamber pacemaker.

Dual-chamber pacing is also known as physiologic pacing because it maintains AV synchrony. This improves cardiac output by maintaining the contribution of atrial systole to ventricular filling. AV synchrony also maintains appropriate valve closure timing, which reduces the risk of significant mitral and/or tricuspid insufficiency. Several studies suggest that patients receiving dual-chamber pacing have a decreased risk of atrial fibrillation and heart failure.

DDD pacing. Dual-chamber pacemakers have two leads, one placed in the right atrium and one located in the right ventricle. DDD pacing is based on electrical feedback from the leads in the atrium and ventricle. If a native atrial signal is sensed, the atrial pacemaker output is inhibited, and if no intrinsic atrial signal is sensed, the pacemaker output is triggered. Likewise, if intrinsic ventricular activity is sensed at the end of a programmable AV interval, the intrinsic ventricular activity inhibits pacemaker output. If intrinsic ventricular activity is not sensed, the pacemaker triggers a spike (Fig. 8.11). The DDD pacing mode permits the pacemaker to respond to increases in sinus node discharge rate, such as occurs during exercise.

Programming the dual-chamber leads to have an adjustable AV interval provides an important benefit in maintaining AV synchrony over a wide range of heart rates. Loss of AV synchrony has many deleterious effects, including reducing cardiac output by 20% to 30% or more, increasing atrial pressure resulting from contraction of the atria against closed mitral and tricuspid valves, and activation of baroreceptors that may induce reflex peripheral vasodilation.

DDI pacing. In the DDI pacing mode there is sensing in both the atrium and ventricle, but the only response to a sensed event is inhibition (inhibited pacing of the atrium and ventricle). DDI pacing is useful when there are frequent atrial tachydysrhythmias that might be inappropriately tracked by a DDD pacemaker and result in rapid ventricular rates.

Rate-Adaptive Pacemakers

Rate-adaptive pacing is considered for patients who do not have an appropriate heart rate response to exercise (i.e., chronotropic incompetence). This syndrome can be caused by drug treatment with negative chronotropic drugs such as β blockers or calcium channel blockers or by pathologic processes such as sick sinus syndrome.

Normally, AV synchrony contributes more to cardiac output at rest and at low levels of exercise, whereas rate adaptation (i.e., a higher heart rate) is more important at higher levels of exercise. Sensors within rate-adaptive pacemakers detect changes in movement (using a piezoelectric crystal) or minute ventilation (by transthoracic impedance) as physical or physiologic signs of exercise. In response, the device makes rate adjustments to mimic the response of a normal sinus node.

Anesthesia for Cardiac Pacemaker Insertion

Most pacemakers are inserted under conscious sedation in the cardiac catheterization laboratory or under monitored anesthesia care in the operating room. Routine anesthetic monitoring is employed. A functioning cardiac pacemaker should be in place or transcutaneous cardiac pacing available before administration of anesthetic drugs. Drugs such as atropine and isoproterenol should be available should a decrease in heart rate compromise hemodynamics before the new pacemaker is functional (Table 8.4).

The incidence of complications related to pacemaker insertion is approximately 5%. An artificial cardiac pacemaker can be inserted intravenously using endocardial leads or via a subcostal incision or median sternotomy (after cardiac surgery) using epicardial or myocardial leads. Early complications are often associated with the venous access and/or surgical access necessary to place the leads. Perioperative

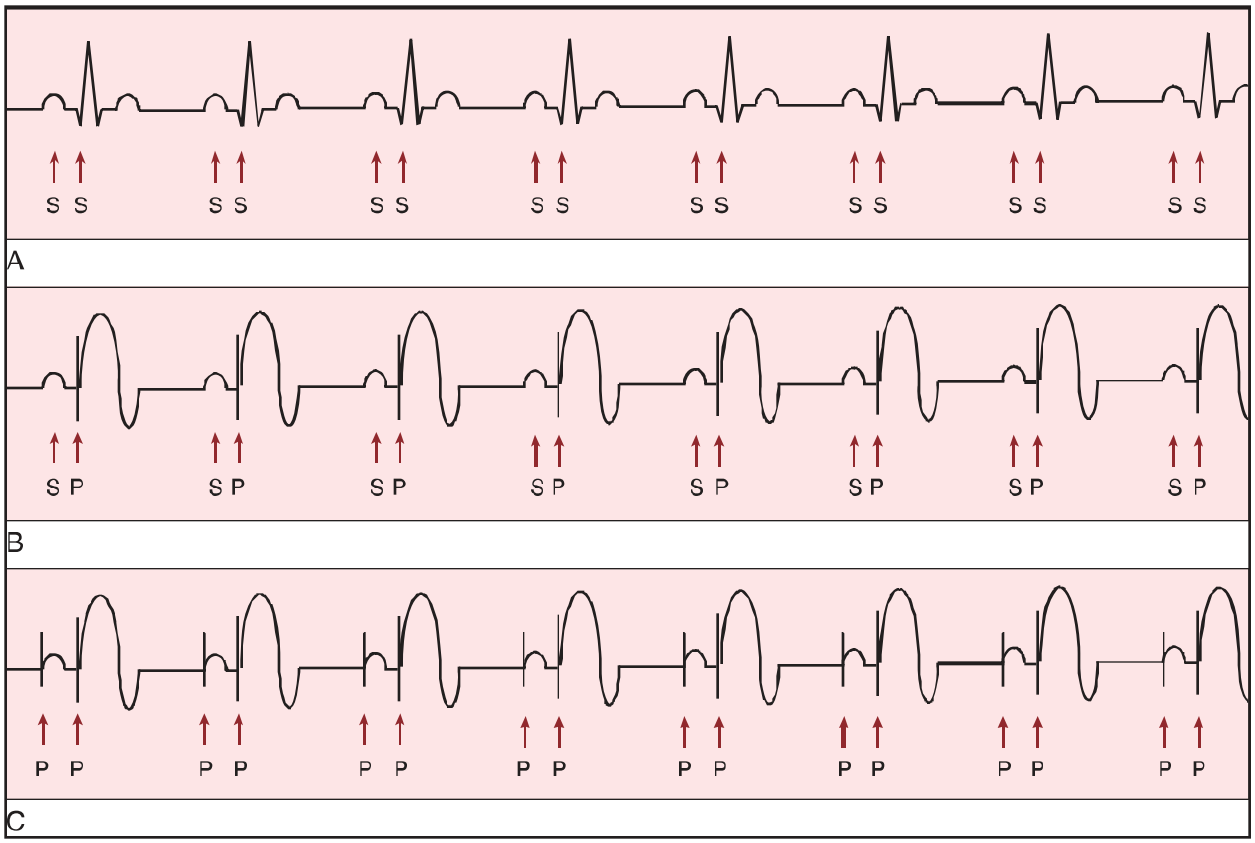

Fig. 8.11 Electrocardiogram (ECG) evidence of pacemaker function with a DDD (dual pacing, dual sensing, inhibition and triggering) pacemaker. (A) Patient has intrinsic atrial and ventricular activity that is sensed by the pacemaker. (B) Patient has intrinsic activity that is not conducted to the ventricle, so the pacemaker senses the atrial activity and paces the ventricle. (C) Patient has no atrial or ventricular activity sensed by the pacemaker, so the pacemaker paces both the atrium and the ventricle. *P*, Paced beat; *S*, sensed beat. (From Allen M. Pacemakers and implantable cardioverter defibrillators. *Anaesthesia* 2006;61:886.)

TABLE 8.4 Factors That Can Alter the Depolarization Threshold of Cardiac Pacemakers

Factors Increasing the Threshold	Factors Decreasing the Threshold
Hyperkalemia	Hypokalemia
Acidosis or alkalosis	Increased catecholamine levels
Antidysrhythmic medication (e.g., quinidine, procainamide, lidocaine, propafenone)	Sympathomimetic drugs
Hypoxia	Anticholinergics
Hypoglycemia	Glucocorticoids
Local anesthetics (lidocaine)	Stress or anxiety
Myocardial ischemia	Hyperthyroidism
Myocardial infarction (scar tissue)	Hypermetabolic states
Acute inflammation around lead tip during first month after implantation	
Hypothermia	

complications include pneumothorax, hemothorax, and air embolism. Pneumothoraces are often small and asymptomatic. However, tension pneumothorax should always be considered if hypotension or pulseless electrical activity develops during or immediately after pacemaker placement. Hemothorax can result from trauma to the great vessels or other vascular structures. Arterial cannulation must be immediately recognized and treated with manual compression or arterial repair. Arterial damage can be minimized by placing a small guidewire under fluoroscopic guidance before placing the much larger introducer sheath. Variable amounts of air can be introduced into the low-pressure venous system during the procedure. Small amounts of air are generally well tolerated, but larger amounts can result in oxygen desaturation, hypotension, and cardiac arrest.

KEY POINTS

- The heart's pumping function is accomplished by the coordinated contraction of 2 to 3 billion cardiac muscle cells (myocytes) within the heart. Stimulation of the myocytes comes from electrical signals generated in specialized tracts of cardiac tissue called the myocardial conduction system. The conduction system includes the SA node, AV node, bundle of His, right and left interventricular bundles, and Purkinje fibers. The conduction system cells communicate with the myocytes by specialized ion channels such as gap junctions, sodium potassium pumps, and calcium channels.
- An intact cardiac conduction system normally ensures conduction of each sinus node impulse from the atria to the ventricles. Inherited abnormalities of the conduction system, certain drugs, iatrogenic trauma, and disease processes can disrupt normal conduction and result in heart block. The classification of conduction block is by the site of disruption and the degree of blockade.
- A variety of acute and chronic conditions can cause or contribute to heart block. Disease processes such as acute myocardial infarction (especially in the distribution of the right coronary artery), myocarditis, rheumatic fever, mononucleosis, Lyme disease, and infiltrative diseases such as sarcoidosis and amyloidosis can contribute to heart block. Iatrogenic causes of heart block include traumatic injury from monitoring or ablation catheters or cardiac surgery, and drug effects such as digitalis toxicity and excessive β blockade or calcium channel blockade.
- Any procedure with the potential to cause edema, impingement, or interruption of the tissues that surround the conduction system can precipitate periprocedural episodes of AV block. Surgeries such as aortic or mitral valve replacement, transcatheter procedures, and catheter ablations have AV block as a known risk.
- Normal, rapid conduction of the depolarization signal results in near simultaneous contraction of the left and right ventricles, which optimizes myocardial pump function. Any delays in conduction, particularly of the lateral wall of the left ventricle (as in LBBB), cause dyssynchrony between the ventricles and impaired efficiency.
- Intraventricular conduction disturbances can be due to structural changes or disease processes, acquired or inherited, effecting the ventricular myocardium. The wide range of causes includes necrosis, fibrosis, calcification, infiltrative lesions, or impaired vascular supply. These abnormalities change the shape and/or duration of the QRS complex.
- A cardiac rhythm greater than 100 bpm is considered a tachycardia. Tachydysrhythmias can be generated from sources above or below the bundle of His. Those whose mechanism involves tissue above the bundle of His are SVTs. Tachydysrhythmias originating at or above the AV node tend to have a narrow QRS complex. Tachydysrhythmias generated from below the AV node have a wide QRS complex.
- Cardiac dysrhythmias caused by enhanced automaticity result from repetitive firing of a focus other than the sinus node. Reentry pathways account for most premature beats and tachydysrhythmias. Reentry or triggered dysrhythmias require two pathways over which cardiac impulses can be conducted at different velocities. Afterdepolarizations are oscillations in membrane potential that occur during or after repolarization. Normally these membrane oscillations dissipate. However, under special circumstances they can trigger a complete depolarization. Once triggered, the process may continue and result in a self-sustaining dysrhythmia.
- Atrial fibrillation is the most common sustained cardiac dysrhythmia in the general population. In 2005 there were about 3 million Americans with the disorder. This number is expected to triple by 2050. The incidence of atrial fibrillation increases with age: It is present in 1% of individuals younger than 60 years and increases to 12% of patients aged 70 to 84 years. A third of patients with atrial fibrillation are older than 80 years.
- Ventricular fibrillation is a rapid, grossly irregular ventricular rhythm with marked variability in QRS cycle length, morphology, and amplitude. It is incompatible with life because no stroke volume is generated by this rhythm. A pulse or blood pressure never accompanies ventricular fibrillation. Ventricular tachycardia often precedes the onset of ventricular fibrillation. Ventricular fibrillation is the most common cause of sudden cardiac death.
- Bradycardia during neuraxial blockade can occur in patients of any age and any ASA physical status class, whether or not they are sedated. The incidence of profound bradycardia and cardiac arrest during neuraxial anesthesia is approximately 1.5 per 10,000 cases. By contrast, cardiac arrest during general anesthesia occurs at a rate of 5.5 per 10,000 cases.
- A patient with a preexisting CIED coming for surgery has at least one of three underlying cardiac problems: sustained or intermittent bradydysrhythmia, tachydysrhythmia, and/or heart failure. Regardless of the indication for the device, any patient with a CIED requiring anesthetic care must undergo a detailed systematic preoperative evaluation. This should include determination of the type of device present, identification of the clinical indication for the device, appraisal of the patient's degree of dependence on the device, and assessment of device function.

RESOURCES

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9

Systemic and Pulmonary Arterial Hypertension

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OUTLINE

SYSTEMIC HYPERTENSION

In 2017, the American College of Cardiology/American Heart Association (ACC/AHA) redefined hypertension as a sustained systolic blood pressure above 130 mm Hg and/or a diastolic pressure above 80 mm Hg. This new definition arose in response to the results of the Systolic Blood Pressure Intervention Trial (SPRINT), which found a significantly lower rate of fatal and nonfatal cardiovascular events in nondiabetic hypertensive patients with a systolic blood pressure target of less than 120 mm Hg, as compared to the standard goal of 140 mm Hg. This new definition qualifies over 100 million people in the United States as hypertensive, nearly one-half of all adults, occurring more frequently in non-Hispanic blacks (40.6%) than non-Hispanic whites (29.7%), non-Hispanic Asians (28.7%), and Hispanics (27.3%). The incidence of hypertension increases with age and is more prevalent in men until age 60, after which elevated blood pressure is present in a higher percentage of women than men.

Public Health Implications

Worldwide, the burden of hypertension disproportionally affects low- and middle-income countries. It is the leading risk factor for morbidity and mortality, accounting for 7% of disability-adjusted life-years and 9.4 million deaths in 2010. It has been estimated that in the United States, the lifetime risk of developing hypertension is close to 90%. The clinical consequences of chronically elevated blood pressure have been well characterized and underscore a high age-related association with ischemic heart disease and stroke (Fig. 9.1), as well as renal failure, retinopathy, peripheral vascular disease, and overall mortality. In the surgical population, multiple studies have found hypertension to be a common risk factor for perioperative morbidity and mortality, particularly with untreated or refractory hypertension. It is not clear, however, if increased blood pressure alone increases surgical risk or if normalization of blood pressure preoperatively significantly reduces these risks. Furthermore, chronic hypertension represents a dynamic spectrum spanning so-called elevated blood pressure to severe disease (Table 9.1), with risk assessment often not clearly differentiating subtypes: isolated systolic hypertension (systolic ⌝130 mm Hg and diastolic ⌜ 80 mm Hg), isolated diastolic hypertension (systolic ⌝130 mm Hg with diastolic ⌜ 80 mm Hg), and combined systolic and diastolic hypertension (systolic ⌝130 mm Hg and diastolic ⌝80 mm Hg). As noted in the Eighth Joint National Committee Report on the Treatment of Hypertension (JNC 8), age dependence, risk association, pharmacologic therapy, and treatment goals can vary among subtypes. In addition to systolic and diastolic pressure abnormalities, an increase in their difference—pulse pressure—has been shown to be a risk factor for cardiovascular morbidity. Considered to be an index of vascular remodeling and "stiffness," some studies have linked increased pulse pressure with intraoperative hemodynamic instability and adverse postoperative outcomes.

Pathophysiology

Given the physiologic importance and complexity of blood pressure regulation, hypertension can result from a wide range of primary and secondary processes that increase cardiac output,

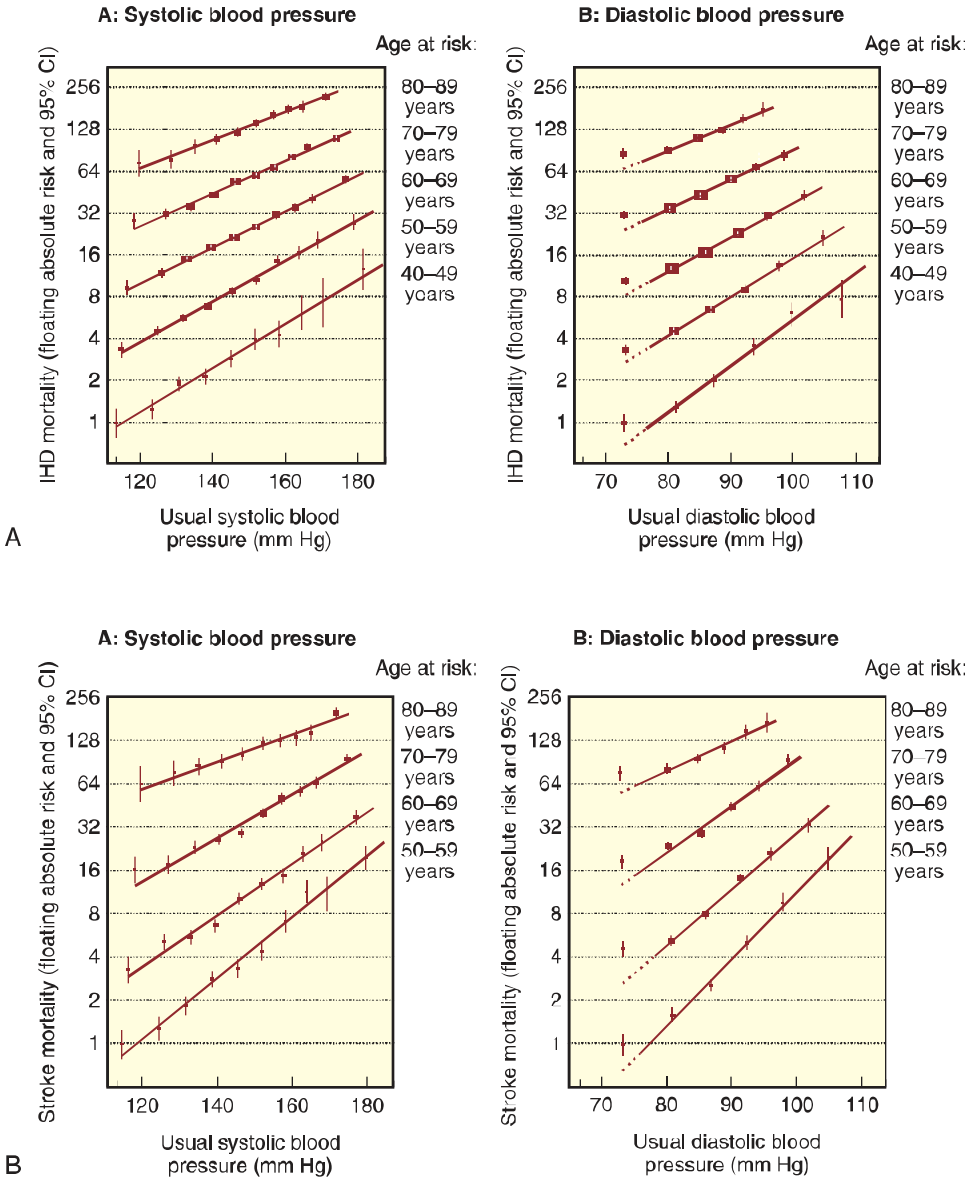

Fig. 9.1 Ischemic heart disease mortality (A) and stroke mortality (B) rates in each decade of age versus usual blood pressure at the start of that decade. Mortality rates are termed *floating* because multiplication by a constant appropriate for a particular population would allow prediction of the absolute rate in that population. *CI*, Confidence interval; *IHD*, ischemic heart disease. (Data from Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual BP to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.)

TABLE 9.1 Classification of Systemic Blood Pressure (BP) in Adults

Category	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Normal	<120	<80
Elevated	120–129	<80
Stage 1 hypertension	130–139	80–89
Stage 2 hypertension	≥140	≥90

Adapted from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018 Jun;71(6):e13–e115.

peripheral vascular resistance, or both. The etiology of primary hypertension (also referred to as essential hypertension) is unclear, but contributing factors include sympathetic nervous system activity, dysregulation of the renin-angiotensin-aldosterone system, and deficient production of endogenous vasodilators (Table 9.2). Importantly, blood pressure elevation is often coincident with other morbidities and may occur in a constellation of symptoms associated with oxidative stress and systemic inflammation. There are defined genetic and lifestyle risk factors such as obesity, alcohol consumption, and tobacco use that are associated with an increased incidence of hypertension.

A small minority of adult patients with elevated blood pressure have secondary hypertension resulting from a potentially

TABLE 9.2 Pathophysiology of Primary Hypertension

Autonomic Nervous System

Normal: Integration of input from cardiac stretch receptors, vascular baroreceptors, and peripheral chemoreceptors with central regulatory processes and emotional stress. Provides acute control of cardiac output, vascular resistance, and blood volume.

Abnormal: Hypertension associated with dysregulation of baroreflex and chemoreflex pathways both peripherally and centrally

New concepts:

- Systemic hypertension and the chronic inflammatory states lead to disruption of the blood-brain barrier and autonomic dysfunction.
- There is evidence for a novel renin-angiotensin system (RAS) within the brain.
- Activation of this pathway in response to oxidative stress and inflammation increases sympathetic nervous system output and arginine vasopressin release and inhibits baroreflex regulation.

Classical Renin-Angiotensin-Aldosterone System

Normal: Provides acute and sustained control of extracellular fluid volume, peripheral resistance, and blood pressure based largely on peripheral sensors and effectors. Renin released from the kidney in response to decreased blood pressure hydrolyzes angiotensinogen → angiotensin I that is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE) located on vascular endothelium in the lung. Angiotensin II → vasoconstriction, adrenal release of aldosterone → kidney reabsorption of salt and water.

Abnormal: Dysregulated renin release leads to elevated renin levels, angiotensin II overproduction, increased aldosterone, and hypertension.

New concepts:

- Local production of angiotensin II occurs in various tissues, including fat, blood vessels, heart, adrenals, and brain.
- AI to AII cleavage by non-ACE enzymes, including the serine protease chymase
- A recently described counterregulatory renin-angiotensin pathway that decreases blood pressure and targets organ damage
- The effect of sex hormones on angiotensin receptor activation and AII metabolism may be responsible for reduced efficacy of ACE-I in females as well as the increased incidence of hypertension in postmenopausal females.

Endogenous Vasodilator/Vasoconstrictor Balance

Normal: In response to pressure and the shear force imparted by pulsatile blood flow, the vascular endothelium produces a range of vasoactive substances, including nitric oxide and endothelin. The natriuretic peptide axis (NPA) also regulates vascular tone through the release of natriuretic peptides (NP). Atrial natriuretic peptide (ANF) and brain natriuretic peptide (BNP) are released from myocardium, C-type natriuretic peptide (CNP) from the endothelium, and urodilatin from the urothelium. These peptides exert vasodilation along with natriuresis and blunting of renin-angiotensin-aldosterone responsiveness by activation of the NP receptors. The NPs have a very short half-life and are degraded by the enzyme neprilysin.

Abnormal: With hypertension, oxidative stress in particular has been linked to impaired endothelial function, leading to "feed-forward" changes in vascular tone, vascular reactivity, and coagulation and fibrinolytic pathways. NPA disruption in heart failure patients results from the decreased release of NPs, NP receptor desensitization, and increased NP degradation through overexpression and activity of neprilysin.

New concepts:

- Angiotensin receptor neprilysin inhibition (ARNI) has been shown to be more effective at slowing progression of heart failure than standard treatment of ACE inhibition.
- A new medication for treatment of heart failure is a combination of ARNI (sacubitril) and angiotensin receptor blocker (ARB) (valsartan). This combination simultaneously promotes vasodilator effects of the NPs while reducing the vasoconstrictor/proinflammatory effects of endothelin 1 and angiotensin II.

correctable physiologic or pharmacologic cause (Table 9.3). The etiology of hypertension is age dependent. In middle-aged adults, hyperaldosteronism, thyroid dysfunction, obstructive sleep apnea, Cushing syndrome, and pheochromocytoma are the most common causes of secondary hypertension. In contrast, the majority of children with elevated blood pressures have secondary hypertension from renal parenchymal disease or coarctation of the aorta (see Table 9.3).

Regardless of the underlying cause, chronic hypertension leads to remodeling of small and large arteries, endothelial dysfunction, and potentially irreversible end-organ damage (Table 9.4). Overall, disseminated vasculopathy plays a major role in ischemic heart disease, left ventricular hypertrophy, congestive heart failure, cerebrovascular disease and stroke, peripheral vascular disease and aortic aneurysm, and nephropathy. The degree to which some abnormalities are reversible is controversial, but early and effective intervention is essential. Improved diagnostic techniques may help provide a more detailed assessment than just blood pressure alone. Ultrasonic measurement of common carotid artery intimal-medial thickness and arterial pulse-wave velocity can provide early diagnosis of vasculopathy, and echocardiographic and electrocardiographic indices may track progression of left ventricular hypertrophy. Early signs of hypertensive nephropathy have become easier to detect, and magnetic resonance imaging (MRI) can be used to follow microangiopathic changes indicative of cerebrovascular damage.

Current Treatment of Hypertension

The general therapeutic goal for hypertension treatment is a blood pressure less than 130/80 mm Hg. However, a substantial number of people with hypertension are unable to attain this goal due to nondiagnosis or misdiagnosis, minimal or adverse responses to medications, or noncompliance with prescribed treatment. In fact, approximately 28 million people in the United States alone have untreated hypertension, and a further 29 million patients on an antihypertensive medication are above their blood pressure goal. Resistant hypertension is defined as above-goal blood pressure despite three or more antihypertensive drugs of different classes given at maximally tolerated doses. Controlled resistant hypertension is defined as controlled blood pressure requiring four or more medications.

TABLE 9-3 Causes of Secondary Hypertension

Select Drugs That May Elevate Blood Pressure

Drug Class	Example
Antiinfective	Ketoconazole
Antiinflammatory	Cyclooxygenase-2 inhibitors, nonsteroidal antiinflammatory drugs
Chemotherapeutic	Vascular endothelial growth factor inhibitors
Herbal	Ephedra, ginseng, ma huang
Illicit	Amphetamines, cocaine
Immunosuppressive agents	Cyclosporine, sirolimus, tacrolimus
Psychiatric	Buspirone, carbamazepine, clozapine, lithium, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants
Sex hormones	Estrogen and progesterone in oral contraceptives; androgens
Steroid	Methylprednisolone, prednisone
Sympathomimetic	Decongestants, diet pills

Most Common Causes of Secondary Hypertension by Age[a]

Age Group	% of Patients With Hypertension With an Underlying Cause	Most Common Etiologies
Children (birth–12 yr)	70–85	Renal parenchymal disease Coarctation of the aorta
Adolescents (12–18 yr)	10–15	Coarctation of the aorta
Young adults (19–39 yr)	5	Thyroid dysfunction Fibromuscular dysplasia Renal parenchymal disease
Middle-aged adults (40–64 yr)	8–12	Hyperaldosteronism Thyroid dysfunction Obstructive sleep apnea Cushing syndrome Pheochromocytoma
Older adults (≥65 yr)	17	Atherosclerotic renal artery stenosis Renal failure Hypothyroidism

[a]Excluding drug causes and the risk factor of obesity. Listed in approximate order of frequency.

Adapted from Viera AJ, Neutze DM. Diagnosis of secondary hypertension: an age-based approach. *Am Fam Physician*. 2010;82:1471–1478.

TABLE 9-4 End-Organ Damage in Hypertension

Vasculopathy
Endothelial dysfunction
Remodeling
Generalized atherosclerosis
Arteriosclerotic stenosis
Aortic aneurysm

Cerebrovascular Damage
Acute hypertensive encephalopathy
Stroke
Intracerebral hemorrhage
Lacunar infarction
Vascular dementia
Retinopathy

Heart Disease
Left ventricular hypertrophy
Atrial fibrillation
Coronary microangiopathy
Coronary heart disease, myocardial infarction
Heart failure

Nephropathy
Albuminuria
Proteinuria
Chronic renal insufficiency
Renal failure

Data from Schmieder RE. End organ damage in hypertension. *Dtsch Arztebl Int*. 2010;107:866–873.

Treatment of resistant hypertension typically includes a long-acting calcium channel blocker (CCB), an angiotensin-converting enzyme (ACE) inhibitor, or an angiotensin receptor blocker (ARB) and a diuretic. Refractory hypertension, defined as uncontrolled blood pressure on five or more drugs, is present in 0.5% of patients. Even more common is intolerance to antihypertensive drugs or pseudoresistant hypertension. Pseudoresistant hypertension can result from blood pressure measurement inaccuracies (including white-coat syndrome) or medication noncompliance. A study of patients with apparent treatment-resistant hypertension who had been prescribed three to five antihypertensive medications revealed that nearly a quarter of the study subjects had no detectable drug in blood or urine samples. It is important to note that currently available blood pressure devices using oscillatory techniques can be highly inaccurate for measuring either systolic or diastolic blood pressure. These devices measure the mean arterial pressure (MAP) more reliably.

Lifestyle Modification

Lifestyle modifications of proven value in lowering blood pressure include weight reduction, moderation of alcohol intake, increased aerobic exercise, and smoking cessation. There is a continuous relationship between increased body mass index (BMI) and blood pressure, with waist-to-hip ratio as an even stronger correlate. Weight loss is an effective nonpharmacologic intervention, through direct blood pressure reduction and synergistic enhancement of antihypertensive drug therapy efficacy. Overweight adults should aim for ideal body weight but can expect a 1 mm Hg reduction in blood pressure for every 1 kg of weight loss. Excessive alcohol consumption can be associated with increased hypertension and may cause resistance to antihypertensive drugs. Even modest increases in physical activity are associated with blood pressure decrease.

Dietary potassium and calcium intake is inversely related to both hypertension and cerebrovascular disease in the general

population. Salt restriction (e.g., Dietary Approaches to Stop Hypertension [DASH] eating plan) is associated with small but consistent decreases in systemic blood pressure. Sodium restriction may be most beneficial in lowering blood pressure in blacks, older adults, diabetics, or those with metabolic syndrome, patient populations with low renin activity that, in total, constitute nearly half of all adults in the United States. Recent findings challenge previous views on salt restriction and improvement in blood pressure or cardiovascular symptoms.

Pharmacologic Therapy

With continual research regarding the physiology and public health implications of hypertension, as well as identification of new cellular and molecular targets for pharmacologic intervention, treatment guidelines remain fluid. It is clear, however, that optimal drug therapy needs to consider ethnicity, advanced age, comorbidities, and end-organ function. The most recent evidence-based guidelines for the management of high blood pressure in adults (the ACC/AHA guidelines of 2017) outlined several broad conclusions:

1. Out-of-office blood pressure measurements are recommended for the diagnosis of hypertension and titration of antihypertensive medications.
2. There is strong evidence to support treating patients with ischemic heart disease, cerebrovascular disease, chronic kidney disease, or with an elevated risk of atherosclerotic cardiovascular disease with blood pressure–lowering medications if systolic blood pressure is 130 mm Hg and above. The recommendation of treating a diastolic blood pressure of 80 mm Hg and above has more limited data but is strongly recommended.
3. There is limited data to support the ACC/AHA Class I recommendation to treat patients without elevated cardiovascular disease risk or cerebrovascular disease with nonpharmacologic therapy if systolic blood pressure is 130 mm Hg and above or diastolic blood pressure is 80 mm Hg and above (stage 1 hypertension) and with blood pressure–lowering medications if systolic blood pressure is 140 mm Hg and above or diastolic blood pressure is 90 mm Hg and above (stage 2 hypertension).
4. The same thresholds and goals are recommended for hypertensive adults with diabetes or nondiabetic chronic kidney disease as for the general hypertensive population.
5. ACE inhibitors, ARBs, CCBs, or thiazide-type diuretics are useful and effective in the nonblack hypertensive population, including those with diabetes.
6. In black adult hypertensives without heart failure (HF) or chronic kidney disease (CKD), including those with diabetes, there is moderate evidence to support initial antihypertensive therapy with a CCB or thiazide-type diuretic.
7. There is moderate evidence to support antihypertensive therapy with an ACE inhibitor or ARB in persons with CKD to improve kidney outcomes.
8. Nonpharmacologic interventions, including weight loss, sodium reduction, potassium supplementation, increased physical activity, and reduced alcohol consumption, are important components to a comprehensive blood pressure management approach.

As noted in the guidelines, first-line antihypertensive therapy consists of diuretics, CCBs, ACE inhibitors, and ARBs. Notably absent from first-line therapy are β blockers, which tend to be reserved for patients with coronary artery disease or tachydysrhythmia, or as a component of multidrug therapy in resistant hypertension. A wide range of antihypertensive drugs are in common use (Table 9.5). A recent review noted that drugs in 15 different classes have been approved for the treatment of hypertension in the United States, many of which are also available in single-pill combinations with other compounds. Importantly, although all the available drugs can reduce blood pressure, their disparate pharmacology is evident in the reported relative risk reduction of hypertension-related events. For example, CCBs may lower the risk of stroke but not HF or mortality, whereas a Cochrane review found that in patients with uncomplicated

TABLE 9.5 Commonly Used Antihypertensive Drugs

Class	Generic Name	Usual Dose Range (mg/d)	Notes
Primary Agents			
Thiazide-type diuretics	Chlorthalidone	12.5–25	Monitor sodium, potassium, calcium, and uric acid levels.
	Hydrochlorothiazide	25–50	
	Indapamide	1.25–2.5	
	Metolazone	2.5–5	
Angiotensin-converting enzyme (ACE) inhibitors	Benazepril	10–40	Do not use in combination with ARBs or a direct renin inhibitor. Avoid in pregnancy. Do not use if history of angioedema. Risk of renal failure with severe bilateral renal artery stenosis.
	Captopril	12.5–150	
	Enalapril	5–40	
	Fosinopril	10–40	
	Lisinopril	10–40	
	Moexipril	7.5–30	
	Perindopril	4–16	
	Quinapril	10–80	
	Ramipril	2.5–20	
	Trandolapril	1–4	

Continued

TABLE 9.5 Commonly Used Antihypertensive Drugs—cont'd

Class	Generic Name	Usual Dose Range (mg/d)	Notes
Angiotensin receptor blockers (ARBs)	Azilsartan	40–80	Do not use in combination with ACE inhibitors or a direct renin inhibitor. Avoid in pregnancy. Do not use if history of angioedema. Risk of renal failure with severe bilateral renal artery stenosis.
	Candesartan	8–32	
	Eprosartan	600–800	
	Irbesartan	150–300	
	Losartan	50–100	
	Olmesartan	20–40	
	Telmisartan	20–80	
	Valsartan	80–320	
(CCBs): dihydropyridines	Amlodipine	2.5–10	Avoid in heart failure with reduced ejection fraction (HFrEF).
	Felodipine	2.5–10	
	Isradipine	5–10	
	Nicardipine SR	60–120	
	Nifedipine LA	30–90	
	Nisoldipine	17–34	
	Clevidipine (IV)	1–32 (mg/hr)	
(CCBs): nondihydropyridines	Diltiazem ER	120–360	Avoid routine use with – blockers. Do not use in HFrEF.
	Verapamil (IR/SR)	120–360	
	Verapamil ER	100–300	
Secondary Agents			
Diuretics: loop	Bumetanide	0.5–2	Preferred in symptomatic HFrEF. Preferred over thiazides with glomerular filtration rate (GFR) ⁻30 mL/min.
	Furosemide	20–80	
	Torsemide	5–10	
Diuretics: potassium sparing	Amiloride	5–10	Avoid in patients with GFR ⁻45 mL/min.
	Triamterene	50–100	
Diuretics: aldosterone antagonists	Eplerenone	50–100	Preferred in primary aldosteronism and resistant hypertension.
	Spironolactone	25–100	
– blockers	Atenolol	25–100	– blockers not first line unless concomitant ischemic heart disease (IHD) or HF. Bisoprolol and metoprolol succinate are preferred in patients with HFrEF. Avoid nadolol and propranolol in patients with reactive airways disease. Nebivolol also has vasodilatory effects. Avoid abrupt cessation.
	Betaxolol	5–20	
	Bisoprolol	2.5–10	
	Metoprolol tartrate	100–200	
	Metoprolol succinate	50–200	
	Nadolol	40–120	
	Nebivolol	5–40	
	Propranolol (IR/LA)	80–160	
α_1 blockers	Doxazosin	1–16	Association with orthostatic hypotension. Second-line agents in patients with bronchopleural fistula.
	Prazosin	2–20	
	Terazosin	1–20	
Combined ⁻ and ⁻ blockers	Carvedilol	12.5–50	Carvedilol is preferred in patients with HFrEF.
	Carvedilol phosphate	20–80	
	Labetalol	200–800	
Centrally acting	Clonidine oral	0.1–0.8	Last-line agents. Significant central nervous system (CNS) adverse effects in older adults. Abrupt discontinuation may induce a hypertensive crisis.
	Clonidine patch	0.1–0.3	
	Methyldopa	250–1000	
Vasodilators	Hydralazine	100–200	Use with a diuretic and – blocker. Associated with water retention and reflex tachycardia.
	Minoxidil	5–100	
Direct renin inhibitor	Aliskiren	150–300	Do not use with ACE inhibitors or ARBs. Avoid in pregnancy. Do not use if history of angioedema. Risk of renal failure with severe bilateral renal artery stenosis.

Adapted from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Pr. *Hypertension.* 2018;71(6):e13–e115.

hypertension, low-dose thiazides reduce mortality and cardiovascular morbidity. Nonetheless, across the range of hypertension etiology and severity, the varying pharmacology of available medications allows for combining drugs with different and potentially beneficial properties in terms of optimizing end-organ function (Table 9.6). Despite the plethora of treatment options already available, the public health burden of hypertension continues to drive research into new pharmacologic targets and therapies, including vaccines and surgical interventions (Table 9.7).

Treatment of Secondary Hypertension

Treatment of secondary hypertension is often interventional, including correction of renal artery stenosis via angioplasty or direct arterial repair, and adrenalectomy for adrenal adenoma or pheochromocytoma. For patients in whom renal artery repair is not possible, blood pressure control may be accomplished with ACE inhibitors alone or in combination with diuretics, although ACE inhibitors, ARBs, and direct renin inhibitors are not recommended in patients with severe bilateral renal artery stenosis as they can hasten progression to renal failure. Primary hyperaldosteronism in women can be treated with an aldosterone antagonist such as spironolactone, whereas amiloride is often used in men owing to the potential for spironolactone-induced gynecomastia. Certain disease entities, such as pheochromocytoma, require a combined pharmacologic and surgical approach for optimal outcome.

Perioperative Implications of Hypertension

Preoperative Evaluation

Assessment of blood pressure in the preoperative area or clinic is often complicated by an anxiety-related hypertensive response (white-coat hypertension). Furthermore, patients are often instructed to interrupt prescribed antihypertensives, such as ACE inhibitors and diuretics, on the day of surgery. Assessing blood pressure in a single moment in time does not give an accurate picture of overall blood pressure optimization and, according to current guidelines, multiple elevated blood pressure readings over time are necessary for a diagnosis of hypertension. Firstly, appropriate blood pressure technique should be confirmed, and, if still elevated, a pressure on the contralateral arm should be obtained. A careful review of prior clinic data, home blood pressure readings, and a thorough patient history are necessary to gain a better overall picture of cardiovascular health. Therefore, in general, elevated blood pressure per se is not a direct prompt to delay surgery in asymptomatic patients without other risk factors. In fact, unless there is marked hypertension (systolic ≥180 mm Hg and/or diastolic ≥110 mm Hg) or end-organ injury that can be ameliorated by aggressive blood pressure control, delaying surgery is not generally recommended.

While secondary hypertension is rare, suspicion of such should prompt a workup. A secondary etiology may be indicated by symptoms (e.g., flushing, sweating, palpitations suggestive of pheochromocytoma), physical examination (e.g., a renal bruit suggestive of renal artery stenosis), laboratory abnormalities (e.g., hypokalemia suggestive of hyperaldosteronism), or age (most hypertension in children ≤12 years of age is secondary).

TABLE 9.6 Drug Combinations With End-Organ Damage

Subclinical End-Organ Damage	
Left ventricular hypertrophy	ACEIs, ARBs, CCBs
Elevated albuminuria	ACEIs, ARBs
Renal dysfunction	ACEIs, ARBs
Irreversible Hypertensive End-Organ Damage	
Prior stroke	Any antihypertensive
Prior MI	BBs, ACEIs, ARBs
Angina pectoris, CHD	BBs, CCBs
Heart failure	Diuretics, BBs, ACEIs, ARBs, MR antagonists
Left ventricular dysfunction	ACEIs, ARB
Atrial fibrillation	
• Prevention, recurrence	
• Permanent	ARBs, ACEIs, BBs, nondihydropyridine CCBs
Tachydysrhythmia	BBs
Chronic renal insufficiency, proteinuria	ACEIs, ARBs, loop diuretics
Peripheral arterial occlusive disease	CCBs

ACEIs, Angiotensin-converting enzyme inhibitors; *ARBs,* angiotensin receptor blockers; *BBs,* β-blockers; CCBs, calcium channel blockers; *CHD,* coronary heart disease; *MI,* myocardial infarction; *MR,* mineralocorticoid
Adapted from Schmieder RE. End organ damage in hypertension. *Dtsch Arztebl Int.* 2010;107:866–873.

TABLE 9.7 New Treatment Approaches for Hypertension

New Drugs
- Mineralocorticoid receptor antagonists
- Aldosterone synthase inhibitors
- Activators of the ACE2/angiotensin-(1–7)/Mas receptor axis
- Centrally acting aminopeptidase inhibitors
- Vasopeptidase inhibitors
- Dual-acting angiotensin receptor–neprilysin inhibitors
- Dual-acting endothelin-converting enzyme–neprilysin inhibitors
- Natriuretic peptide receptor agonists
- Vasoactive intestinal peptide receptor agonist
- Soluble epoxide hydrolase inhibitors
- Intestinal Na^+/H^+ exchanger 3 inhibitor
- Dopamine β-hydroxylase (DβH) inhibitor

Vaccines
- Vaccine against angiotensin II
- Vaccine against angiotensin II type 1 receptor

Novel Approaches to Preeclampsia Treatment
- Antidigoxin antibody fragment
- Recombinant antithrombin

Interventional Procedures
- Renal denervation
- Baroreflex activation therapy
- Carotid body ablation
- Arteriovenous fistula creation
- Neurovascular decompression
- Renal artery stenting (revascularization)

ACE, Angiotensin-converting enzyme.
Adapted from Oparil S, Schmieder RE. New approaches in the treatment of hypertension. *Circ Res.* 2015;116:1074–1095.

These patients often present as severely hypertensive with no prior diagnosis of hypertension, and they would be exception to the "no delay" approach to preoperative hypertension. In fact, there have been multiple reports of a pheochromocytoma being "diagnosed" by induction of general anesthesia for an incidental procedure.

Once the decision is made to proceed with surgery, it is now common practice to continue antihypertensive medications, with the possible exception of high-dose ARBs and ACE inhibitors. Some authors advocate discontinuing these drugs at least 10 hours prior to surgery owing to concerns about refractory hypotension. In contrast, others believe there is little direct association between chronic use of ARBs and ACE inhibitors and sustained hypotension and therefore support continuing these drugs up to the time of surgery, especially in ambulatory patients. In addition, cessation of _-adrenergic antagonists or clonidine can be associated with rebound effects. Interruption of CCBs is associated with increased perioperative cardiovascular events.

Intraoperative Considerations

Although guidelines do not support delaying surgery for poorly controlled blood pressure, perioperative hypertension increases blood loss as well as the incidence of myocardial ischemia and cerebrovascular events. Furthermore, owing to a combination of physiologic factors (volume depletion, loss of vascular elasticity, baroreceptor desensitization) in combination with antihypertensive treatment, hypertensive patients are prone to intraoperative hemodynamic volatility. When superimposed on organ damage from chronic hypertensive disease, even brief periods of hypotension are associated with acute kidney injury, myocardial injury, and death. Ultimately, regardless of treatment efficacy at the time of surgery, hypertension as a disease entity has long been known to be an independent predictor for adverse perioperative cardiovascular events, especially when combined with other risk factors. Accordingly, clinicians need to consider acute intraoperative changes in blood pressure in the context of alterations in end-organ functional reserve brought about by chronic disease. Particular emphasis has been placed upon ischemic heart disease and the implications of left ventricular hypertrophy on cardiac relaxation and filling during diastole (Fig. 9.2). Nevertheless, guidelines for optimal systolic and diastolic blood pressures and MAP are lacking and impossible to derive, as blood pressure itself provides little guidance about microvascular blood flow and resistance.

Induction of Anesthesia and Monitoring

As already noted, hypertensive patients can be hemodynamically volatile, with induction of anesthesia producing hypotension and subsequent laryngoscopy and tracheal intubation eliciting hypertension and tachycardia. To lessen this risk it has been suggested that placement of an intraarterial catheter followed by a multimodal induction that includes transient ☐ blockade with esmolol may be beneficial. Poorly controlled hypertension is often accompanied by relative volume depletion, especially if a diuretic is part of chronic therapy. In some patients, modest volume loading prior to induction of anesthesia may provide hemodynamic stability, although this approach may be counterproductive in patients with marked left ventricular hypertrophy and significant diastolic dysfunction.

As with any procedure, a management plan for hemodynamic monitoring and vasoactive drug therapy for hypertensive patients should consider age, functional reserve, preoperative

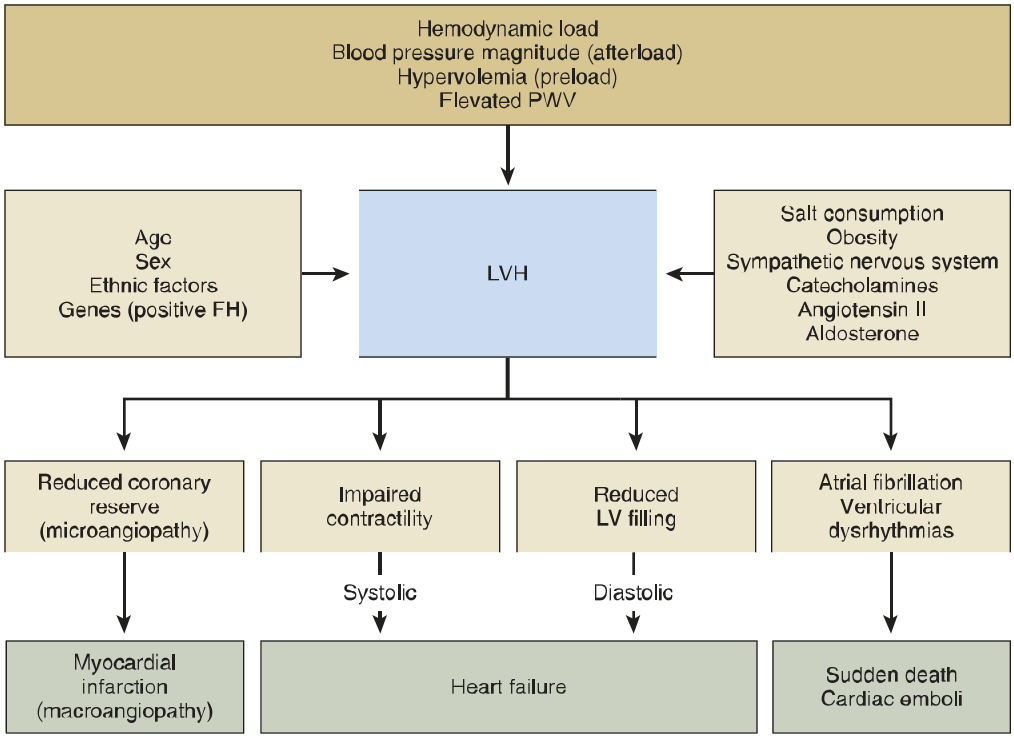

Fig. 9.2 Pathogenetic factors and clinical presentation of hypertensive heart disease. *FH,* Family history; *LV,* left ventricle; *LVH,* LV hypertrophy; *PWV,* pulse wave velocity. (From Schmieder RE. End organ damage in hypertension. *Dtsch Arztebl Int.* 2010;107:866–873.)

pharmacotherapy, and the planned operation. For example, intention-to-treat thresholds for patients undergoing repair of aortic dissection or women with peripartum hypertension will be lower than for the general surgical population. While arterial catheterization provides useful continuous information, the decision to use invasive monitoring is typically reserved for select patients based on magnitude of surgery, severity of disease, functional capacity, and comorbidities. Assessment of fluid status can be challenging in patients with long-standing hypertension, especially those with a history of heart failure with preserved ejection fraction (HFpEF). Left ventricular hypertrophy reduces chamber compliance such that with volume infusion, right heart pressures rise despite the fact that the left ventricle is relatively underfilled. Ultimately, intraoperative use of a pulmonary artery catheter is controversial, and pressure measurements from a central venous catheter may not provide a clear representation of volume status. Overall, echocardiographic evaluation of cardiac volumes may be the most useful in patients with HFpEF, but this has its own inherent risks and requires specialized personnel.

Maintenance of Anesthesia

Achieving hemodynamic stability may be more important than targeting an arbitrary intraoperative blood pressure, especially given the influence of other comorbidities, surgical procedure and position, volume status, mechanical ventilation, and depth of anesthesia. The management of intraoperative blood pressure over the wide range of potential clinical scenarios is beyond the scope of this review. However, it is important to consider that although high-dose anesthetics can acutely control blood pressure in many patients, this approach can have side effects, slows emergence, and cannot be continued into the postoperative phase. Accordingly, addition of sympathomodulators (esmolol, metoprolol, labetalol) or titrated calcium channel blocker therapy (nicardipine or clevidipine) can facilitate transition from the operating room to postanesthesia care unit (PACU) or intensive care unit (ICU).

Hypertensive Crises

Hypertensive crises are categorized as either urgent or emergent, based on the presence or absence of progressive organ damage. Patients with chronic hypertension tend to tolerate a higher systemic blood pressure than previously normotensive individuals and are more likely to require urgent (as opposed to emergent) intervention. Emergencies that may present in the perioperative setting include manifestations of central nervous system injury (hypertensive encephalopathy, intracerebral hemorrhage, subarachnoid hemorrhage, acute stroke), kidney injury (hypertension-induced acute renal dysfunction), and cardiovascular insult (hypertension associated with unstable angina, acute myocardial infarction, acute heart failure, and acute aortic dissection). In addition, women with pregnancy-induced hypertension may show evidence of end-organ dysfunction, in particular encephalopathy, with a diastolic blood pressure of less than 100 mm Hg. Current guidelines for peripartum hypertension recommend immediate intervention for systolic blood pressure of 160 mm Hg and above and/or diastolic blood pressure of 110 mm Hg and above with either oral nifedipine or intravenous hydralazine or labetalol.

Given the familiarity of perioperative physicians with vasoactive drug infusions and invasive monitoring, intervention for severe hypertension can generally be accomplished quickly, but care must be taken to titrate blood pressure down slowly to avoid overshoot hypotension. Placement of an intraarterial catheter to continuously monitor blood pressure can facilitate this process. Multiple vasodilator drugs are available, with different pharmacologic properties preferable under certain circumstances (Table 9.8). Labetalol has been described as the first-line drug for peripartum hypertension, whereas the addition of a blocker (esmolol, labetalol) to an arteriolar dilator is especially desirable in aortic dissection. For rapid arterial dilation and blood pressure reduction, sodium nitroprusside infusion has long been the standard, since it offers fast onset and dose titration, but cost constraints have lessened drug availability.

TABLE 9.8 Treatment for Hypertensive Emergencies

Cause/Manifestation	Primary Agents	Cautions	Comments
Encephalopathy and intracranial hypertension	Clevidipine, nitroprusside, labetalol, nicardipine	Cerebral ischemia may result from lower blood pressure (BP) due to altered autoregulation. Risk of cyanide toxicity with nitroprusside. Nitroprusside increases intracranial pressure.	Lower BP may lessen bleeding in intracerebral hemorrhage. Elevated BP often resolves spontaneously.
Aortic dissection	Clevidipine, nicardipine, esmolol, labetalol	Vasodilators may cause marked drop in BP that can result in end-organ ischemia.	Goal is lessening of pulsatile force of left ventricular contraction.
Acute kidney injury	Clevidipine, nicardipine, labetalol	Same as above	May require emergent hemodialysis if it progresses to renal failure.
Preeclampsia and eclampsia	Labetalol, nicardipine	blockers may reduce uterine blood flow and inhibit labor.	Definitive therapy is delivery. ACE inhibitors and ARBs are teratogenic and contraindicated during pregnancy.
Pheochromocytoma	Phentolamine, phenoxybenzamine, propranolol, labetalol	Unopposed -adrenergic stimulation following - blockade worsens hypertension.	
Cocaine intoxication	Labetalol, dexmedetomidine, clevidipine	Unopposed -adrenergic stimulation following blockade worsens hypertension.	

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker

Adapted from Whelton PK, Carey RN, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018 Jun;71(6):e13–e115.

More recently, clevidipine, a third-generation dihydropyridine CCB with an ultrashort duration of action (≈1-minute half-life) and selective arteriolar vasodilating properties, has become available. Nicardipine, a second-generation dihydropyridine CCB, can also be used but has a longer half-life (≈30 minutes), making it less quickly titratable than clevidipine.

Acute Postoperative Hypertension

Acute postoperative hypertension (APH) has been described as a significant elevation in blood pressure during the immediate postoperative period, which may lead to serious neurologic, cardiovascular, or surgical site complications requiring urgent management. Although APH is widely recognized, there is no standardized definition for this disorder. However, a postoperative systolic blood pressure of 180 mm Hg and above or diastolic blood pressure of 110 mm Hg and above would typically be considered APH and treated. Complications associated with APH can be both technical (surgical site bleeding, disruption of vascular anastomoses) and physiologic (myocardial ischemia, dysrhythmia, congestive heart failure with pulmonary edema, intracranial hemorrhage, cerebral ischemia, stroke, and encephalopathy).

Given the interplay of preexisting pathophysiology and perioperative stressors, the etiology of APH is undoubtedly multifactorial: autonomic nervous system activation at multiple levels, stress-induced disruption/activation of the renin-angiotensin-aldosterone system, medication withdrawal, hypercarbia, bladder distension, emergence delirium, pain, anxiety, and shivering. A study of nearly 20,000 general surgical patients found that about 2% developed APH and were at increased risk for hospital mortality. Other studies have reported the overall incidence of PACU hypertension in general surgical patients to be 0.6% to 1.1%. The highest incidence (20–60%) is following carotid endarterectomy, abdominal aortic surgery, radical neck dissection, and intracranial surgery, suggesting that disruption of normal homeostatic mechanisms regulated by perivascular structures (baroreceptors, chemoreceptors) may play a role.

Common factors (pain, anxiety, hypoxemia, hypercarbia, shivering, bladder distension) should be addressed before administration of specific antihypertensive therapy. Treatment of APH is generally a clinical decision based on the surgery (noncardiac vs. cardiac, presence of vascular anastomoses, intracranial), underlying comorbidities, and risks of treatment. Cardiac, transplant, and neurosurgical patients are typically recovered in closely monitored postoperative settings with relatively tight limits for blood pressure incorporated into care plan protocols. For general surgical patients, however, the risk/benefit of aggressive postoperative blood pressure control in a PACU environment remains unclear. When no identifiable treatable cause is apparent, titration of a short-acting intravenous drug is recommended because of the risk of subsequent hypotension once the hypertensive stimulus abates. Sympatholysis with esmolol or labetalol is often the first-line choice, with clevidipine or nicardipine as alternatives or adjuncts. Escalating doses of ACE inhibitor or ARB can also be used, as can hydralazine, but the longer half-life of these drugs may complicate management should secondary hypotension occur.

Although rare, withdrawal from clonidine (a centrally acting $_2$ agonist) can present as marked postoperative hypertension and often tachycardia. Occurring 18 to 24 hours after clonidine cessation, the greatest risk of rebound hypertension is in patients taking more than 1 mg/day. Prevention is accomplished by switching to a clonidine patch preoperatively. Although predominantly the result of excessive sympathetic nervous activity, hypertension may be aggravated by simultaneous use of a nonselective ¯blocker (e.g., propranolol) that blocks vasodilatory ¯$_2$ receptors without affecting vasoconstrictive ¯ receptors. There is no parenteral replacement for clonidine, but dexmedetomidine, a rapid-acting intravenous $_2$-adrenergic agonist, may have utility in patients with clonidine withdrawal syndrome.

PULMONARY ARTERIAL HYPERTENSION

Unlike systemic hypertension that can be diagnosed with a noninvasive blood pressure cuff, and efficacy of treatment monitored on a daily basis, the diagnosis and treatment of chronic pulmonary hypertension (PH) are more complex. The Sixth World Symposium on Pulmonary Hypertension held in 2018 redefined pulmonary hypertension as a mean pulmonary artery pressure (mPAP) over 20 mm Hg. Pulmonary hypertension is further divided into three hemodynamic profiles based on pulmonary arterial wedge pressure (PAWP) and pulmonary vascular resistance (PVR). These classifications are isolated precapillary PH, combined pre- and postcapillary PH, and isolated postcapillary PH (Table 9.9).

Right heart catheterization is required for a definitive PH diagnosis, classification, and formulation of an optimal therapeutic plan. Importantly, whereas systemic hypertension tends to reflect arterial pathology, PH can result from abnormalities in either arterial or venous components of the lung circulation, sometimes including contributions from both. Improved understanding of the pathogenesis and pathophysiology of PH also has led to new drug therapies for PH of arterial origin and improved survival. At the same time, a clear association between the increasing obesity rate and the potential for more widespread PH has emerged. Ultimately, the likelihood of patients with PH—treated or untreated—presenting for anesthesia and surgery is increasing.

The impact of PH on cardiac surgical outcomes has been relatively well described in large measure because PH is often identified with routine preoperative testing. Furthermore,

TABLE 9.9 Hemodynamic Definitions of Pulmonary Hypertension (PH)

	mPAP	PAWP	PVR	Groups
Isolated precapillary PH	20 mm Hg	15 mm Hg	3 WU	1, 3, 4, 5
Isolated postcapillary PH	20 mm Hg	15 mm Hg	3 WU	2, 5
Combined pre- and postcapillary PH	20 mm Hg	15 mm Hg	3 WU	2, 5

mPAP, pulmonary arterial pressure; *PAWP*, pulmonary arterial wedge pressure; *PVR*, pulmonary vascular resistance; *WU*, Woods Units

cardiac surgical patients are more prone to be managed in a perioperative setting where insertion of a pulmonary artery catheter is commonplace and ICU admission is routine. In contrast, specific risk factors for PH patients undergoing noncardiac surgery are less well defined, possibly reflecting the fact that across the etiologic spectrum and need for invasive diagnosis, PH may be occult or undertreated preoperatively. This section will first review the diagnosis and classification of PH in general and then focus upon perioperative implications of precapillary pulmonary arterial hypertension (PAH) in noncardiac surgery.

Definitions and Classification

Definition

As noted earlier, pulmonary hypertension as a broad entity is defined as mPAP over 20 mm Hg measured by right heart catheterization. It is important to understand, however, that mPAP can be increased by a variety of mechanisms: (1) elevated resistance to blood flow within the arterial circulation, (2) increased pulmonary venous pressure from left heart disease, (3) chronically increased pulmonary blood flow, or (4) a combination of these processes. Importantly, PH is not always associated with increased PVR, which may be normal despite an elevated mPAP. PVR is calculated from right heart catheterization data using the difference between the mPAP and pulmonary arterial wedge pressure (PAWP) divided by the cardiac output (CO) (PVR = (mPAP − PAWP)/CO). It is commonly expressed in Wood units (WU) or in dyne/s/cm^5 (WU × 79.9).

Hemodynamic Classification

Owing to the ease and noninvasive nature of echocardiography, it is commonly used to estimate pulmonary arterial systolic pressure (PASP) as a screening tool for PH. However, although echocardiographic PASP above 41 mm Hg is relatively sensitive and specific for PH, it cannot provide the accurate mPAP measurement needed for definitive diagnosis. Once right heart catheterization is performed, severity of PH based upon measurements obtained at rest is characterized as mild (mPAP ≤ 20–30 mm Hg), moderate (mPAP ≈ 31–40 mm Hg), or severe (mPAP ≥40 mm Hg). It is important to note that the normal pulmonary circulation can accommodate approximately a fourfold increase in cardiac output without a marked change in mPAP. Studies conducted under high-altitude conditions have shown that when the pulmonary circulation is constricted by hypoxia, there is a much greater rise in mPAP with increased flow, but a normal right ventricle can acutely adapt to the added load.

It is useful to consider the physiologic mechanisms responsible for the hemodynamic response. Precapillary PH is defined as PVR of 3.0 or more WU without significant elevation of the left atrial pressure or more commonly its surrogate, PAWP. In general, a PAWP below 15 mm Hg is considered normal. Isolated postcapillary PH results from increased pulmonary venous pressure, most commonly the result of elevated left atrial pressure secondary to valve disease or inotropic/lusitropic dysfunction of the left ventricle. Isolated postcapillary PH is characterized by a PAWP above 15 mm Hg, with normal values for PVR. Combined pre- and postcapillary PH reflects chronic pulmonary venous hypertension with secondary pulmonary arterial vasoconstriction and remodeling. This is also known as reactive PH and is most commonly related to left heart failure. The mixed variety is characterized by a PAWP above 15 mm Hg and ultimately a PVR more than 3.0 WU. Combined PH can be subcategorized as fixed or vasoreactive depending on the response to vasodilators, diuretics, or mechanical assistance. High-flow PH occurs without an elevation in PAWP or PVR and results from increased pulmonary blood flow secondary to systemic-to-pulmonary shunt or high cardiac output states.

WHO Clinical Classification

The World Health Organization (WHO) clinical classification of PH was most recently updated in 2019 (Table 9.10). PAH (WHO group 1) is a rare disease with a prevalence of approximately 15 cases per million people per year. Idiopathic PAH (IPAH)—cases with no familial context and no identifiable risk factor—accounts for nearly half of all PAH diagnoses. Nearly one in eight of these patients have long-term clinical and

TABLE 9.10 Updated Classification of Pulmonary Hypertension (PH)

1. **Pulmonary arterial hypertension (PAH)**
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
     - 1.4.1 Connective tissue disease
     - 1.4.2 HIV infection
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart diseases
     - 1.4.5 Schistosomiasis
   - 1.5 PAH long-term responders to calcium channel blockers
   - 1.6 PAH with overt features of venous/capillaries involvement
   - 1.7 Persistent PH of the newborn (PPHN)
2. **PH due to left heart disease**
   - 2.1 Left ventricular systolic dysfunction (LVEF)
   - 2.2 Left ventricular diastolic dysfunction (LVpEF)
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired conditions leading to postcapillary PH
3. **Pulmonary hypertension due to lung diseases and/or hypoxia**
   - 3.1 Obstructive pulmonary disease
   - 3.2 Restrictive lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive/obstructive pattern
   - 3.4 Hypoxia without lung disease
   - 3.5 Developmental lung diseases
4. **Chronic thromboembolic pulmonary hypertension (CTEPH)**
   - 4.1 Chronic thromboembolic PH
   - 4.2 Other pulmonary artery obstructions
5. **Pulmonary hypertension with unclear multifactorial mechanisms**
   - 5.1 Hematologic disorders
   - 5.2 Systemic disorders and metabolic disorders
   - 5.3 Others
   - 5.4 Complex congenital heart disease

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hemodynamic improvements with calcium channel blockers. This group was added to the WHO updated classification system, PAH long-term responders to calcium channel blockers. Another 3% of PAH diagnoses are deemed heritable PAH, with mutations in bone morphogenetic protein receptor type 2 *(BMPR2)* most prominent. The majority of remaining cases are designated "associated PAH," since they can be ascribed to manifestations of drugs, toxins, or other diseases. Etiology remains unclear for less than 1% of diagnoses. Traditionally characterized primarily as a disease of young women, with median survival from time of PAH diagnosis of about 3 years, current data indicate a demographic shift, with older patients and more men being diagnosed. Overall, despite improved diagnosis and therapy, 1-year mortality is estimated to be 15%. The poorest prognosis is in patients with PAH associated with scleroderma and/or a reduced distance on a 6-minute walk test (<300 m), right ventricular (RV) enlargement/dysfunction, central venous pressure above 20 mm Hg, cardiac index below 2 L/min/m^2, and elevated brain natriuretic peptide.

The impact of pulmonary venous hypertension (WHO group 2 PH) on morbidity and mortality in cardiac surgical patients is well described. Pulmonary hypertension secondary to lung disease and/or hypoxia (WHO group 3) may represent an emerging focus for perioperative physicians. Recent data indicate that about 60% of the US population is overweight or frankly obese. The associated rise in obesity-related obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS) may impact PH-related perioperative morbidity; it is estimated that PH is present in 20% of OSA patients and 50% of those with OHS. Patients with chronic thromboembolic PH (WHO group 4) may be refractory to medical management and require balloon dilation or high-risk surgery. Those with unclear and/or multifactorial PH (WHO group 5) may present with occult disease. Complex congenital heart disease was recently added to this group.

When all PH etiologies are considered, prevalence in the surgical population is probably substantial. Using echocardiographic estimates of PASP as a screening tool, investigators found that 25% of the residents in a Minnesota county had a PASP above 30 mm Hg, and that the magnitude of rise was age dependent. Using an estimated PASP threshold of 40 mm Hg, 9.1% of over 10,000 residents in western Australia were found to have PH. Overall, elevated PASP was more prominent in women and primarily related to left heart disease.

Pathophysiology and Pharmacologic Treatment

The development of PAH seems to involve multiple events accumulating on top of a genetic predisposition to generate complex changes in the expression of genes that promote cell proliferation and altered metabolism. Ultimately, sustained vasoconstriction and pro-remodeling processes lead to pathologic distortion of small pulmonary arteries (intimal hyperplasia, medial hypertrophy, adventitial thickening, and in situ thrombosis). Current theories indicate that PAH may be associated with a pro-apoptotic insult to the vascular endothelium, resulting in endothelial dysfunction and selection of apoptosis-resistant cell populations that go on to form the plexiform lesions characteristic of the disease. It has been suggested that PAH exhibits a neoplastic-like pathobiology.

Pharmacologic targets for PAH treatment continue to emerge, with a range of new therapeutic options under investigation. In addition to adjuncts such as diuretics and anticoagulants, and nonspecific calcium channel blockers in a relatively small subset, there are currently three main classes of pulmonary vasodilator drugs used for the treatment of PAH: prostanoids, endothelin receptor antagonists (ERAs), and those working through nitric oxide/guanylate cyclase pathways. Given the different mechanisms of action, it is not uncommon for patients to receive combination therapy.

Prostanoids

Prostanoids mimic the effect of prostacyclin to produce vasodilation while inhibiting platelet aggregation. They also have anti-inflammatory effects and may reduce proliferation of vascular smooth muscle cells. Currently available drugs include epoprostenol (intravenous), iloprost (inhaled), treprostinil (subcutaneous, intravenous, inhaled, oral), and most recently the oral drug beraprost. All have been shown to provide symptomatic improvement, but only epoprostenol has been proven to reduce mortality.

Endothelin Receptor Antagonists

The vascular endothelial dysfunction associated with PAH involves an imbalance between vasodilating (nitric oxide) and vasoconstricting (endothelin) substances. Currently available ERAs are all oral drugs and include bosentan, ambrisentan, and most recently macitentan. As a class, ERAs have been shown to improve hemodynamics and exercise capacity.

Nitric Oxide/Guanylate Cyclase

When endogenously released by endothelial cells or exogenously inhaled, nitric oxide produces pulmonary vasodilation by stimulating guanylate cyclase activity and subsequent cyclic guanosine monophosphate (cGMP) formation in smooth muscle cells. This effect is transient because nitric oxide is quickly bound by hemoglobin and other molecules, and cGMP is rapidly degraded by phosphodiesterase type 5 (PDE5). Continuously inhaled nitric oxide has been widely used in both perioperative and critical care settings, and preparations for home use have become available. More commonly, chronic therapy has been directed toward PDE5 inhibition with the oral drugs sildenafil and tadalafil. Multiple randomized controlled trials have confirmed efficacy of these drugs. Recently the oral guanylate cyclase stimulant riociguat was introduced. This drug both augments nitric oxide activation of soluble guanylate cyclase and stimulates the enzyme directly.

Perioperative Considerations

Preoperative Evaluation

It is important to consider that the specifics of many surgical procedures may not be known to some physicians asked to provide preoperative clearance. While all should be familiar with the ACC/AHA guidelines defining high-risk procedures (emergent major operations, aortic and major vascular surgery, peripheral vascular surgery, and prolonged procedures associated with the potential for large blood loss or fluid shifts), "high-risk" takes on a somewhat different connotation for patients with PAH. Particular consideration needs to be given to procedures with the potential for venous embolism (air, fat, cement), elevations in

venous and/or airway pressure (laparoscopy, Trendelenburg positioning), hypoxic pulmonary vasoconstriction (HPV) or reduction in pulmonary vascular volume (single-lung ventilation, lung compression, or resection), a profound perioperative systemic inflammatory response, and emergency procedures.

Identifying patients at risk for PH of any etiology that has gone underappreciated or undiagnosed is especially important. Patients suffering from PAH often present with nonspecific symptoms of fatigue, exertional dyspnea, and cough. With more advanced disease, angina pectoris, presyncope, and syncope can occur with exercise because coronary blood flow cannot meet supply/demand needs of a markedly hypertrophied right ventricle, and cardiac output cannot increase to meet metabolic demands. The New York Heart Association (NYHA) functional heart failure classification has been adapted for PH, with class 1 representing no symptoms with physical activity, and at the other end of the spectrum, class 4 exhibiting symptoms with minimal or no exertion. On physical examination, patients—especially those with uncompensated PAH and RV dysfunction—may exhibit a parasternal lift, an S_3 gallop, jugular venous distention, peripheral edema, hepatomegaly, and ascites. Rarely, hoarseness due to left recurrent laryngeal nerve paralysis secondary to compression by a dilated pulmonary artery (Ortner syndrome) may be present.

Assessing Risk Factors

A known or suspected history of PH should prompt further evaluation of functional status (exercise capacity, often a 6-minute walk), cardiac performance (especially RV function), and pulmonary function tests. For patients with moderate or severe PH by history or transthoracic echocardiography, or for those with related comorbidities, a right heart catheterization prior to high- or moderate-risk surgery is recommended. Owing to the potential for discrepancies between PAWP and actual left ventricular end-diastolic pressure, left heart catheterization should also be performed in patients with coexisting left heart disease because inaccurate estimation of left ventricular end-diastolic pressure may lead to misclassification of PH and inappropriate application of treatment paradigms. Vasoreactivity testing, often with inhaled nitric oxide, is performed during right heart catheterization in PAH patients to determine responsiveness to vasodilator therapy. A substantial number of patients with PAH show little response (85–90% are deemed nonresponders), but those found responsive to inhaled nitric oxide (defined as a ↑10 mm Hg decline in mPAP to ↓40 mm Hg, along with no change or increase in cardiac output) tend to also respond to CCBs and/or may benefit from advancing other targeted therapy (inhaled, parenteral, or oral) preoperatively (Fig. 9.3).

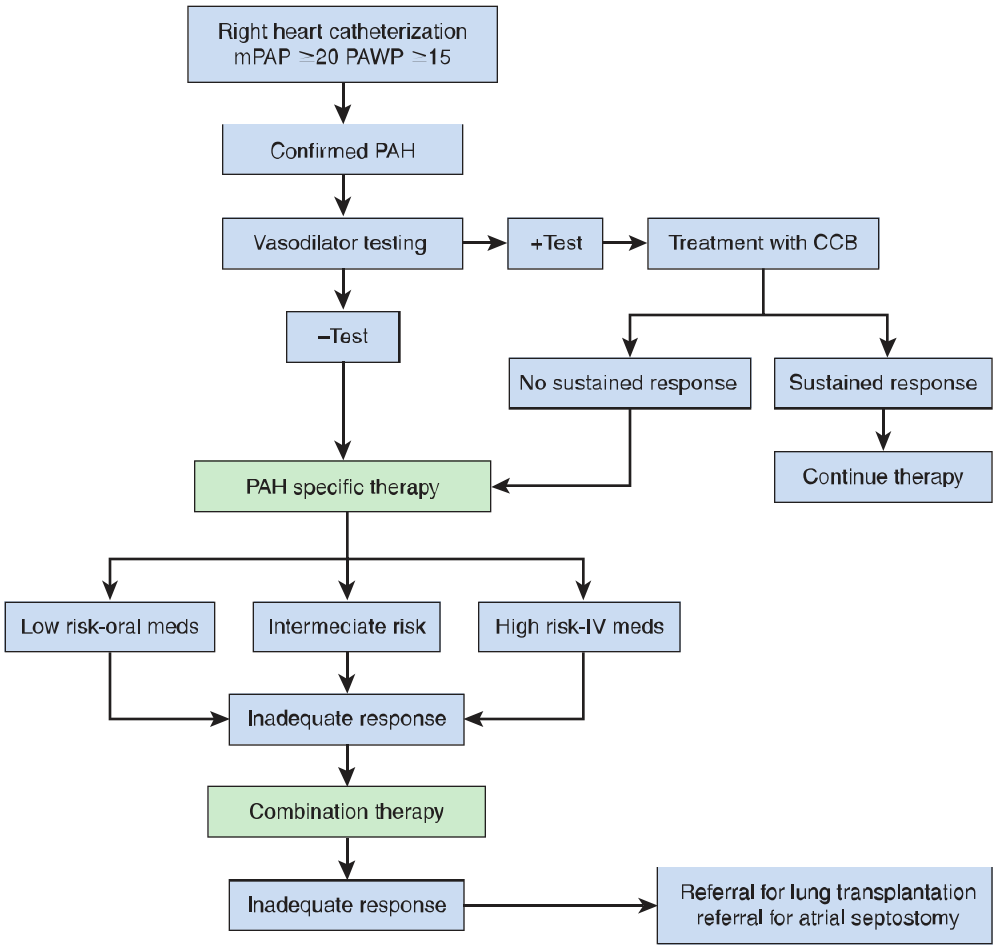

Fig. 9.3 Outpatient treatment of pulmonary arterial hypertension. *CCBs*, calcium channel blockers; *IV*, intravenous; *mPAP*, mean pulmonary arterial pressure; *PAH*, pulmonary arterial hypertension; *PAWP*, pulmonary arterial wedge pressure. (From Sahni S, Ojrzanowski M, Majewski S, et al. Pulmonary arterial hypertension: a current review of pharmacological management. *Pneumonol Alergol Pol.* 2016;84(1):47–61. doi:10.5603/PiAP.a2015.0084.)

Outcome Studies

Interpretation of studies analyzing outcomes for PAH patients undergoing noncardiac surgery is complicated by inconsistency in how the disease was diagnosed and categorized (echo vs. right heart catheterization), how severity of disease was defined, and use of modern vasodilator therapy. Nonetheless, it is clear that PAH is associated with a high rate (up to 42% in one study) of perioperative morbidity (respiratory failure, dysrhythmia, heart failure, hemodynamic instability, prolonged intubation) and mortality (3.5–18%). In a prospective survey of 114 well-characterized PAH patients undergoing surgery in the era of current vasodilator therapy, there was a 6.1% major complication rate and perioperative mortality of 3.5%. Importantly, mortality was higher for emergency procedures (15%) than nonemergent (2%), and risk was not different between general or spinal anesthesia. Recognized risk factors are summarized in Table 9.11.

Perioperative Physiology

Appreciation of the risk associated with PAH and the specific challenges presented to anesthetic management has prompted publication of reviews in the anesthesiology, cardiology, critical care, and surgical literature. Ultimately all emphasize the primary goal of maintaining optimal "mechanical coupling" between the right ventricle and pulmonary circulation to promote adequate left-sided filling and systemic perfusion. Any intervention that may affect RV preload, inotropy, afterload (including contributions from both small and large vessels), and oxygen supply/demand relationships needs to be considered. This takes on added complexity in the perioperative environment, where relatively common and generally benign events (transient hypotension, mechanical ventilation, modest hypercarbia, small bubbles in an intravenous line, Trendelenburg position, pneumoperitoneum, single-lung ventilation) can have potentially serious consequences.

Right ventricular afterload. A hallmark of PAH is increased RV afterload, leading to RV dilation, increased wall stress, and in the more chronic state, RV hypertrophy. Although often described simply as PVR (the steady-state mean pressure/mean flow relationship largely dictated by small vessels), the true interaction between the right ventricle and the pulmonary circulation is pulsatile and dynamic and involves the compliance and "stiffness" of large vessels as well as the resistance of small ones. This is particularly relevant to acute insults that may occur during surgery and affect RV pulsatile load. For example, large vessel compliance may be altered by events such as a change to prone or Trendelenburg positions, pneumoperitoneum during a laparoscopic procedure, or direct compression or displacement of the large pulmonary artery branches. In addition, ventilator management can have distinct effects on RV afterload via addition of positive end-expiratory pressure (PEEP), hypoventilation with hypercarbia and acidosis, and promotion of atelectasis.

Right ventricular inotropy. Some authors have advocated that for patients with PAH, attempts should be made to maintain the heart in a hypercontractile state. However, aspects of anesthetic care and intraoperative course can affect myocardial contractile performance via both direct and indirect mechanisms. Many of the drugs used for induction and maintenance of anesthesia have dose-related negative inotropic effects and tend to depress the autonomic nervous system. Alternatively, high neuraxial anesthesia can produce an acute cardiac sympathectomy. Nonetheless, acute RV decompensation from direct myocardial depression and/or sympatholysis has not been featured in outcome studies. Clinical and basic science investigations have suggested that the impact of negative inotropy on pump function of the left ventricle is offset to some degree by a simultaneous decline in afterload. Intriguingly, studies of the inhaled anesthetics isoflurane and desflurane have indicated a different effect on the right ventricle. For example, data show that when the pulmonary circulation is normal, isoflurane increases total RV afterload. Whether the same response occurs in the setting of PAH is unclear, but clinical experience has not suggested that isoflurane or other volatile anesthetics are contraindicated. In contrast, acidosis is clearly detrimental both for effects on afterload and contractility. Even modest reductions in extracellular pH can negatively affect inotropy, and this effect becomes hemodynamically more pronounced when cardiac performance is tenuous to begin with.

Myocardial supply and demand. In contrast to the left ventricle, the thinner-walled right ventricle is subjected to greater wall tension for the same degree of increase in end-diastolic volume, leading to increased RV myocardial oxygen demand. Under normal circumstances the RV intramyocardial pressure is lower than the aortic root pressure, and the RV coronary

TABLE 9.11 Risk Factors for Morbidity and Mortality in Noncardiac Surgery in Patients With Pulmonary Arterial Hypertension

Patient Factors
History of PE, CAD, chronic renal disease
NYHA/WHO FC III–IV
Higher ASA class
RAD on ECG
Echo parameters: RVH, RVMPI 0.75
Hemodynamics: higher PAP, RVSP/SBP ratio 0.66
Operative Factors
Emergency surgery
Intermediate- or high-risk operations
High risk for venous embolism (air, fat, cement)
Elevation in venous pressure (Trendelenburg positioning, insufflation)
Reduction in lung vascular volume (lung compression or resection)
Induction of severe systemic inflammatory response
Longer duration of anesthesia
Intraoperative vasopressor use

ASA, American Society of Anesthesiologists; *CAD*, coronary artery disease; *ECG*, electrocardiogram; *FC*, functional class; *NYHA*, New York Heart Association; *PAP*, pulmonary artery pressure; *PE*, pulmonary embolism; *RAD*, right axis deviation; *RVH*, right ventricular hypertrophy; *RVMPI*, right ventricular myocardial performance index; *RVSP*, right ventricular systolic pressure; *SBP*, systolic blood pressure; *WHO*, World Health Organization.

Adapted from Goldsmith YB, Ivascu N, McGlothlin D, et al. Perioperative management of pulmonary hypertension. In Klinger JR, Frantz RP, editors. *Diagnosis and Management of Pulmonary Hypertension*. New York: Springer; 2015:437–464.

perfusion occurs throughout the cardiac cycle. However, owing to the elevated RV intramyocardial pressure present in PAH, more coronary flow occurs during diastole, making the RV vulnerable to systemic hypotension, which worsens the mismatch between oxygen demand and supply and can precipitate ischemia even in the absence of coronary occlusive disease. Ultimately, systemic hypotension in combination with RV ischemia and high afterload may result in the "lethal combination" of RV dilatation, interventricular septal bulging, insufficient left ventricular filling, reduced stroke volume, and further systemic hypotension.

Procedural Considerations

The added risk of PH in labor and delivery is understood by all clinicians involved with the parturient's care. With other procedures, however, the potential interaction of PH may be underappreciated. This takes on added importance given recent data showing a shift in PH demographics toward an older population with more comorbidities.

Orthopedics

Although many procedures are amenable to regional or neuraxial anesthesia, concomitant intraoperative sedation can promote hypoventilation and hypercarbia. Superimposed on this is the added potential for embolic sequelae during major joint repair or replacement. Echocardiography studies have indicated embolic showers produced by different stages of joint replacement procedures that can acutely increase RV afterload. Consistent with these observations, database analysis has demonstrated a substantial increase in risk of perioperative morbidity and mortality in patients with PH undergoing hip and knee replacement.

Laparoscopy

Although laparoscopy has clear benefits in terms of postoperative pain and recovery time, the required carbon dioxide pneumoperitoneum has an acute impact on biventricular load and pump function. For the right ventricle in particular the combination of pneumoperitoneum, head-down position, and the increased inspiratory pressure required for mechanical ventilation and prevention of atelectasis affects filling pressures and both the magnitude and character of afterload. Even in otherwise healthy individuals, pneumoperitoneum can reduce cardiac output and produce an increase in pulmonary arterial pressure that may not immediately decline when the pneumoperitoneum is relieved. This has been linked to retained carbon dioxide and hypercarbia. Overall, although laparoscopy is generally well tolerated in normal individuals, it may not be in patients with PH and poorly compensated RV function.

Thoracic Surgery

The postoperative benefits of minimally invasive thoracoscopy are becoming increasingly clear, but the short-term stresses on the right ventricle can be profound. Although thoracoscopy does not universally entail sustained pressurization of the chest similar to that produced in the abdomen during laparoscopy, it does involve nonventilation and atelectasis of the operative lung. Three features of this intentional lung collapse are particularly relevant to the PH patient: (1) some centers transiently pressurize the chest to facilitate onset of atelectasis, (2) there is a potential for systemic hypoxia, and (3) HPV will further increase RV afterload. To facilitate perioperative care, patients with PAH are often converted from oral to inhaled or parenteral pulmonary vasodilator therapy. Although the specific effect of parenteral pulmonary vasodilators on HPV during single-lung ventilation is not well described, to lessen the potential for HPV inhibition and systemic hypoxia, it has been recommended that inhaled pulmonary vasodilators be administered during single-lung ventilation to allow for limiting or even discontinuing intravenous therapy for a period of time. Finally, removal of lung tissue will decrease pulmonary vascular surface area, raising the probability that mPAP and PVR will remain increased from preoperative levels even when the operative lung is reexpanded.

KEY POINTS

- Hypertension is a significant risk factor for cardiovascular disease, stroke, and renal disease. Updated guidelines now define a goal of antihypertensive therapy to decrease the systemic blood pressure to less than 130/80 mm Hg, but a high percentage of patients remain poorly controlled.
- Hypertensive patients coming for surgery can pose management dilemmas for the anesthesiologist. However, the relationship between blood pressure control and perioperative complications is unclear, and clinical practices vary widely.
- Preoperative evaluation of a patient with hypertension should focus on the adequacy of blood pressure control, the antihypertensive drug regimen, and most importantly the presence of end-organ damage.
- There is no clear evidence that the incidence of postoperative complications is increased when patients with uncomplicated hypertension undergo elective surgery. However, hypertension associated with end-organ damage does increase surgical risk.
- Hemodynamic instability is common during anesthesia and surgery in hypertensive patients, even those patients effectively treated with antihypertensive drugs.
- Defined as a mean pulmonary artery pressure (mPAP) above 20 mm Hg, pulmonary hypertension (PH) can result from a range of processes that directly constrict and remodel arteries, elevate pulmonary venous pressure, or chronically increase blood flow to initiate vascular remodeling.
- Pulmonary arterial hypertension (PAH) represents one of five PH groups defined by the World Health Organization. Patients with PAH exhibit endothelial dysfunction, maladaptive arterial remodeling and cell proliferation, and in situ thrombosis.
- Right heart catheterization is required to provide a definitive PAH diagnosis and guide treatment. Only a small

percentage respond to calcium channel blockade. Most current pulmonary vasodilator therapy consists of prostacyclin analogues, endothelin receptor antagonists, and drugs activating the nitric oxide/guanylate cyclase pathway. PAH is the only class of PH found to exhibit therapeutic benefit in response to pulmonary vasodilator treatment. Although quality of life and survival have improved with increased vasodilator options, the prognosis for PAH patients remains poor.

- PH in general and PAH in particular increase the risk of perioperative morbidity and mortality. PAH patients receiving vasodilator therapy should have it continued intraoperatively and postoperatively, with plans made to convert from oral to parenteral or inhaled drugs when necessary.

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10

Heart Failure and Cardiomyopathies

Julie K. Freed, Paul S. Pagel, Wanda Popescu, Justin Tawil

OUTLINE

HEART FAILURE

Definition

The ability of the left ventricle to function as one of the body's two main pumping chambers depends on how efficiently it ejects and subsequently fills with oxygenated blood. This implicit duality indicates that heart failure may occur either when the left ventricle is unable to eject blood at a rate sufficient to meet tissue metabolic requirements or when it cannot fill completely without elevated pressures. Simply, heart failure is defined as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. Tissue hypoperfusion results in clinical symptoms such as fatigue, dyspnea, weakness, edema, and weight gain. Structural abnormalities of the pericardium, myocardium, endocardium, heart valves, or great vessels can result in heart failure. Functional impairment of the myocardium, during either systole or diastole, is more commonly associated with this clinical syndrome. Heart failure with reduced ejection fraction (HFrEF) is classified as an ejection fraction of 40% or less, whereas heart failure with preserved ejection fraction (HFpEF; previously termed diastolic heart failure) is diagnosed in patients with an ejection fraction of 50% or more. A patient with clinical symptoms with an ejection fraction between 40% and 50% is labeled as having borderline HFpEF. The distinction between these two types of heart failure based solely on ejection fraction is clearly somewhat artificial, as HFrEF and HFpEF most likely represent different phenotypes rather than unique clinical entities. Diastolic dysfunction is present in both HFrEF and HFpEF, and myocardial contractility is abnormal in HFpEF when quantified using more sensitive indices (e.g., left ventricular [LV] end-systolic pressure volume relations, tissue Doppler imaging) despite relatively normal ejection fraction. Indeed, the patterns of LV dilation and remodeling (e.g., concentric vs eccentric hypertrophy), and not ejection fraction per se, are major distinguishing features between HFrEF and HFpEF, along with their differential responses to medical treatment. Nevertheless, the classification system remains useful because ejection fraction is easily measured using echocardiography and because the risk factors, responsible mechanisms, treatment, and outcomes of HFrEF and HFpEF have been established based on this definition. Patients suffering from HFpEF or HFrEF present for surgery on a regular basis and anesthesiologists must be familiar with clinical characteristics and treatment of these disorders

to provide successful perioperative care for these often-complex patients.

Epidemiology and Etiology

Heart failure is an emerging worldwide epidemic. Current estimates suggest that more than 8 million patients in the United States alone will be treated for the condition by 2030 at an annual cost of $53 billion. Approximately half of the patients who present with heart failure have an LV ejection fraction that is relatively normal (>50%). The proportion of patients with HFpEF is steadily increasing compared with those in whom reduced ejection fraction (<40%) is present (HFrEF) in large part because the prevalence of conditions with which the former is more closely associated, including poorly controlled essential hypertension, atrial fibrillation, diabetes mellitus, obesity, metabolic syndrome, chronic obstructive pulmonary disease (COPD), renal insufficiency, anemia, and generalized deconditioning, continues to rise as the population ages (Table 10.1). In contrast, patients with HFrEF are more likely to have modifiable risk factors (e.g., tobacco abuse, hyperlipidemia) and have a higher prevalence of myocardial ischemia and myocardial infarction (MI), previous percutaneous coronary intervention, coronary artery bypass graft surgery, and peripheral vascular disease compared with those with HFpEF. Nevertheless, as many as 70% of patients with HFpEF also have evidence of coronary artery disease.

A recent survey indicated that 52% of heart failure cases were classified as HFpEF, whereas 33% were HFrEF and 16% had modestly depressed LV systolic function (ejection fraction between 40% and 49%; "borderline"). Women are more likely to be affected by HFpEF than men (as opposed to the male predominance of HFrEF), and this gender disparity widens

TABLE 10.1 Comparison of Heart Failure With Reduced and Preserved Ejection Fraction

	HFrEF	HFpEF
Clinical Features		
Relative age	Younger	Older
Sex	Men > women	Women > men
Medical comorbidities	CAD	HTN
	CABG/PCI	Atrial fibrillation
	Tobacco abuse	DM
	HLD	Obesity/metabolic syndrome
	PVD	COPD
		CRF
		Anemia
		Deconditioning
Physical findings	S_3 gallop	PND
		Peripheral edema
		JVD
		Elevated PCOP
Pathophysiology		
Myocardial contractility	Markedly depressed	Depressed
LV ESPVR	Reduced E_{es}	Elevated E_{es} (systolic stiffening)
LV end-diastolic pressure	Increased	Increased
LV relaxation	Delayed	Delayed
Passive myocardial stiffness	Normal to increased	Markedly increased
LV size	Enlarged	Normal
LV geometry	Eccentric hypertrophy	Concentric hypertrophy
LV mass	Increased	Increased
Cardiac myocyte dimension	Increased length	Increased diameter
Extracellular matrix	Less interstitial fibrosis	Greater interstitial fibrosis
BNP concentration	Markedly elevated	Modestly increased
LV afterload	Increased secondary to neurohormonal activation	Prominent arterial stiffening
LV-arterial coupling	Variable E_a	Elevated E_a
LA systolic and diastolic dysfunction	Less common	More common
PAH/RV dysfunction	Common	Common
Chronotropic incompetence	Less common	More common
Echocardiography		
LV ejection fraction	<40%	>50%
Tissue Doppler velocity	Reduced	Reduced
LV diastolic dysfunction	Secondary to LV systolic dysfunction	Pathognomonic
LV dimensions	Enlarged	Normal
LV wall thickness	Variable	Markedly increased
Positive Response to Treatment		
Diuretic	Yes	Yes
β blocker	Yes	No
RAAS inhibitor	Yes	No
Digoxin	Yes	No
PDE V inhibitor	No	No
Nitrate	Yes	No
Statin	Yes	Questionable
Exercise training	Yes	Yes
Weight loss	Yes	Yes
Control of medical comorbidities	Yes	Yes

BNP, Brain natriuretic peptide; *CABG,* coronary artery bypass graft; *CAD,* coronary artery disease; *COPD,* chronic obstructive pulmonary disease; *CRI,* chronic renal insufficiency; *DM,* diabetes mellitus; E_a, effective arterial elastance; E_{es}, slope of the LV ESPVR; *ESPVR,* end-systolic pressure-volume relationship; *HFpEF,* heart failure with preserved ejection fraction; *HFrEF,* heart failure with reduced ejection fraction; *HLD,* hyperlipidemia; *HTN,* hypertension; *JVD,* jugular venous distension; *LV,* left ventricle; *PAH,* pulmonary arterial hypertension; *PCI,* percutaneous coronary intervention; *PCOP,* pulmonary capillary occlusion pressure; *PDE,* phosphodiesterase; *PND,* paroxysmal nocturnal dyspnea; *PVD,* peripheral vascular disease; *RAAS,* renin-angiotensin-aldosterone system; *RV,* right ventricle.

with advancing age. For example, the incidence of HFpEF in women older than 80 years of age was reported to be 8% to 10% compared with 4% to 6% in men. The signs, symptoms, degree of functional impairment, morbidity, and mortality of both forms of heart failure are very similar, although death from a primary cardiovascular cause is more common in patients with HFrEF, whereas hospital admission and readmission for noncardiac causes occur more often in those with HFpEF.

PATHOPHYSIOLOGY OF HEART FAILURE

Left Ventricular Diastolic Dysfunction

Whereas fundamental abnormalities of contractile function characterize HFrEF, left ventricular diastolic dysfunction (LVDD) is a primary determinant of HFpEF. LV diastole encompasses a complicated sequence of temporally interrelated heterogeneous events (Fig. 10.1; Tables 10.2 and 10.3). Pulmonary venous blood flow, left atrial (LA) function, mitral valve dynamics, pericardial restraint, and the active (relaxation) and passive elastic (compliance) properties of the left ventricle during diastole determine its ability to properly fill. LV diastolic function is considered normal when these factors combine to provide an LV end-diastolic volume (i.e., preload) that provides sufficient cardiac output to satisfy cellular metabolism without elevations in pulmonary venous and mean LA pressures (normal values of ~10 mm Hg for each). It is essential to recognize that no single index of LV diastolic function completely characterizes this period of the cardiac cycle or selectively identifies patients at highest risk of developing heart failure resulting from abnormal relaxation, filling, and compliance. The vast majority of indices of LVDD are also highly dependent on heart rate, loading conditions, and myocardial contractility, and as a result abnormalities in diastolic function require thoughtful interpretation. Despite these inherent limitations, invasively derived LV end-diastolic pressure-volume relations uniformly demonstrate that higher LV filling pressures are required to achieve normal end-diastole volume in patients with HFpEF (Fig. 10.2). The steeper rise of the end-diastole pressure-volume curve is indicative of delayed LV relaxation (such as is commonly observed in pressure-overload hypertrophy resulting from long-standing essential hypertension) and an increase in passive myocardial stiffness resulting in a reduction in LV compliance that restricts LV filling and precipitates LA hypertension, LA systolic and diastolic dysfunction, pulmonary venous congestion, and exercise intolerance.

Relaxation is an active, energy-dependent process requiring extrusion of calcium (Ca^{2-}) from the myoplasm and its resequestration into the sarcoplasmic reticulum, thereby facilitating prompt dissociation of the contractile proteins and

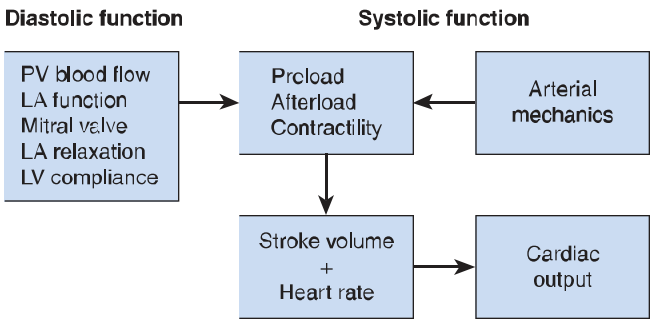

Fig. 10.1 Diastolic versus systolic dysfunction. This illustration depicts the major factors that determine left ventricular *(LV)* diastolic *(left)* and systolic *(right)* function. Note that pulmonary venous *(PV)* blood flow, left atrial *(LA)* function, mitral valve integrity, LA relaxation, and LV compliance combine to determine LV preload. (Reproduced with permission from Pagel PS, Freed JK. Cardiac physiology. In: Kaplan JA, Augoustidis JGT, Manecke Jr GR, et al., eds. *Kaplan's Cardiac Anesthesia for Cardiac and Noncardiac Surgery*. Philadelphia, PA: Elsevier; 2017:143–178.)

TABLE 10.2 Determinants of Left Ventricular Diastolic Function

Heart rate and rhythm
LV systolic function
Wall thickness
Chamber geometry
Duration, rate, and extent of LV relaxation
LV elastic recoil and untwisting
Magnitude of diastolic suction
LA-LV pressure gradient
Passive elastic properties of LV myocardium
Viscoelastic effects (rapid LV filling and LA systole)
LA structure and function
Mitral valve structure and function
Pulmonary venous blood flow
Pericardial restraint
RV loading conditions and function
Ventricular interdependence
Coronary blood flow and vascular engorgement
Extrinsic mediastinal compression

LA, Left atrium; *LV*, left ventricle; *RV*, right ventricle.
Reproduced with permission from Pagel PS, Freed JK. Cardiac physiology. In: Kaplan JA, Augoustidis JGT, Manecke Jr GR, et al., eds. *Kaplan's Cardiac Anesthesia for Cardiac and Noncardiac Surgery*. Philadelphia, PA: Elsevier; 2017:143–178.

TABLE 10.3 Common Causes of Left Ventricular Diastolic Dysfunction

Age >60 years
Acute myocardial ischemia (supply or demand)
Myocardial stunning, hibernation, or infarction
Ventricular remodeling after infarction
Pressure-overload hypertrophy (e.g., aortic valve stenosis, essential hypertension)
Volume-overload hypertrophy (e.g., aortic or mitral valve regurgitation)
Hypertrophic obstructive cardiomyopathy
Dilated cardiomyopathy (e.g., viral, postpartum, idiopathic)
Restrictive cardiomyopathy (e.g., amyloidosis, hemochromatosis)
Pericardial diseases (e.g., tamponade, constrictive pericarditis)

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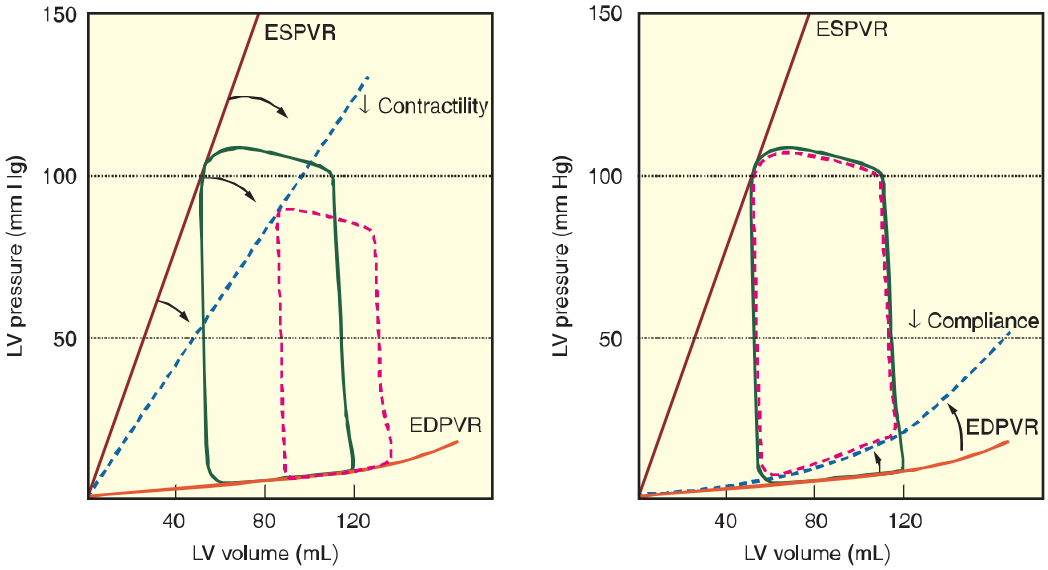

Fig. 10.2 Alterations in left ventricular *(LV)* pressure-volume loops during heart failure. These schematic illustrations demonstrate alterations in the steady-state LV pressure-volume diagram produced by a reduction in myocardial contractility as indicated by a decrease in the slope of the end-systolic pressure-volume relation *(ESPVR; right panel)* and a decrease in LV compliance as indicated by an increase in the position of the end-diastolic pressure-volume relation *(EDPVR; right panel)*. These diagrams emphasize that heart failure may result from LV systolic or diastolic dysfunction independently. (Reproduced with permission from Pagel PS, Freed JK. Cardiac physiology. In: Kaplan JA, Augoustidis JGT, Manecke Jr GR, et al., eds. *Kaplan's Cardiac Anesthesia for Cardiac and Noncardiac Surgery.* Philadelphia, PA: Elsevier; 2017:143–178.)

rapid recoil of elastic elements compressed during contraction. Delays in relaxation are a form of "active stiffening" because failure of actin-myosin cross bridges to dissociate occurs when energy supply is inadequate (e.g., ischemia) or intracellular Ca^{2+} homeostasis is dysfunctional (e.g., heart failure resulting from a variety of causes). LV relaxation is highly dependent on afterload, and this afterload sensitivity is markedly enhanced in the failing heart. The phenomenon is particularly notable in HFpEF because hypertension is almost invariably present, thereby producing further delays in LV relaxation, compromising early LV filling by attenuating the LA-LV pressure gradient, blunting torsional recoil, inhibiting the diastolic suction mechanism (which facilitates LV filling during hypovolemia and exercise), and raising LV diastolic pressures. Failure of LV relaxation to proceed more rapidly in response to tachycardia during exercise also exacerbates this process and is an important mechanism responsible for the often-profound exercise intolerance that patients with HFpEF experience despite only modestly depressed LV systolic function. In addition, delays in LV relaxation prolong compression of intramyocardial coronary arterioles and restrict early diastolic coronary blood flow, actions that contribute to the development of subendocardial ischemia and further compromise exercise tolerance in HFpEF.

Hooke's law governs the passive mechanical behavior of myocardium, an elastic material that develops a resisting force (stress) as its length (strain) increases. It can be easily shown that an exponential relationship between stress and strain accurately models the passive stiffness of myocardium. An increase in this myocardial stiffness occurs in HFpEF that contributes to the steeper slope of the LV end-diastolic pressure-volume curve. The determinants of myocardial stiffness are multifactorial, as components of the cardiac myocyte, extracellular matrix, interstitium, and coronary microvasculature have all been implicated in the presence of a chronic proinflammatory state characterized by elevated nitrosative-oxidative stress that contributes to interstitial fibrosis and cardiac myocyte stiffening. Cardiac myocyte diameter and myofibrillar density were greater, and excess collagen volume was present in endomyocardial biopsies obtained from patients with HFpEF. These factors increase myocardial stiffness. Excessive collagen deposition resulting from an imbalance between synthesis and degradation contributes to increased extracellular matrix stiffness. Coronary microvascular density is reduced in HFpEF and is correlated to the magnitude of myocardial fibrosis, factors that contribute to impaired coronary blood flow reserve. Microvascular endothelial dysfunction also leads to a relative paucity of nitric oxide bioavailability, a decrease in intracellular cyclic guanosine monophosphate concentration, and a decline in protein kinase G activity, actions that adversely modulate the phosphorylation state of specific isoforms of titin. A large, highly elastic protein, titin acts as a bidirectional length sensor to exert restoring forces as a cardiac myocyte approaches its maximum and minimum length, thereby preventing excessive stretch and compression, respectively. Sufficient diastolic recoil of titin and other elastic elements (e.g., elastin, collagen, actin, myosin) within the myocardium is an essential determinant of both LV compliance and diastolic suction. The changes in titin isoform phosphorylation state and expression occur in HFpEF that have also been closely linked to increases in myocardial stiffness.

Cardiac catheterization is required to quantify the LV compliance curve using end-diastolic pressure-volume relations in

patients with HFrEF or HFpEF. This approach is clearly impractical for the vast majority of patients with heart failure who present for diagnostic evaluation. Instead echocardiography is used to estimate LV compliance based on two-dimensional imaging and Doppler measurement of blood flow and mitral annular velocities. Evidence of impaired LV filling, attenuated systolic pulmonary venous blood flow, reduced tissue Doppler velocities, enlarged LA size, and increased LV wall thickness with normal chamber dimensions are common echocardiographic findings in many patients with HFpEF. However, one-third of patients present with subclinical HFpEF, and LVDD may only be detected using echocardiography with provocative testing. It is noteworthy that the presence of LVDD alone does not establish the diagnosis of HFpEF without clinical symptomatology, as approximately 70% of patients over the age of 75 years have some echocardiographic evidence of LVDD. Nevertheless, the presence of moderate or severe LVDD in patients without heart failure is a predictor for the subsequent development of HFpEF. LVDD also invariably accompanies HFrEF, as LVDD most often occurs as a consequence of LV systolic dysfunction under these circumstances. Regardless of the cause, the severity of LVDD and its response to medical therapy are important determinants of exercise tolerance and mortality in patients with HFrEF or HFpEF. The anesthesiologist should recognize that LVDD has significant implications on LV response to acute alterations in loading conditions that occur during and after surgery independent of LV systolic dysfunction, as higher LV filling pressures may be required to achieve adequate stroke volume, and patients may be more susceptible to hypotension when anesthetics or other vasodilators are administered.

Left Ventricular Systolic Dysfunction

The defining characteristic of HFrEF is a reduction in myocardial contractility, most commonly resulting from ischemia, infarction, or cardiomyopathy (e.g., viral, postpartum, idiopathic). Pressure-volume analysis provides a useful illustration of the pathophysiology of myocardial contractility as an underlying cause for HFrEF. A shallow slope of the LV end-systolic pressure-volume relation (E_{es}) indicates that contractility is reduced compared with the normal heart (see Fig. 10.2) and is usually accompanied by compensatory LV dilation (movement of the pressure-volume diagram to the right to higher volumes) along the LV end-diastolic pressure-volume curve. The increase in LV end-diastolic volume may preserve stroke volume and cardiac output but occurs at the cost of higher LV filling pressures and pulmonary venous congestion. Chronic neurohormonal activation (e.g., sympathetic predominance of autonomic nervous system tone, stimulation of the renin-angiotensin-aldosterone axis) also serves to mitigate decreases in cardiac output and mean arterial pressure (MAP) observed in HFrEF, but this response also inadvertently increases heart rate, LV afterload, and myocardial oxygen consumption that further undermine LV systolic function.

In contrast to the marked depression of E_{es} and LV dilatation observed in HFrEF, a steep slope of the LV end-systolic pressure-volume (consistent with systolic stiffening) (Fig. 10.3) and lower LV volumes are characteristic features of HFpEF. Despite the increase in baseline E_{es}, myocardial contractility is abnormal in patients with HFpEF as indicated by tissue Doppler echocardiography, strain imaging, and estimates of LV pressure-volume relations. Depression of myocardial contractility is substantially less severe under resting conditions in patients with HFpEF

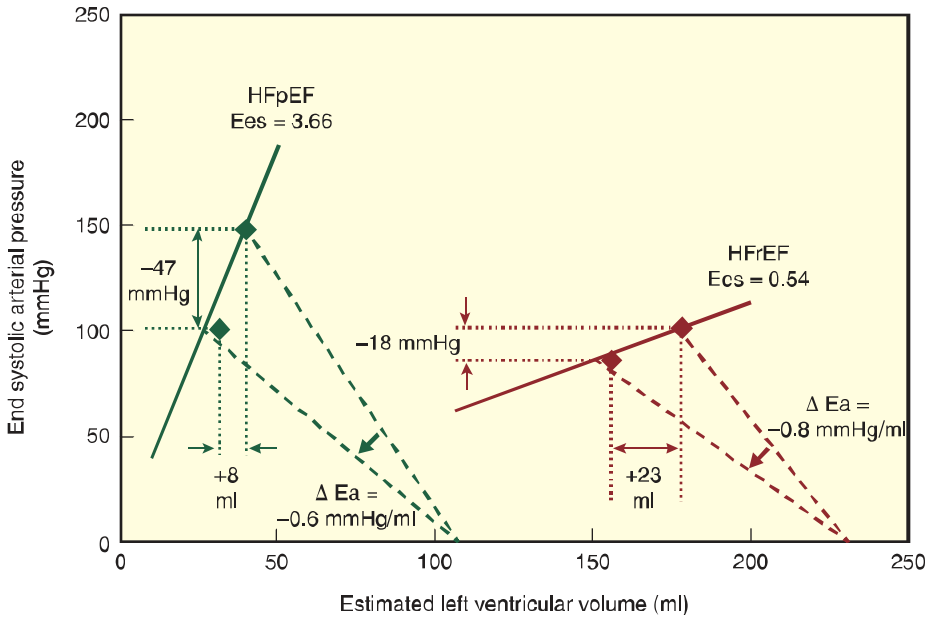

Fig. 10.3 Contractility is severely depressed (low E_{es}) and the end-systolic pressure-volume relationship *(solid line)* is very shallow in heart failure with reduced ejection fraction (HFrEF; *red*). Under these circumstances, a reduction in LV afterload (E_a) produces a relatively minor decrease in arterial pressure, but a large increase in stroke volume. In contrast, E_{es} is high in heart failure with preserved ejection fraction (HFpEF; *black;* indicative of systolic stiffening) and a similar reduction in LV afterload causes a prominent decline in arterial pressure concomitant with a small increase in stroke volume. (Reproduced with permission from Reddy YNV, Borlaug BA. Heart failure with preserved ejection fraction. *Curr Prob Cardiol.* 2016;41:145–188.)

versus HFrEF, but the ability to augment contractility and raise cardiac output during physiologic stress is markedly attenuated. The limitation of systolic reserve is an important cause of exercise intolerance in patients with HFpEF. The systolic stiffening of HFpEF also has important implications for vasodilator therapy. Afterload reduction substantially improves stroke volume with only modest declines in arterial pressure in HFrEF because of the shallow slope of the LV end-systolic pressure-volume relation, but this beneficial effect is not observed in the presence of systolic stiffening associated with HFpEF, as vasodilation causes substantial hypotension with only a modest increase in stroke volume (see Fig. 10.3). As a result, vasodilator therapy is a mainstay in the treatment of HFrEF but not HFpEF.

Ventricular-Arterial Stiffening and Abnormal LV-Arterial Coupling

A reduction in compliance of the aorta and proximal great vessels is a cardinal feature of HFpEF that substantially increases arterial pulse pressure, LV afterload, and myocardial oxygen demand. The magnitude of arterial stiffening observed in HFpEF has been shown to exceed that predicted on solely the basis of the presence of chronic hypertension or advanced age alone. When combined with LV systolic and diastolic stiffening, this increase in arterial stiffness is an important contributing factor to marked lability in arterial pressure that commonly occurs in patients with HFpEF. A series elastic chamber model of the cardiovascular system facilitates understanding of this interaction between arterial and LV systolic stiffening in HFpEF. Effective arterial elastance (E_a, the ratio of LV end-systolic pressure and stroke volume) is an estimate LV afterload that combines its compliance and resistance components (Fig. 10.4). Both E_a and E_{es} are increased in patients with HFpEF (reflecting increased arterial and LV systolic stiffening, respectively), assuring optimal mechanical energy transfer (i.e., stroke volume) from the left ventricle to the great vessels and proximal arterial circulation under resting conditions (see Fig. 10.3). However, the steep slopes of E_a and E_{es} imply that even modest reductions in preload or afterload produced by diuretics or arterial vasodilators may precipitate large declines in arterial pressure. In contrast, LV-arterial coupling is abnormal at rest in HFrEF, primarily because myocardial contractility is depressed (reduced E_{es}) while arterial stiffness (E_a) remains relatively unaffected. In this situation, a decrease in LV afterload (E_a; produced by a vasodilator, for example) is beneficial because matching between the LV and arterial circulation improves and greater forward flow occurs as a result. The elevated LV-arterial stiffening observed in HFpEF also adversely affects the hemodynamic responses of these patients during exercise. Vasodilation is poorly tolerated, and limited LV systolic reserve attenuates increases in myocardial contractility resulting from activation of the sympathetic nervous system. This phenomenon can be especially pronounced in women because arterial stiffness is often greater in women than men, an observation that may contribute to the greater prevalence of HFpEF in women.

Left Atrial Systolic and Diastolic Dysfunction

The left atrium's systolic contribution to LV filling directly increases through the Frank-Starling mechanism when LV

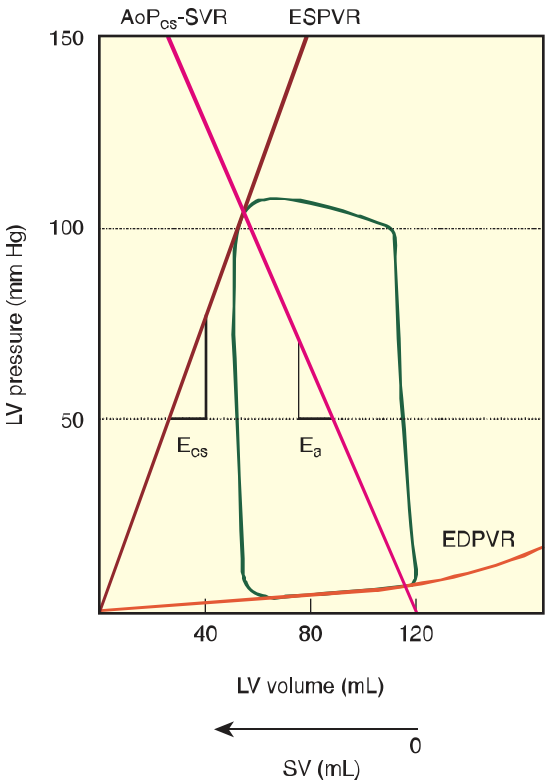

Fig. 10.4 This schematic diagram illustrates the left ventricular *(LV)* end-systolic pressure-volume and aortic end-systolic pressure-stroke volume relations (*ESPVR* and A_cP_{es}-SVR, respectively) used to determine LV-arterial coupling as the ratio of end-systolic elastance (E_{es}; the slope of ESPVR) and effective arterial elastance (E_a; the slope of A_cP_{es}-SVR). (Reproduced with permission from Pagel PS, Freed JK. Cardiac physiology. In: Kaplan JA, Augoustides JGT, Manecke Jr GR, et al., eds. *Kaplan's Cardiac Anesthesia for Cardiac and Noncardiac Surgery.* Philadelphia, PA: Elsevier; 2017:143–178.)

compliance is reduced or LV diastolic pressures are elevated. However, this compensatory augmentation of LA contractility declines as heart failure progresses because LA afterload continues to increase and the left atrium dilates, stretching its myofilaments beyond their ideal operational length, thereby attenuating the chamber's pumping ability and rendering it less capable of actively contributing to LV preload. LA contractile failure eventually occurs as LV compliance continues to decline and end-diastolic pressure increases. LA dilation resulting from chronic increases in LA pressure also reduces the chamber's compliance and its ability to collect pulmonary venous blood. Indeed, remodeling and reduced compliance of the left atrium occur in response to LV diastolic dysfunction, effects that further restrict pulmonary venous blood flow into the left atrium during its reservoir and conduit (diastolic) phases. This LA systolic and diastolic dysfunction occurs in both forms of heart failure but is especially apparent in patients with HFpEF. LA dysfunction in HFpEF has been identified as another factor that limits exercise tolerance in these patients and is associated with pulmonary arterial hypertension (PAH), right ventricular (RV) dysfunction, and mortality. LA dilation is a primary cause of atrial fibrillation, which is present in as many as two-thirds of patients with HFpEF. When LVDD is present in HFpEF or HFrEF, the onset of new

atrial fibrillation often acutely precipitates signs and symptoms of acute decompensation because the loss of LA contraction and elevated heart rate (reduced diastolic filling time) lead to inadequate LV filling and cardiac output. More profound exercise limitations, lower quality of life, increased rate of rehospitalization, and higher mortality are observed in patients with atrial fibrillation versus sinus rhythm in HFpEF.

ACUTE VERSUS CHRONIC HEART FAILURE

Whereas chronic heart failure is classified as those with long-standing disease, acute heart failure is generally described as rapid onset of clinical symptoms of heart failure that requires immediate treatment as these patients often present in life-threatening conditions. Patients may require hospitalization with treatment aimed at decreasing volume status and stabilizing hemodynamics. The term *acute heart failure* applies to both patients who present with worsening symptoms of their preexisting condition (acute decompensated heart failure [ADHF]) and those who present for the first time with signs and symptoms of heart failure (de novo acute heart failure [de novo AHF]). ADHF symptoms include signs of fluid retention leading to congestion (weight gain, dyspnea) as the result of decompensation due to inadequacy or failure of compensatory mechanisms. As opposed to decompensation of a chronic state, de novo AHF is characterized by a sudden increase in intracardiac filling pressures and/or acute myocardial dysfunction. This rapid change in myocardial dynamics leads to an overall decrease in peripheral perfusion and pulmonary edema. Cardiac ischemia due to coronary artery occlusion is the leading cause of de novo HF, therefore management is focused on not only stabilizing hemodynamics but restoring myocardial perfusion to improve myocardial contractility. Less common nonischemic etiologies of de novo HF include viral, drug-induced (toxic), and peripartum cardiomyopathy. Patients who present with de novo HF may experience long-term cardiac dysfunction (chronic heart failure); however, management of underlying insults (e.g., thyroid storm) may lead to complete restoration of myocardial function.

DIAGNOSIS OF HEART FAILURE

Signs and Symptoms

The diagnosis of heart failure is based on a well-known constellation of clinical signs and symptoms, among which fatigue, tachypnea, dyspnea at rest or on exertion, paroxysmal nocturnal dyspnea, orthopnea, a S_3 gallop, jugular venous distention, peripheral edema, exercise intolerance, and evidence of reduced tissue perfusion are the most prominent. Whereas paroxysmal nocturnal dyspnea, pulmonary edema, and dependent edema are more common in patients with HFpEF, S_3 gallop is heard more frequently in those with HFrEF. Notably, jugular venous distention, among other clinical signs, was shown to be the strongest predictor of elevated LV end-diastolic pressures (LVEDPs) in patients with HFpEF. When ejection fraction is reduced, the presence of heart failure symptoms usually establishes the diagnosis of HFrEF following standard guidelines in the absence of other causes (e.g., pericardial or valvular disease). In contrast to HFrEF, the initial diagnosis of HFpEF is often more difficult to make, especially when the patient is asymptomatic or only mildly symptomatic at rest. Many of heart failure symptoms are also relatively generic in nature and can suggest a large differential of other possible cardiac and noncardiac etiologies that require careful assessment to exclude. Cardiac catheterization to define elevated LV systolic and diastolic stiffness using pressure-volume analysis or provocative testing (e.g., exercise, rapid intravascular volume expansion) to fully manifest overt clinical symptoms or characteristic echocardiographic findings may be required for HFpEF to become readily apparent. Direct measurement of RV filling pressures under resting conditions or during exercise also offers useful information about the severity of HFpEF. Mean pulmonary capillary occlusion pressure greater than 15 mm Hg at rest or 25 mm Hg during exercise provides strong evidence of HFpEF and is a predictor of mortality.

Medical Imaging

Chest Radiography

Chest radiography (posteroanterior and lateral views) may detect the presence of pulmonary disease, cardiomegaly, pulmonary venous congestion, and interstitial or alveolar pulmonary edema. An early radiographic sign of LV failure and associated pulmonary venous hypertension is distention of the pulmonary veins in the upper lobes of the lungs. Perivascular edema appears as hilar or perihilar haze. The hilum appears large with ill-defined margins. Kerley lines, which reflect edematous interlobular septae in the upper lung fields (Kerley A lines), lower lung fields (Kerley B lines), or basilar regions of the lungs (Kerley C lines) and produce a honeycomb pattern, may also be present. Alveolar edema produces homogeneous densities in the lung fields, typically in a butterfly pattern. Pleural effusion and pericardial effusion may be observed. Radiographic evidence of pulmonary edema may lag behind the clinical evidence of pulmonary edema by up to 12 hours. Likewise, radiographic patterns of pulmonary congestion may persist for several days after normalization of cardiac filling pressures and resolution of symptoms.

Echocardiography

The American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) published guidelines for the diagnosis of HFpEF (Table 10.4). The ACC/AHA recommendations depend on three factors: heart failure symptoms, ejection fraction greater than 50%, and evidence of LVDD. This approach is useful for patients with clear symptomatology but may be too simplistic when subclinical HFpEF is present. The ESC criteria are more specific and incorporate several echocardiographic indices based on two-dimensional measurements (LV size, wall thickness, and mass; LA size), transmitral blood flow velocity (early LV filling peak "E" velocity), and tissue Doppler imaging (mitral annulus e' wave velocity, E/e' ratio). As should be clear from this definition, the ESC guidelines rely entirely on resting echocardiographic assessment and, like the ACC/AHA guidelines, are limited because they do not incorporate provocative testing.

TABLE 10.4 Diagnostic Criteria for Heart Failure With Preserved Ejection Fraction: Comparison of Major Cardiology Organization Definitions

American College of Cardiology Foundation/ American Heart Association

Heart failure symptoms
LV ejection fraction ≥50%
Evidence of LV diastolic dysfunction

European Society of Cardiology

Heart failure symptoms
LV ejection fraction ≥50%
LV end-diastolic volume <97 mL/m²
Evidence of LV diastolic dysfunction
- Mean e' TDI <9 cm/sec
- E/e' ≥13
- LA volume index >34 mL/m²
- LV mass index ≥115 g/m² (men); ≥95 g/m² (women)
- BNP ≥35 pg/ml or NT-proBNP ≥125 pg/ml (suggestive)

BNP, Brain natriuretic peptide; *LA*, left atrium; *LV*, left ventricle; *NT*, N-terminal; *TDI*, tissue Doppler imaging.

Electrocardiography

Abnormalities on a 12-lead electrocardiogram (ECG) are common in the majority of heart failure patients; however, they are typically the result of the underlying pathology. For instance, there may be evidence of LV hypertrophy, previous MI, various arrhythmias (e.g., atrial fibrillation), and conduction abnormalities that include but are not limited to left or right bundle branch block and a widened QRS complex. Due to the common presence of these abnormalities, the ECG has a low predictive value for the diagnosis or risk prediction of heart failure.

Laboratory Values

Efforts continue toward the discovery of a circulating biomarker that will facilitate early diagnosis, to effectively monitor treatment regimens, and to allow for risk stratification within the population. Measurement of brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) concentrations is an important part of the ESC criteria, as these assessments have been shown to be very useful prognostic indicators in patients with HFpEF. Natriuretic peptide concentrations are related to LV end-diastolic wall stress, which is higher in HFrEF because LV dilation resulting from eccentric remodeling is common. In contrast, concentric hypertrophy and relatively normal LV chamber size are characteristic features of HFpEF. This LV geometry is associated with lower LV end-diastolic wall stress, which is reflected in lower BNP or NT-proBNP levels. Thus changes in BNP and NT-proBNP levels are reflective of hemodynamic alterations within the heart.

While BNP and NT-proBNP remain the most important heart failure biomarkers for diagnosis and risk prediction, other potential biomarkers have emerged that are worth mentioning. For instance, levels of highly sensitive troponins (e.g., troponin T and I; high-sensitivity troponin T/I [hs-TnT/I]) released systemically due to myocardial damage serve as a measure of risk prediction. Both C-reactive protein (CRP) and growth differentiation factor-15 (GDF15) increase within the circulation and represent the inflammatory component of heart failure in noninfected patients. Although not routinely used clinically, next-generation biomarkers, including soluble suppression of tumorigenicity 2 (sST2), galectin-3 (Gal-3), and a few candidate microRNAs (miRNAs) that are primarily released secondary to myocardial fibrosis and hypertrophy, may prove useful to diagnose heart failure and improve risk prediction.

Regardless of the criteria used to identify HFrEF or HFpEF, these diagnoses are essential for anesthesiologists to recognize because they predict major adverse cardiovascular events, including mortality in patients undergoing cardiac or major noncardiac surgery independent of ejection fraction.

CLASSIFICATION OF HEART FAILURE

Both the New York Heart Association (NYHA) and the ACC/AHA have created complementary classification systems for heart failure patients. The NYHA system focuses primarily on the degree of limitation during physical activity, whereas the ACC/AHA provides information regarding both the presence and severity of the disease. Since progression of heart failure is linked to reduced 5-year survival, it is important to note that these stages are progressive and do not allow for regression to a lower classification. Often patients are classified using a combination of both scoring systems. For example, a patient diagnosed with severe aortic stenosis using echocardiography, who experiences shortness of breath with ordinary activity, would be classified as NYHA II, ACC/AHA stage D (2D). Categories of both the NYHA functional classification and the ACC/AHA stages of heart failure can be found in Table 10.5.

TABLE 10.5 Classification Systems for the NYHA and ACC/AHA Stages of Heart Failure

NYHA Functional Classification

Class I:	No limitation of physical activity. Usual physical activity does not result in clinical symptoms.[a]
Class II:	Slight limitation of physical activity. The patient is comfortable at rest; however, activity may cause clinical symptoms.
Class III:	Marked limitation of physical activity. Patient is comfortable at rest; however, low physical activity causes clinical symptoms.
Class IV:	Patient is unable to perform any physical activity without clinical symptoms and experiences these symptoms at rest.

ACC/AHA Stages of Heart Failure

Class A:	No structural evidence of cardiovascular disease. No functional limitation in ordinary physical activity.
Class B:	Evidence of minimal structural cardiovascular disease. Comfortable at rest but slight limitation during ordinary activity.
Class C:	Evidence of moderately severe structural cardiovascular disease. Comfortable only at rest and with limitation in activity due to clinical symptoms.
Class D:	Objective evidence of severe structural cardiovascular disease. Experiences clinical symptoms at rest.

[a]Clinical symptoms include fatigue and/or shortness of breath.
ACC/AHA, American College of Cardiology/American Heart Association; *NYHA*, New York Heart Association.

MANAGEMENT OF HEART FAILURE

Medical Management

Chronic Heart Failure

Survival of patients with HFrEF has steadily improved during the past three decades, but mortality in those with HFpEF remains essentially unchanged. These epidemiologic data emphasize the relative futility of standard pharmacologic therapy (which is clearly beneficial in patients with HFrEF) when applied to those with HFpEF. Indeed, mitigation of heart failure symptoms, aggressive treatment of associated conditions (e.g., hypertension, diabetes), weight loss, and exercise training are the primary objectives for patients with HFpEF (Fig. 10.5) because β blockers and inhibitors of the renin-angiotensin-aldosterone system (RAAS), medications that form the foundation upon which chronic HFrEF management rests, have been consistently shown to lack verifiable efficacy in HFpEF.

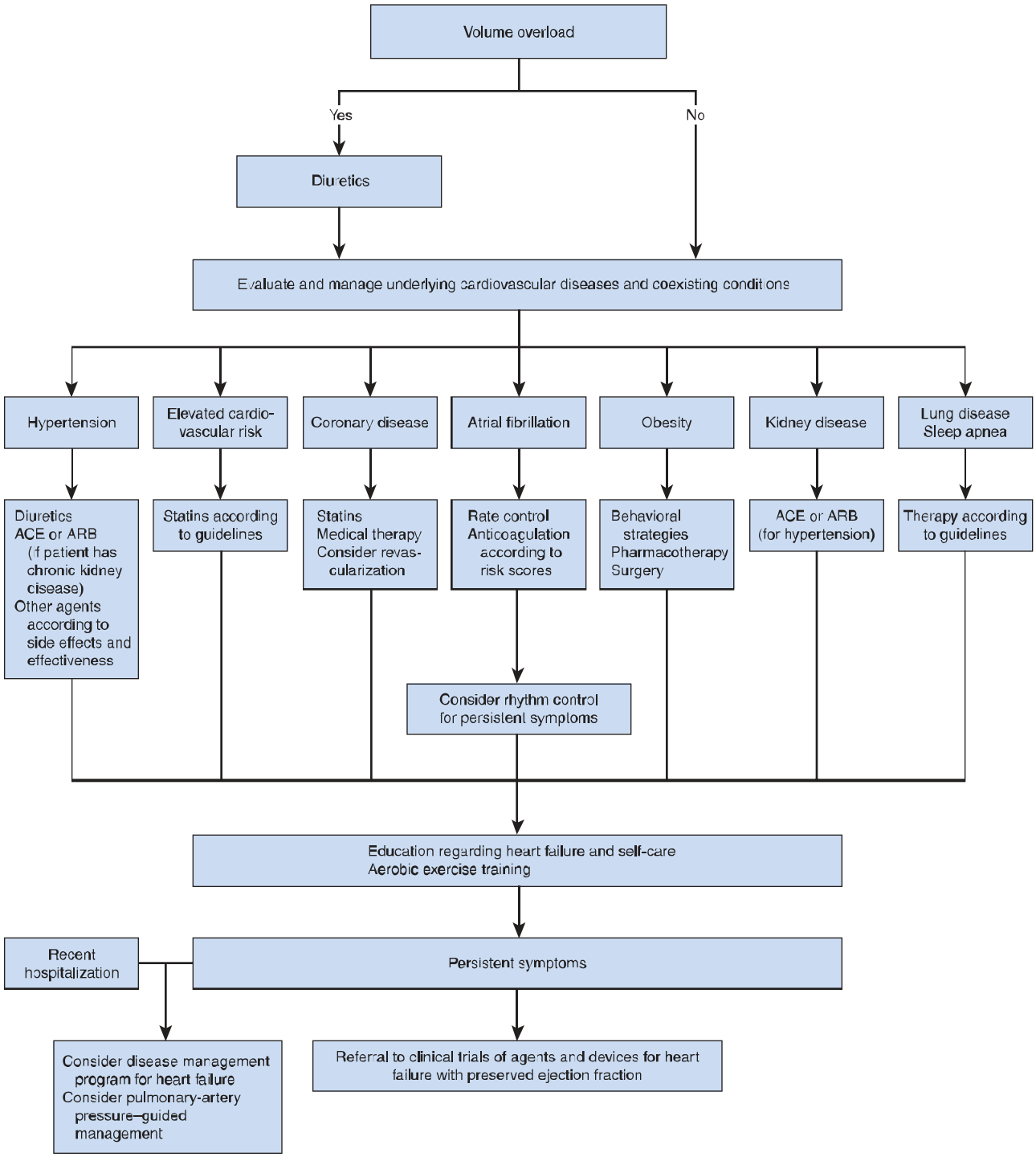

Fig. 10.5 Treatment algorithm for heart failure with preserved ejection fraction. ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker. (Reproduced with permission from Redfield MM. Heart failure with preserved ejection fraction. *N Engl J Med.* 2016;375:1868–1877.)

Diuretics. Furosemide and other loop diuretics reduce LV filling pressures, decrease pulmonary venous congestion, and improve clinical symptoms in patients with acute or chronic HFrEF and HFpEF. These medications are strongly recommended by the ACC/AHA and ESC guidelines. Thiazide diuretics may also be useful in patients with poorly controlled hypertension to reduce the incidence of new HFpEF, an observation that stresses the importance of control of comorbid conditions when managing this condition. An implanted wireless pulmonary artery pressure (PAP) monitor was shown to provide unique information to guide diuretic treatment, decrease LV filling pressures, and reduce heart failure hospitalizations in NYHA class III patients with either HFrEF or HFpEF. These interesting results not only suggest that novel hemodynamic monitoring devices may eventually prove to have utility for heart failure treatment but also emphasize the central role of diuretic therapy in its management.

β blockers. Several major randomized controlled clinical trials demonstrated that β blockers are beneficial for the treatment of HFrEF. These medications are strongly recommended for this clinical indication (class I evidence) in the most recent ACC/AHA and ESC guidelines. In contrast, whether β blockers have utility in patients with HFpEF could not be definitively established in the multitude of observational studies and clinical trials that addressed this question to date. The β blocker nebivolol reduced mortality and cardiovascular-related hospital admission in elderly patients with heart failure, but no differences were observed in those with HFrEF versus HFpEF. Notably, the definition of HFpEF used in this study included patients with ejection fraction greater than 35% (as opposed to the currently accepted value of 50%), suggesting that any salutary effect of nebivolol observed in the HFpEF group may have resulted from inclusion of a substantial number of patients with HFrEF. Another randomized controlled trial showed that long-term treatment with nebivolol did not reduce clinical symptoms or improve exercise capacity (as quantified using a 6-minute walk distance test) in patients with HFpEF. Cardiovascular mortality and hospitalization related to heart failure were similar in patients with HFpEF who received carvedilol compared with placebo, although this study's findings were later criticized because the dose of carvedilol may have been insufficient to positively influence outcome. A propensity-matched cohort study examined the impact of β blockers on mortality in 8244 patients with HFpEF. The results indicated that use of β blockers was associated with modest, but statistically significant, declines in 1- and 5-year mortality compared with conventional treatment. Conversely, a large retrospective study of 4123 Medicare patients with HFpEF indicated that β blockers did not affect mortality or rehospitalization rates. Two meta-analyses also suggested that all-cause mortality may be marginally lower in HFpEF patients treated with β blockers, but no differences were observed in hospitalization rates for heart failure. To date, no large-scale randomized clinical trial of β blockers has been performed to further define the role of this class of medications in HFpEF. Thus use of β blockers in patients with HFpEF should be restricted to other clinical indications (e.g., treatment of hypertension or MI; rate control in atrial fibrillation).

Inhibitors of the renin-angiotensin-aldosterone system. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are mainstays of medical therapy for HFrEF. Five major randomized clinical trials conducted to date studied the effects of ACE inhibitors and ARBs on mortality and hospitalization rates in patients with HFpEF, but their collective findings have been remarkably disappointing. The ARB candesartan did not change cardiovascular mortality during a 3-year follow-up in 1514 patients with HFpEF compared with placebo. This trial did show that hospitalization rates were lower in those treated with candesartan, but these patients also had a higher rate of adverse side effects. Similar to the findings of this trial, the ACE inhibitor perindopril did not improve 3-year survival compared with placebo in elderly HFpEF patients (≥70 years). Nevertheless, a modest increase in exercise tolerance and a decrease in NYHA classification were observed in those treated with perindopril, most likely because hypertension was more effectively managed with the ACE inhibitor. Another RAAS inhibitor trial compared the effects of the ARB irbesartan against placebo in patients with HFpEF. After more than 4 years of follow-up, no differences in mortality or hospitalization rate for heart failure were observed between groups. Not surprisingly, a meta-analysis incorporating these three trials also concluded that ACE inhibitors or ARBs did not reduce mortality or hospitalization in those with HFpEF.

The effects of the aldosterone antagonist spironolactone were subsequently compared with placebo in another randomized double-blind trial of 3445 patients with HFpEF. No differences in the primary composite end points, including cardiovascular mortality, survival after cardiac arrest, and total hospital admissions for heart failure, were observed between groups. Nevertheless, the rate of heart failure hospital admission was lower in those receiving spironolactone, suggesting that the medication may have some modest utility in these patients. Most recently, an eagerly awaited randomized clinical trial demonstrated that the angiotensin receptor neprilysin inhibitor valsartan-sacubril did not reduce cardiovascular mortality or total hospitalizations for heart failure in patients with HFpEF compared with placebo. These latter findings were particularly disheartening not only because valsartan-sacubril had been previously shown to increase survival and decrease hospitalization rate in patients with HFrEF compared with the ACE inhibitor enalapril, but also because the drug combination favorably reduced NT-proBNP concentration, LA size, and NYHA functional class compared with the valsartan alone in those with HFpEF. Despite these negative results, ACE inhibitors and ARBs continue to be useful for control of arterial pressure in patients with hypertension and HFpEF.

Other medications. The results of clinical trials in which other medications were studied have also failed to yield encouraging results in patients with HFpEF. The effects of digoxin on cardiovascular mortality and heart failure hospitalizations were compared with placebo in patients with HFpEF. No differences between groups were observed after 37 months of follow-up. Another trial examined the effects of chronic treatment with phosphodiesterase (PDE) fraction V inhibitor sildenafil on functional capacity in HFpEF. Sildenafil did not improve peak

oxygen consumption, 6-minute walk distance, quality-of-life scores, or indices of LV diastolic function after 24 weeks of treatment compared with placebo. Similar results were reported in a clinical trial of isosorbide mononitrate. More recently, exercise capacity, daily activity, NYHA functional class, E/e' ratio (an echocardiographic estimate of LA pressure), and NT-proBNP concentrations were similar in patients with HFpEF treated with a 4-week course of an inhaled inorganic nitrite compared with those receiving placebo. Some data suggest that statins may have beneficial effects on survival and hospitalization rates in patients with HFpEF, but the evidence supporting this contention is inconsistent. A small observational study indicated that statins, but not β blockers, RAAS inhibitors, or Ca^{2+} channel antagonists, reduced mortality and cardiovascular-related hospitalization in HFpEF. These findings were supported by the results of two meta-analyses and a retrospective propensity-matched study from the Swedish Heart Failure Registry. Nevertheless, rosuvastatin failed to provide these salutary effects in HFpEF when a subanalysis of a large sample of heart failure patients was conducted. A multicenter randomized controlled trial is needed to clearly define whether statins play an important role in HFpEF.

Lifestyle modifications and control of comorbidities. Exercise training augments aerobic fitness, reduces clinical symptoms, and increases self-reported quality of life in patients with HFrEF and HFpEF. These salutary effects result primarily from enhanced peripheral oxygen utilization, but some direct cardiac benefits may be accrued as well. When combined with exercise training, weight loss achieved through caloric restriction provided additive benefits on aerobic capacity. The type, intensity, and duration of exercise and the magnitude of weight loss required to maintain such favorable effects are yet to be clearly defined, but such lifestyle modifications also significantly mitigate the impact of major risk factors for heart failure, including hypertension and diabetes. Simple diet modifications may also be helpful to partially reverse some of the adverse hemodynamic consequences of heart failure. For example, a 3-week course of a salt-restricted Dietary Approaches to Stop Hypertension (DASH) diet improved indices of LV diastolic function, decreased arterial stiffness, and facilitated more favorable LV-arterial coupling in patients with HFpEF.

Hypertension is a major risk factor for HFrEF and HFpEF, so it is not surprising that control of arterial pressure (using diuretics, β blockers, or RAAS inhibitors) is of paramount importance to reduce the incidence and severity of heart failure, especially in the elderly. A recent large randomized clinical trial showed that the incidence of heart failure was reduced by 37% when systolic arterial pressure was maintained less than 120 mm Hg compared with 140 mm Hg in nondiabetic, hypertensive patients with increased cardiovascular risk. This aggressive control of hypertension was especially beneficial in elderly patients. The results of these and other trials examining the impact of hypertension control on cardiovascular outcome emphasize one of the most notable consequences of such an intervention is the reduction in heart failure risk. Unfortunately, this strategy does not appear to extend to patients with type 2 diabetes mellitus, as intensive blood pressure control was not associated with a lower risk of heart failure in this patient population. In contrast, tighter glycemic control using sodium-glucose cotransport protein 2 (SGLT2) inhibitors has been shown to substantially reduce heart failure hospitalizations and mortality in diabetics. Coronary artery disease is very common in patients with both phenotypes of heart failure, and the current ACC/AHA guidelines recommend coronary artery surgery if myocardial ischemia is determined to be a contributing factor. Atrial fibrillation is also frequently observed in patients with HFrEF or HFpEF, a complication that is independently associated with RV dysfunction, tricuspid regurgitation, exercise intolerance, and mortality. Reestablishing and maintaining sinus rhythm may be an important theoretical goal in patients with heart failure and atrial fibrillation, but this objective is sometimes not feasible despite antiarrhythmic medications or multiple catheter-based or surgical radiofrequency or cryoablation interventions because of fundamental time-dependent alterations in LA structure and function. Nevertheless, rate control in chronic atrial fibrillation appears to be an acceptable alternative to restoration of sinus rhythm in patients with HFrEF. Indeed, symptom reduction is the primary goal of atrial fibrillation management following established guidelines. A highly anticipated new clinical trial will undoubtedly provide additional insight into the impact of coexisting disease management on outcome in elderly patients with HFpEF.

Acute Heart Failure

As patients may present either in ADHF or de novo HF, the anesthesiologist may be faced with stabilizing these patients for emergent or urgent surgery. Likewise, decompensation may occur in heart failure patients during routine elective cases. The hemodynamic profile includes a low cardiac output state, high ventricular filling pressures, and hypertension or hypotension.

Diuretics. Despite limited clinical trial data showing efficacy, diuretics remain a first-line therapy for patients presenting in acute heart failure. Per the 2013 ACC/AHA heart failure guidelines, diuretics should be immediately administered in patients with significant fluid overload. Rapid administration of a loop diuretic not only controls the symptoms related to volume overload (dyspnea) but may also improve in-hospital mortality as shown in a large multicenter, prospective observational study. However swift administration of diuretics may not be ideal in patients with severe hypotension or cardiogenic shock, in which case the patient may first require hemodynamic or mechanical circulatory support prior to diuretic therapy. Furosemide, bumetanide, and torsemide, used as continuous infusions or as bolus administrations, are commonly used to encourage diuresis in this patient population. The reduction in intravascular volume leads to decreased central venous and pulmonary capillary wedge pressures (PCWP), thus reducing overall pulmonary congestion. There is further evidence that furosemide, and potentially other loop diuretics, cause the release of prostaglandins and decrease acute pulmonary edema irrespective of the effect on intravascular volume.

Vasodilators. The use of vasodilators has also proven to be efficacious in correcting elevated filling pressures and reducing afterload. Similar to diuretics, evidence pertaining to efficacy in

the acute heart failure setting is lacking. Careful consideration of the vasodilator is critical and is based on the underlying hemodynamics. Use of nitroprusside is an effective approach to rapidly decrease left ventricular afterload in patient with severe hypertension, whereas nitroglycerin, which primarily decreases venous tone, is commonly used as an adjunct to diuretic therapy. As with many heart failure treatments, the routine use of vasodilators in acute situations does not improve outcomes, including mortality or rehospitalization rates.

Vasopressin receptor antagonists. Vasopressin receptor antagonists such as tolvaptan have emerged as potential adjunct therapy with the goal of reducing arterial constriction, hyponatremia, and volume overload associated with acute heart failure. The ACC/AHA guidelines recommend reasonable, short-term use of vasopressin antagonists in hospitalized patients with persistent severe hyponatremia due to volume overload, placing them at risk for cognitive dysfunction.

Inotropic support. The mainstay treatment for patients presenting with acute reduced contractility, or cardiogenic shock, are positive inotropic agents. Several pharmacologic agents are available to be administered intravenously with the goal to increase cyclic adenosine monophosphate (cAMP) levels. The rise in cAMP promotes an increase in intracellular calcium and efficient excitation-contraction coupling. Each inotropic agent increases cAMP via different mechanisms, giving each a unique set of side effects. Catecholamines (epinephrine, norepinephrine, dopamine, dobutamine) directly interact with β receptors on the myocardium to activate adenylyl cyclase to increase cAMP, whereas PDE inhibitors (milrinone) indirectly increase cAMP by inhibiting its degradation. Mechanism of action as well as hemodynamic effects of commonly used inotropic agents are shown in Table 10.6.

Calcium sensitizers. A paradigm shift with regard to inotrope development has occurred within the last decade. As opposed to traditional inotropes that increase intracellular levels of calcium, which increase myocardial oxygen consumption, heart rate, and cause dysrhythmias, myofilament calcium sensitizers are a novel approach to increasing contractility. To date, only three such drugs have been developed: levosimendan, pimobendane, and omecamtiv mecarbil. Of the three, levosimendan has been utilized the most in a clinical setting. Interestingly, levosimendan is also capable of eliciting vasodilation, and at higher doses it can inhibit PDE. These pleiotropic effects extend beyond the heart and possibly protect renal, hepatic, and neural cells from reperfusion injury. Omecamtiv mecarbil is also emerging as a potential therapy with recent a clinical trial (GALACTIC-HF) showing a lower incidence of heart failure events or death compared to placebo.

TABLE 10.6 Commonly Used Inotropic Agents in Patients With Acute Heart Failure

Medication	Mechanism	CO	MAP	HR
Epinephrine	β1 = β2 > α	hh	hh	hh
Norepinephrine	α > β1 > β2	h	h	↔ or g
Dobutamine	β1 > β2 > α	↔ or g	hh	hh
Dopamine	D > β (α with HD)	h	h	hhh
Milrinone	PDE inhibition	h	↔ or g	↔ or h
Levosimendan	Calcium sensitization	hh	‹ › or g	hh

α, Adrenergic α receptor; β, adrenergic β receptor; *CO*, cardiac output; *D*, dopamine receptor; *HR*, heart rate; *MAP*, mean arterial pressure.

Exogenous B-type natriuretic peptide. Nesiritide, a recombinant BNP that binds to both the A- and B-type natriuretic receptors, inhibits the RAAS and promotes arterial, venous, and coronary vasodilation, thereby decreasing LVEDP and improving dyspnea. It also induces diuresis and natriuresis, can relax cardiac muscle, and lacks any prodysrhythmic effects. Enthusiasm for nesiritide as an effective therapy has diminished as it has not shown superiority over traditional vasodilators such as nitroglycerin or nitroprusside. The extended half-life compared to other vasodilators also allows side effects such as hypotension to persist, which may account for the worsening renal function observed in clinical trials.

Ularitide, a synthetic analog of the kidney peptide hormone urodilatin, also binds to A-type natriuretic receptors and promotes diuresis and natriuresis. Phase 1 clinical trials found that it decreases both systemic vascular resistance and PCWP while increasing cardiac index and stroke volume in patients in acute heart failure. Findings from larger scale studies have shown that ularitide can exert beneficial hemodynamic effects yet fails to reduce myocardial injury and affect overall outcomes.

Surgical Management

Chronic Heart Failure

Despite development of pharmacologic therapy to improve outcomes, the overall burden of congestive heart failure remains high. Initially, systolic dysfunction (HFrEF) was thought secondary to impairment of the contractile properties of the myocardium. However, advancement in our understanding of heart failure has led to the belief that increases in ventricular chamber volume and chamber dilation precede contractile dysfunction. Myocardial remodeling is referred to as the pathologic change in chamber length and shape causing the heart to dilate resulting in greater wall tension, decreased subendocardial blood flow, and increased incidence of arrhythmias. The goal of surgical treatment for chronic heart failure is to prevent ventricular remodeling in an attempt to retain the natural geometry of the heart.

Revascularization therapy. Coronary revascularization therapy, either via coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), can be very effective at reversing LV dysfunction following MI. Successful early revascularization may prevent permanent reductions in ejection fraction by recovering viable "stunned" myocardium when the ischemic insult is acute; however, it is also capable of restoring function in chronic ischemic hearts or "hibernating" myocardium. CABG has been shown to reduce 10-year overall mortality by 7%. Surgical revascularization is recommended in patients with heart failure and reduced LV function combined with significant left main coronary artery disease, left main equivalent disease (≥70% stenosis of proximal left anterior descending artery [LAD] and proximal left circumflex artery), or proximal LAD stenosis with two- to three-vessel disease.

The STICH (Surgical Treatment for Ischemic Heart Failure) trial examined the effects of CABG plus medical therapy to medical therapy alone on mortality due to sudden death and fatal pump failure events. The inclusion of CABG resulted in an overall decrease in death due to MI 2 years following surgery. This benefit is slightly offset by the increase in postprocedure deaths in the CABG plus medical therapy cohort.

Cardiac resynchronization therapy. Cardiac resynchronization therapy (CRT) is aimed at patients with heart failure who have a ventricular conduction delay (QRS prolongation on ECG). Such a conduction delay creates a mechanical dysynchrony that impairs ventricular function and worsens prognosis. CRT, also known as biventricular pacing, consists of placement of a dual-chamber cardiac pacemaker (RA and RV leads), with an additional lead introduced via the coronary sinus into an epicardial coronary vein and advanced until it reaches the lateral wall of the left ventricle. With this lead in place and the timing adjusted, the heart can contract more synchronously and efficiently and eject a larger cardiac output. Classically, CRT has been recommended for patients with NYHA class III or IV disease with left ventricular ejection fraction (LVEF) less than 35% and a QRS duration of 120 to 150 ms. Recent trials suggest a benefit of CRT in heart failure patients with an ejection fraction above 30% and even mild symptoms. Patients who undergo CRT have fewer symptoms of heart failure, better exercise tolerance, improved ventricular function, fewer hospitalizations, and decreased mortality compared with similar patients receiving drug therapy alone. The reverse remodeling process induced by CRT appears to be the main reason for the improved survival seen in some patients. However, this form of therapy fails to produce an improvement in about one-third of patients.

Permanent leads within the heart have their own inherent risks, including infection, malposition, and failure requiring removal and replacement. Leadless systems that include a subcutaneous pulse generator and a small receiver electrode implanted in the LV myocardium are gaining interest for use in this patient population. Another potential pacing technology that uses electromagnetic induction through a subcutaneous transmitter, along with a receiver that is implanted in the ventricle, is in development.

Implantable hemodynamic monitors. Implantable hemodynamic monitoring has shown promise to remotely observe changes in intracardiac pressures in an attempt to prevent decompensation and reduce hospitalization rates. The CardioMEMS Heart Failure system allows for management of LV filling pressures with proactive titration of medications based on daily measurement of PAP obtained noninvasively at home by the patient and then uploaded to the physician managing the heart fail. The sensor unit contains a wireless system to measure PAP that does not require battery power for operation, nor does it have any replaceable parts. It is implanted via right heart catheterization into the pulmonary artery, and an external antenna allows for determination of the resonant frequency of the device, which is converted to a pressure waveform. The COMPASS-HF trial (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) found a modest reduction in hospitalizations and emergency room visits in patients with the device.

Implantable cardioverter-defibrillators. Implantable cardioverter-defibrillators (ICDs) are used for prevention of sudden death in patients with advanced heart failure. Approximately one-half of deaths in heart failure patients are sudden and due to cardiac dysrhythmias. Recent studies have demonstrated that patients treated with a combination of CRT and ICD placement have fewer hospitalizations and better survival rates at 2 years than patients who receive only ICD therapy. However, this advantage comes at the cost of higher device-related complication rates in the first 30 days after implantation.

Left ventricular assist devices. While heart transplantation remains the gold standard for end-stage heart failure, the shortage of donors combined with the contraindications for transplant limit this as an option for most suffering from heart failure. Patients in the terminal stages of heart failure may benefit from mechanical circulatory support (MCS) by a device such as a ventricular assist device (VAD) or a total artificial heart. Studies have demonstrated not only increased survival but also improved quality of life in heart failure patients treated with VADs compared to those treated with medical therapy alone. These mechanical pumps can take over partial or total function of the damaged ventricle and facilitate restoration of normal hemodynamics and tissue blood flow. A VAD drains blood returning to the failed side of the heart and pumps it downstream of the failed ventricle. These devices are useful in patients who require temporary ventricular assistance to allow the heart to recover its function (bridge to recovery), in patients who are awaiting cardiac transplantation (bridge to therapy), in patients who are on inotropic drugs or intraaortic balloon pump (IABP) counterpulsation with potentially reversible medical conditions (bridge to decision), and in patients with advanced heart failure who are not transplant candidates (destination therapy).

First-generation left ventricular assist devices (LVADs) captured the entire cardiac output and ejected it in a pulsatile fashion into the ascending aorta to simulate the work of the native left ventricle. This pulsatile flow required a complicated mechanism that included valves preventing systolic retrograde blood flow. As a result, first-generation LVADs were noisy, fairly large, and prone to significant complications due to mechanical pump failure and thromboembolic events. With the advent of modern miniaturization technology and a general acceptance by the medical community that nonpulsatile flow can be well tolerated, second- and third-generation LVADs were developed. Modern continuous flow centrifugal pumps have largely replaced the use of axial and older pulsatile VADs. The durability, injury to blood components, and need for anticoagulation continue to improve with each iteration. The most commonly used devices are the HeartWare and the Heartmate II and III (Heartmate II is shown in Fig. 10.6). These devices are surgically implanted into the LV apex through sternotomy or thoracotomy and attached by tube graft to the aorta. Externalized drive lines are tunneled through the skin for external power and control mechanisms. The only user control is the RPM setting, which is controlled in the range of 2400 to 10,000 RPM, depending on the device. These pumps typically provide 4 to 7 L

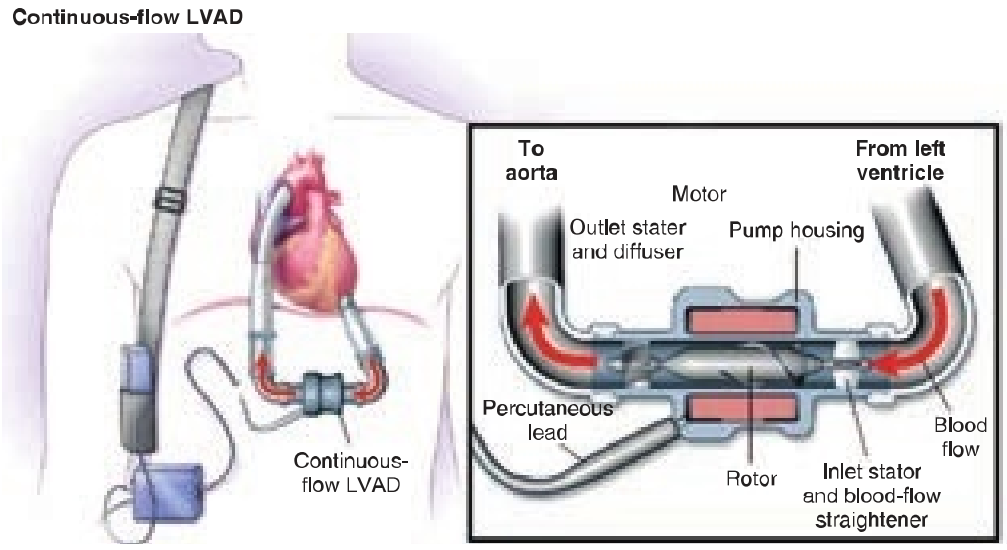

Fig. 10.6 HeartMate II left ventricular assist device *(LVAD)*. Blood is drawn through the inflow cannula attached to the ventricular apex into the pump and is ejected into the ascending aorta through the outflow cannula. The percutaneous lead is the drive line, which exits the right side of the abdomen and connects the pump to the external console and power source.

of flow per minute with the capacity up to 10 L/min. Inpatient monitoring consoles provide estimations of flow by analyzing RPM setting and power utilization. These three variables (RPM, power, and flow) can help determine the presence and location of a suspected device thrombus based on available manufacturer data. In addition to these data, monitors also display either a continuous flow versus time waveform or a proprietary "pulsatility index." Ventricular contractions provide cyclic augmentation of device preload. Either waveform analysis or pulsatility index information is helpful to patient management. Management algorithms based on flow, waveforms or pulsatility index, central venous pressure (CVP), and MAP can help clinicians generate a differential diagnosis, indicate needed testing, and suggest therapeutic interventions.

Patients with fixed pulmonary hypertension requiring biventricular support for extended periods of time may benefit from implantation of a total artificial heart (TAH). A TAH can be implanted in the chest in lieu of the native heart. Such a device generates pulsatile flow and consists of two mechanical pumps, each operating as a "ventricle," with each pump having two valves. Currently the SynCardia Total Artificial Heart is approved as a bridge to cardiac transplantation and has received designation as a humanitarian use device (HUD), so it can also be used as destination therapy. The maximum dynamic stroke volume of each "ventricle" in this system is 70 mL, allowing generation of flow rates (cardiac output) of up to 9.5 L/min. It also comes in a 50-mL size intended for most women, small adults, and adolescents.

Acute Heart Failure

In the acute setting, when medical management fails or disease progression is so severe that organ dysfunction is present, urgent placement of MCS is indicated. Under the sponsorship of the National Heart, Lung, and Blood Institute (NHLBI), the Society of Thoracic Surgeons (STS) developed an Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) that utilizes patient clinical profiles to assist in the MCS decision-making process (Table 10.7). Profile 1 and 2 likely require emergent workup and placement of mechanical support. Temporary support allows time for the multidisciplinary workup to be completed and prevent organ failure that may limit options and outcomes.

Broad categories of complications include vascular injury and loss of limb(s), infection, bleeding, stroke/intracranial hemorrhage, gastrointestinal bleeding, and multiorgan failure. MCS support benefits are primarily from a reduction in exposure to inotropes, reduced influence of ventricular arrythmia, unloading of dilated ventricles, and increased end-organ perfusion. MCS initiation after irreversible end-organ injury is unlikely to be of significant benefit to the patient, but early and aggressive use may also subject patients to harm that may not have needed such invasive therapies.

Intraaortic balloon pump. Balloon counterpulsation functions by cyclic helium inflation of a balloon after aortic valve closure, followed by deflation during LV systole. Significant aortic valve incompetence and aortic dissection represent the main absolute contraindication to use. IABP provides significant improvement to LV coronary perfusion by increased diastolic pressure and reduced LVEDP. Transesophageal echocardiography (TEE) and x-ray are the primary modalities for placement evaluation. Radiopaque markers are seen at the limits of the balloon portion and should be seen just below the aortic knob on x-ray (Fig. 10.7). The support provided by IABP varies based on the set augmentation (amount of inflation/deflation), the size of balloon, and the ratio of supported beats. Full support would be 1:1 or an inflation for every heartbeat; however, in the setting of tachycardia, a setting of 1:2 (one inflation per every two heartbeats) is ideal. Overall, this therapy provides only modest improvements in cardiac output (0.5–1 L/min) and generally immobilizes patients, limiting its use as a long-term support device.

TABLE 10.7 INTERMACS Profile System

	Description	Rest Symptoms	Activity Tolerance	Notes
1	Crashing	Severe	Intolerant	Critically ill and moribund
2	Failing on inotropes	Present	Intolerant	Inpatients with congestion despite inotropes
3	Inotrope dependent	Variable	Variable	May be home and active
4	Symptoms at rest	Present	Intolerant	At home with oral therapy
5	Exertion intolerance	None	Intolerant	Significant limitations
6	Exertion limited	None	Some	Generally independent
7	NYHA class III	None	Minimal discomfort	History of CHF

CHF, congestive heart failure; *NYHA*, New York Heart Association.

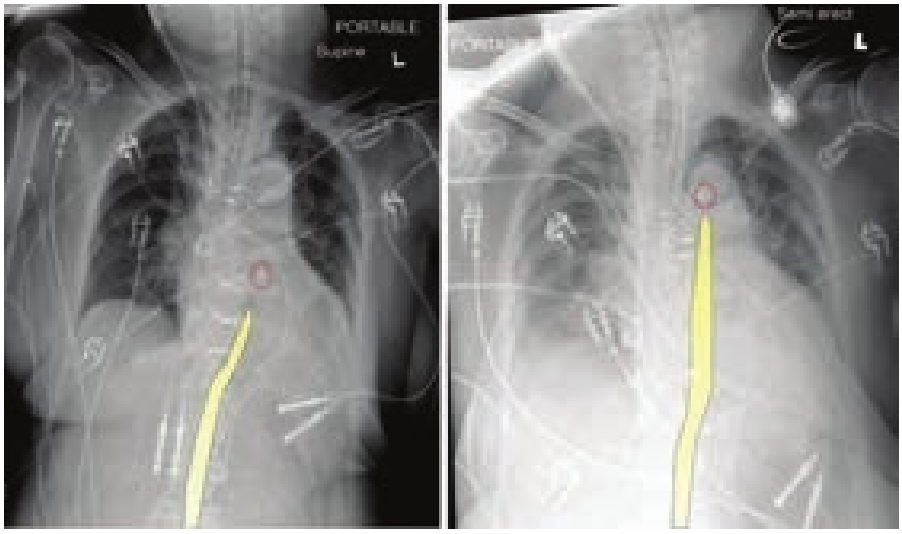

Fig. 10.7 Verifying proper placement of intraaortic balloon pump (IABP). The blue circles in each image represent the aortic knob in a semiupright portable chest x-ray. The red circle identifies the radiopaque marker signifying the proximal end of the balloon that should be within 2 cm of the aortic knob. The balloon can be seen inflated and is outlined by the yellow shape. The left image shows the balloon too distal, potentially obstructing visceral vessels. The image on the right shows the balloon's proximal marker slightly too high, likely at the level of the left subclavian origin.

Impella. The Impella (Abiomed) is a VAD that can be placed percutaneously to reduce LV strain and myocardial work in the setting of acute heart failure. This temporary support can be utilized for up to 14 days and can serve as a transition to recovery or as a bridge to a definitive cardiac procedure (e.g., coronary artery stenting, CABG, VAD insertion, TAH, or heart transplant). Clinical trials have shown that percutaneous VADs offer superior hemodynamic support; however, they fail to decrease 30-day mortality compared to IABP. The Impella system consists of a miniaturized axial-flow rotary blood pump that is inserted via the femoral artery and advanced under fluoroscopic or TEE guidance until it passes through the aortic valve and is situated in the LV cavity (Fig. 10.8). The pump draws blood continuously from the left ventricle through the distal port and ejects it into the ascending aorta through the proximal port of the device. Impella 2.5, CP, LD, 5.0, and 5.5 are US Food and Drug Administration (FDA) approved for temporary support with different clinical indications. For instance, the 5.0 and 5.5 devices require surgical placement into larger arteries, such as the carotid artery, or directly into the thoracic aorta via an axillary graft. In the event that right-sided support is needed, the device (Impella RP) would be inserted via a central vein

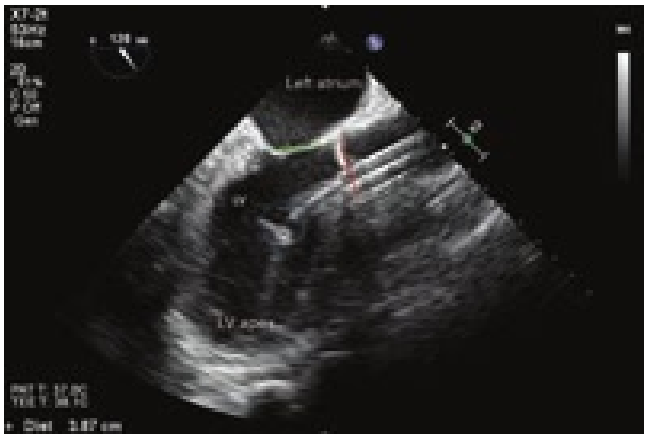

Fig. 10.8 Transesophageal echocardiography (TEE) image of proper Impella placement. Midesophageal long-axis TEE image. The Impella device is in ideal position approximately 3.5 cm from the aortic valve and directed away from the mitral valve into the midcavity of the left ventricle *(LV)*. Red line represents the aortic valve. Green line represents the mitral valve. The two parallel lines crossing the aortic valve are the external housing of the Impella device. The blue circle highlights the inflow opening that is seen as a gap or occasionally as a shimmering generated by the spinning impeller.

into the right ventricle, and ejection of blood from the distal port would enter the pulmonary arteries. Device placement is confirmed with x-ray or echocardiography. TEE provides optimal viewing since the inlet and outlet can be identified, as well as any interaction with the mitral valve structures. Ideally, the inlet should be visualized within the ventricular midcavity, approximately 3.5 cm from the aortic valve to inlet opening.

Impella flow can range from 2 to 6 L/min, which is estimated from the power setting (p-level). Impella placement is contraindicated in the presence of a prosthetic aortic valve, severe aortic stenosis, aortic regurgitation, or severe peripheral vascular disease. However, in such cases the axillary artery could serve as the insertion site of an Impella 5.0 or 5.5. Complications typically arise from thrombotic events, aortic insufficiency, aortic valve injury, dysrhythmias, atrial fibrillation, cardiac tamponade, vascular injury with limb ischemia, thrombocytopenia, and infection.

Peripheral VAD/ECMO. Both the TandemHeart and the ProtekDuo (both manufactured by TandemLife) are extracorporeal support devices that can be used to provide extracorporeal membrane oxygenation (ECMO). The Tandem pump and controller are smaller, which can be valuable during transport, but also generate more heat resulting in more hemolysis and lower flows. TandemLife has recently introduced its own centrifugal pump, LifeSPARC, which maintains portability and reduces heat production with a magnetically levitating pump head. If these percutaneous devices have an oxygenator in-line they are considered ECMO, as opposed to having no oxygenator, but used to provide support for either the right (RVAD) or left (LVAD) side of the heart. Various cannula configurations are possible to produce a flow rate in the range of 2 to 7 L/min (Fig. 10.9).

The TandemHeart system utilizes a long, femorally inserted cannula that traverses the atrial septum to drain blood from the left atrium, then centrifugally pumped back into the femoral artery. While the device offers LV support, flow is often limited to 2 to 5 L/min. In addition, femoral return of blood can increase LV afterload and reduce the effectiveness on intrinsic LV function. One benefit to this configuration is that an oxygenator is not required since oxygenated blood is drawn into the pump from the pulmonary return.

The ProtekDuo also relies on a long peripherally inserted dual lumen cannula that can be placed in the right internal jugular or subclavian vein. This system is designed to drain the right ventricle at the proximal lumen and subsequently return the blood to the pulmonary artery through the distal lumen as a peripheral RVAD or ECMO depending on the absence or presence of an oxygenator, respectively. Cannula placement is typically performed under fluoroscopy, and TEE can be used to confirm accuracy and to ensure the outflow of blood is within the pulmonary artery as opposed to being directed back into the right ventricle, thus causing a recirculation phenomenon. Iatrogenic superior vena cava (SVC) syndrome is a complication of ProtekDuo cannulation as the cannula may significantly obstruct venous drainage at, or above, the level of the SVC.

Central VAD/ECMO. Central ECMO may be necessary for cardiorespiratory support or as an alternative to peripheral ECMO if adequate flow rates are not achievable. Central placement of cannulas in the right atrium (outflow) and aorta (inflow) is maximally invasive and requires sternotomy or thoracotomy for access. The benefits to central ECMO are complete ventricular decompression, avoidance of limb complications, and avoidance of SVC syndrome. The main disadvantages arise from the invasiveness of the approach and include bleeding, infection, aortic dissection, patient immobility, and the potential of ischemic events during cannula placement.

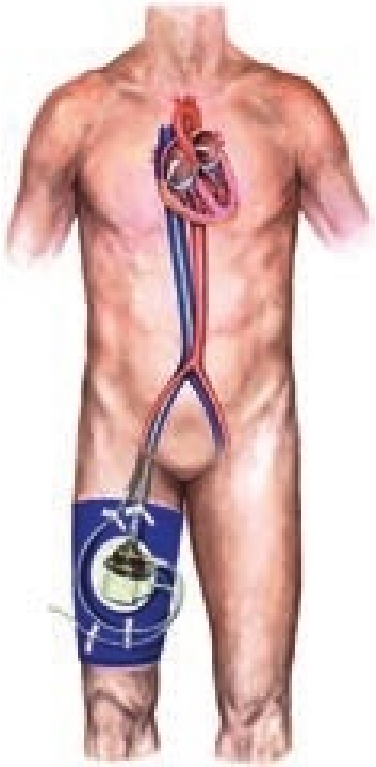

Fig. 10.9 TandemHeart percutaneous ventricular assist device. The inflow cannula is placed in the femoral vein and advanced into the right atrium. It then pierces the interatrial septum to draw oxygenated blood from the left atrium. The outflow cannula pumps blood retrograde into the aorta via the femoral artery.

It is important to stress that despite possibly having normal lung function, patients on ECMO likely have reduced lung perfusion as blood bypasses the lungs prior to return in the aorta. Uptake of inhalational anesthetic may be significantly limited by functional shunting around the lungs. End-tidal CO_2 monitoring may serve to differentiate patients with and without meaningful pulmonary uptake of anesthetic gases. Total intravenous anesthesia (TIVA) should be considered for patients requiring procedures while on ECMO. It is also important to recognize that the ECMO membrane is lipophilic causing many agents, including fentanyl, to become sequestered within the circuit. Morphine, dexmedetomidine, midazolam, lorazepam, and propofol do not experience this sequestration. It is crucial that the anesthesiologist be prudent during transport of ECMO patients as cannula dislodgement would prove fatal. Continuous monitoring of invasive blood pressures and large bore venous access are highly recommended.

Biventricular Assist Device (BiVAD). While central ECMO is an effective strategy to offer full cardiopulmonary support, it limits the ability to separately examine the patient's underlying cardiac or pulmonary function. Once a patient on central ECMO has stabilized, it may be desirable to decouple support of the ventricles with two independent circuits to allow for weaning of either the left- or right-sided support. This may prove critical during next-phase planning to determine whether the patient may require a heart transplantation or TAH, or whether the right side of the heart has recovered, which would allow for implantation of a LVAD. Separate circuits can be achieved by percutaneous placement of a ProtekDuo and Impella to support the right and left sides, respectively. An alternative approach would be to centrally cannulate the right and left sides separately (right atrium to main pulmonary for the right side, and left ventricle to aorta for the left side).

ANESTHETIC MANAGEMENT

Preoperative Evaluation

The presence of heart failure has been described as the single most important risk factor for predicting perioperative cardiac morbidity and mortality. Heart failure patients have an increased risk of developing renal failure, sepsis, pneumonia, and cardiac arrest; require longer periods of mechanical ventilation; and have an overall increased 30-day mortality. Thus all precipitating factors for heart failure should be sought and aggressively treated before proceeding with elective surgery.

All patients with known heart failure should have a comprehensive exam prior to surgery with the goal of determining whether they are appropriately compensated or require further optimization prior to their procedure. Functional status should be determined, and the patient should be thoroughly examined for signs and symptoms suggestive of decompensation. For instance, elevated jugular venous pressure, S_3 or S_4 gallop, and peripheral edema may suggest volume overload. Comorbidities that would place the patient at risk for adverse postoperative events, such as uncontrolled hypertension or diabetes, unstable angina, atrial fibrillation, and renal function, should be examined. Even if the patient is optimized, prior knowledge of these comorbidities may influence the anesthesiologist's decision on type of anesthetic as well as interventions to avoid exacerbation thus decreasing the patient's risk for an adverse outcome. Surgery should be postponed in patients presenting in a decompensated state, a recent change in clinical status, or in de novo acute heart failure.

Patients treated for heart failure usually take several medications that may affect anesthetic management. It is generally accepted that diuretics may be discontinued on the day of surgery. Maintaining β blocker therapy is essential since many studies have shown that β blockers reduce perioperative morbidity and mortality. Owing to inhibition of the RAAS, ACE inhibitors may put patients at increased risk of intraoperative hypotension. This hypotension can be treated with a sympathomimetic drug such as ephedrine, an α agonist such as phenylephrine, or vasopressin. Despite the known hypotensive effect of both ACE inhibitors and ARBs, the 2014 ACC/AHA guidelines on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery recommend maintaining this therapy in the perioperative period.

While routine preoperative cardiac testing, including right or left cardiac catheterization, is typically not indicated, per the 2014 ACC/AHA guidelines, a 12-lead ECG is recommended in any patient with known cardiovascular disease to not only assess for ischemia and/or arrhythmia but serve as a baseline for comparison during the perioperative period. A transthoracic echocardiogram (TTE) is indicated in patients who report worsening dyspnea during their preoperative evaluation. Chest radiography may add value for the decompensated patient to evaluate the cause of dyspnea but is otherwise not indicated. Results of recent electrolytes, liver function, coagulation status, and complete blood counts should be reviewed; however, measurement of BNP is not routinely recommended. ICDs and pacemakers should be interrogated.

Intraoperative Management

Monitoring

Choice of monitoring is based on both the complexity of the surgery and the patient. Invasive blood pressure monitoring via an intraarterial catheter allows for assessment of moment-to-moment changes in blood pressure and the monitoring of respirophasic variations to guide fluid replacement. Ideally, the intraarterial catheter is placed prior to induction of anesthesia. Continuous ECG monitoring allows for detection of ST-segment changes to identify myocardial ischemia and alterations in heart rhythm. A central venous catheter (CVC) may prove advantageous if there is potential for significant blood loss, large fluid shifts, or if continuous infusions of inotropic or vasoactive drugs are required. Placement of a CVC would also allow for monitoring trends in CVP. Multiple lines of evidence suggest that pulmonary artery catheter (PAC) monitoring offers little benefit in both cardiac and noncardiac surgery; however, a CVC and PAC may prove useful to measure PAP and cardiac output using the thermodilution technique.

Other minimally invasive devices include the FloTrac, the ClearSight, the LiDCO, the PiCCO, among others. The FloTrac (Edwards Biosciences) provides flow-based hemodynamic parameters measured through an existing arterial line. The ClearSight (Edwards Biosciences) is a noninvasive method that does not require an arterial line, but rather is a device placed on the finger and utilizes both the volume clamp and Physiocal method to reconstruct the brachial artery waveform. Stroke volume is then calculated by analyzing the area under the systolic portion of the blood pressure curve. The LiDCO system requires only a peripheral venous catheter to measure cardiac output by the dye dilution method, using lithium solution as the "dye." The PiCCO (pulse index continuous cardiac output) device requires both an arterial catheter and a CVC. It combines pulse contour analysis and transcardiopulmonary thermodilution techniques to measure cardiac output, preload, afterload, contractility, and volume responsiveness. Esophageal Doppler monitoring is another noninvasive approach to assess changes in hemodynamics. A small probe is placed in the esophagus parallel to the blood flow in the descending aorta; it is connected to a

monitor that shows continuous data on stroke volume and cardiac output and offers an estimation of systemic vascular resistance. Use of this device requires minimal training and expertise and has been validated for fluid optimization in multiple clinical situations.

TEE remains the gold standard for intraoperative hemodynamic monitoring. TEE is extremely sensitive in identifying hypovolemia, left and/or right ventricular dysfunction, tamponade, valvular regurgitation, and dynamic left ventricular outflow tract (LVOT) obstruction. While TEE may be a more suitable alternative, it requires trained personnel to perform the study and interpret the results.

Choice of Anesthetic

As with other surgeries, the anesthetic plan should be decided based on both surgery requirements and patient preference. Regional anesthesia is not only acceptable in heart failure patients but also has been shown to provide benefits that include decreased risk of pneumonia and preemptive analgesia for postoperative pain control. These benefits must be weighed against the potential for developing a sympathectomy leading to hypotension. In the event that hypotension does develop, use of α_1 receptor antagonists (e.g., phenylephrine) or direct/indirect sympathomimetics (e.g., ephedrine) is preferred as opposed to administering volume. The main objective for general anesthesia is to create an unconscious state and avoid hypotension secondary to administration of induction agents and volatile anesthetic. Both intravenous and volatile anesthetics can be used for maintenance of anesthesia; however, volatile anesthetics should be titrated appropriately as they are considered myocardial depressants. Opioids seem to have a particularly beneficial effect in heart failure patients because of their effect on the δ receptor, which inhibits adrenergic activation.

Fluid Replacement

Minimal or moderately invasive surgical procedures may only require maintenance fluid replacement using crystalloid and/or colloids (1–2 mL/kg/hr). Major surgeries with large fluid shifts and hemodynamic instability may require a blood transfusion. Restrictive transfusion strategies are generally preferred; however, one may consider a transfusion if the hemoglobin level falls to 8 or below in a heart failure patient with continuing blood loss, coagulopathy, or evidence of decreased end-organ perfusion. The anesthesiologist should be prudent and avoid rapid fluid administration to prevent an exacerbation of the heart failure. Use of fluid warmers is also highly recommended to avoid shivering and its associated rise in oxygen consumption. Diuretics may be administered for treatment of hypervolemia in the perioperative period.

Anesthetic Considerations for Heart Transplant Patients

Special consideration must be given to patients who have undergone cardiac transplantation and now require other surgeries. These patients are receiving long-term immunosuppressive therapy and are at very high risk of infection. Strict aseptic technique is necessary when performing any invasive procedure such as central line placement or neuraxial blockade. The transplanted heart is denervated, therefore an increase in heart rate can be achieved by administering direct-acting β-adrenergic agonists such as isoproterenol and epinephrine. A blunted response to indirect-acting α-adrenergic agonists is observed. A change in heart rate will *not* occur with administration of atropine or pancuronium. The transplanted heart increases cardiac output by increasing stroke volume, making these patients considered preload dependent and require adequate intravascular volume. However, diastolic dysfunction can be a result of chronic graft rejection. Intraoperative fluid administration decisions must be made knowing that adequate preload is a requirement for optimal function of the transplanted heart, but excessive fluid administration increases the risk of pulmonary edema.

Anesthetic Considerations for Patients With Implantable Nonpulsatile VADs

With more and more VADs being utilized in heart failure patients, there will also be a growing number of patients with these devices requiring noncardiac surgery. The anesthesiologist may need to manage anticoagulation therapy, cardiac rhythm devices, and antibiotic prophylaxis. Avoidance of chest compressions is suggested as to not dislodge the VAD components. Use of surgical electrocautery can cause electromagnetic interference and ultimately affect pump flow. Bipolar cautery should be used when feasible, or the grounding electrode of monopolar cautery should be placed to direct the current away from the VAD generator.

Hemodynamic monitoring of a patient with an implantable nonpulsatile device represents a particular challenge. Neither a noninvasive blood pressure monitor nor a pulse oximeter can be used reliably, since the majority of these patients have nonpulsatile flow. A small number of patients will intermittently eject some blood from their ventricle, which can allow for measurement of oxygen saturation via pulse oximetry. As a substitute for pulse oximetry, a cerebral oximeter that does not rely on pulsatile flow can be used (e.g., near-infrared spectroscopy [NIRS]). Intermittent monitoring of oxygen saturation can also be accomplished by arterial blood gas analysis. An intraarterial catheter is required for measurement of MAP. Placement of an arterial catheter into a nonpulsatile artery can be challenging and is usually facilitated by use of ultrasound. TEE represents one of the most useful monitoring techniques for patients with VADs since it provides real-time information regarding volume status, RV function, and inflow-outflow cannula function.

The three main causes of hypotension occurring in patients with continuous-flow LVADs are decreased preload, RV failure, and increased afterload. Intravascular volume optimization is a major concern in patients with VADs, but it is of particular importance with nonpulsatile devices, as continuous drainage of an underfilled left ventricle will cause bowing of the interventricular septum toward the left side, also known as a suction event. Movement of the interventricular septum alters RV geometry and ultimately decreases right heart contractility. Suction events can be rapidly diagnosed by TEE and can be treated by decreasing the VAD pump speed in combination with volume expansion. Good RV function is critical

for optimal LVAD flow. Factors that increase pulmonary vascular resistance (PVR), such as hypercarbia or vasoconstrictor drugs, will impair RV function and impede blood flow to the left side of the heart. Both decreases and increases in afterload can significantly impact LVAD flow. Small doses of vasopressor medications that have less impact on PVR (e.g., vasopressin) may be used to counteract the decrease in afterload seen with general anesthesia. However, high doses of vasopressors, especially in the presence of hypovolemia, will invariably lead to a decrease in LVAD flow. High output from an LVAD can paradoxically increase preload and worsen RV failure in susceptible patients. Excellent communication among the entire perioperative team (anesthesiologist, surgeon, nurses, VAD engineer, and perfusionist) is essential for good outcomes in this patient population.

Postoperative Period

Patients with evidence of acute heart failure during surgery should be transferred to an intensive care unit postoperatively to facilitate monitoring and treatment. Pain should be adequately treated, since its presence and hemodynamic consequences may worsen heart failure. Home medications should be restarted as soon as possible.

CARDIOMYOPATHIES

According to the AHA, cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure–related disability.

Cardiomyopathies can be divided into two groups: primary cardiomyopathies and secondary cardiomyopathies. Primary cardiomyopathies are those exclusively (or predominantly) confined to heart muscle; they can be genetic, acquired, or of mixed origin. Secondary cardiomyopathies demonstrate pathophysiologic involvement of the heart in the context of a multiorgan disorder (Tables 10.8 and 10.9). It is important to emphasize that previously used terms *ischemic cardiomyopathy, restrictive cardiomyopathy,* and *obliterative cardiomyopathy* are not utilized in the current classification system. The following sections address the cardiomyopathies most often seen by an anesthesiologist: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), stress cardiomyopathy, peripartum cardiomyopathy, secondary cardiomyopathies with restrictive physiology, and cor pulmonale.

TABLE 10.8 Classification of Primary Cardiomyopathies

Genetic: Hypertrophic cardiomyopathy, dysrhythmogenic right ventricular cardiomyopathy, left ventricular noncompaction, glycogen storage disease, conduction system disease (Lenègre disease), ion channelopathies (long QT syndrome, Brugada syndrome, short QT syndrome)
Mixed: Dilated cardiomyopathy, primary restrictive nonhypertrophic cardiomyopathy
Acquired: Myocarditis (inflammatory cardiomyopathy): viral, bacterial, rickettsial, fungal, parasitic (Chagas disease)
Other: Peripartum cardiomyopathy, stress cardiomyopathy (Takotsubo cardiomyopathy)

TABLE 10.9 Classification of Secondary Cardiomyopathies

Infiltrative: Amyloidosis, Gaucher disease, Hunter syndrome
Storage: Hemochromatosis, glycogen storage disease, Niemann-Pick disease
Toxic: Drugs: cocaine, alcohol; chemotherapy drugs: doxorubicin, daunorubicin, cyclophosphamide; heavy metals: lead, mercury; radiation therapy
Inflammatory: Sarcoidosis
Endomyocardial: Hypereosinophilic (Löffler) syndrome, endomyocardial fibrosis
Endocrine: Diabetes mellitus, hyperthyroidism or hypothyroidism, pheochromocytoma, acromegaly
Neuromuscular: Duchenne-Becker dystrophy, neurofibromatosis, tuberous sclerosis
Autoimmune: Lupus erythematosus, rheumatoid arthritis, scleroderma, dermatomyositis, polyarteritis nodosa

Hypertrophic Cardiomyopathy

HCM is a complex cardiac disease with unique pathophysiologic characteristics and a great diversity of morphologic, functional, and clinical features. The disease can affect patients of all ages and has a prevalence in the general population of about 2 to 5 in 1000 persons. It is the most common genetic cardiovascular disease and is transmitted as an autosomal dominant trait with variable penetrance. HCM is characterized by LV hypertrophy in the absence of any other cardiac disease capable of inducing ventricular hypertrophy (e.g., hypertension, aortic stenosis). The most common form of HCM presents as hypertrophy of the interventricular septum and anterolateral free wall. However, in other types of HCM the hypertrophy can be concentric (Fig. 10.10) or may involve both ventricles, only the

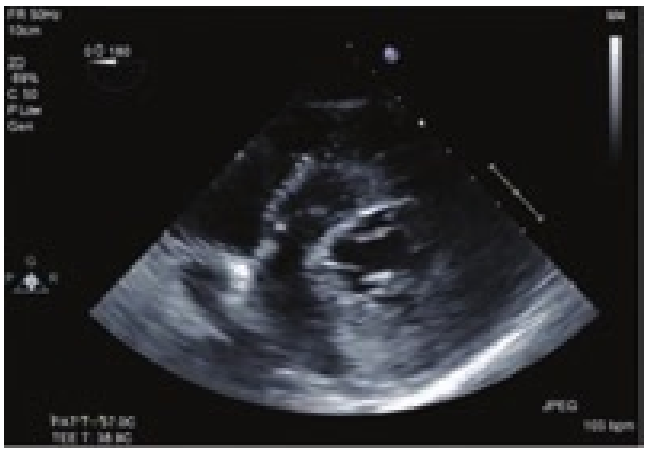

Fig. 10.10 Two-dimensional echocardiographic image showing a transgastric short-axis view of the left ventricle in a patient with hypertrophic cardiomyopathy. Note the concentric thickness of the left ventricular walls. Rod bar indicates hypertrophied anterior wall.

LV free wall, or only the apex of the heart. Histologic features include hypertrophied myocardial cells and areas of patchy myocardial scarring.

The pathophysiology of HCM is related to the following features: myocardial hypertrophy, dynamic LVOT obstruction, systolic anterior movement of the mitral valve causing mitral regurgitation, diastolic dysfunction, myocardial ischemia, and dysrhythmias. Cardiac imaging studies using positron emission tomography (PET) suggest that decreased blood flow in these patients is primarily due to microvascular dysfunction. During systole, contraction of the hypertrophied septum accelerates blood flow through the narrowed LVOT, creating a Venturi effect on the anterior leaflet of the mitral valve and induces anterior movement of the anterior mitral valve leaflet during systole. The presence of this systolic anterior movement (SAM) accentuates the dynamic LVOT obstruction and causes significant mitral regurgitation. LVOT obstruction can be present at rest or can be induced by Valsalva maneuver or exercise. Situations that worsen LVOT obstruction are listed in Table 10.10. However, it must be noted that only 40% to 70% of patients with HCM have LVOT obstruction. HCM can be classified as nonobstructive (with peak pressure gradients across the LVOT <30 mm Hg), obstructive (peak pressure gradients >30 mm Hg), and latent (exercise-induced pressure gradients >30 mm Hg). Diastolic dysfunction is seen virtually in all patients with HCM. The hypertrophied myocardium has a prolonged relaxation time and decreased compliance. Myocardial ischemia is present in patients with HCM whether or not they have coronary artery disease. Myocardial ischemia is caused by several factors, including abnormal coronary arteries, a mismatch between ventricular mass and coronary artery size, increased LVEDP that compromises subendocardial coronary perfusion, decreased diastolic filling time, increased oxygen consumption caused by the hypertrophy, and the presence of a metabolic derangement in the use of oxygen at the cellular level. Dysrhythmias, the cause of sudden death in young adults with HCM, result from the disorganized cellular architecture, myocardial scarring, and expanded interstitial matrix.

Signs and Symptoms

The clinical course of HCM varies and most patients remain asymptomatic throughout their lives. Some may experience symptoms of severe heart failure and others experience sudden death. The principal symptoms of HCM include angina pectoris, fatigue, syncope (which may represent aborted sudden death), tachydysrhythmias, and heart failure. The supine position often relieves the angina pectoris of HCM by presumably changing the LV size thus decreasing LV outflow obstruction.

Physical examination may reveal a double apical impulse, gallop rhythm, and cardiac murmurs and thrills. The murmurs can result from LV outflow obstruction or mitral regurgitation, which can be confused with aortic or intrinsic mitral valve disease. The intensity of these murmurs can change markedly with certain maneuvers. For example, the Valsalva maneuver, which increases LV outflow obstruction, will enhance the systolic murmur, heard best along the left sternal border. The murmur of mitral regurgitation also intensifies with the Valsalva maneuver.

TABLE 10.10 Factors Influencing Left Ventricular Outflow Tract Obstruction in Patients With Hypertrophic Cardiomyopathy

Events That Increase Outflow Obstruction
Increased myocardial contractility
β-adrenergic stimulation (catecholamines)
Digitalis
Decreased preload
Hypovolemia
Vasodilators
Tachycardia
Positive pressure ventilation
Decreased afterload
Hypotension
Vasodilators
Events That Decrease Outflow Obstruction
Decreased myocardial contractility
β-adrenergic blockade
Volatile anesthetics
Calcium entry blockers
Increased preload
Hypervolemia
Bradycardia
Increased afterload
Hypertension
α-adrenergic stimulation

Nitroglycerin and standing (vs lying down) also increase the intensity of these murmurs.

Severity of the ventricular hypertrophy is directly related to the risk of sudden death. Young individuals with massive hypertrophy, even if they have few or no symptoms, should be considered for an intervention to prevent sudden death. Sudden death is especially likely to occur in patients between the ages of 10 and 30 years. For this reason, there is general agreement that young patients with HCM should not participate in competitive sports.

Diagnosis

In asymptomatic patients, unexplained LV hypertrophy may be the only sign of the disease. The 12-lead ECG shows abnormalities in 75% to 90% of patients. These abnormalities include high QRS voltage, ST-segment and T-wave alterations, abnormal Q waves resembling those seen with MI, and left atrial enlargement. The diagnosis of HCM should also be considered in any young patient whose ECG findings are consistent with previous MI.

Echocardiography can demonstrate the presence of myocardial wall thickness greater than 15 mm in adults. Ejection fraction is usually higher than 80%, reflecting the hypercontractile state of the heart. However, in terminal states of disease the ejection fraction can be severely depressed. Echocardiography can also assess the mitral valve apparatus and detect the presence of SAM. Color flow Doppler imaging can reveal either the presence of LVOT obstruction, by demonstrating turbulent outflow as well as mitral regurgitation, or the presence of midcavity LV obstruction.

Cardiac catheterization allows direct measurement of the increased LVEDP and the pressure gradient between the left ventricle and the aorta. Provocative maneuvers may be required to evoke evidence of LVOT obstruction. Ventriculography characteristically shows near cavity obliteration of the left ventricle.

Definitive diagnosis of HCM is made by endomyocardial biopsy and DNA analysis, but these diagnostic modalities are usually reserved for patients in whom the diagnosis cannot be otherwise established.

Treatment

The diverse clinical and genetic features of HCM make it impossible to define precise guidelines for management of this disorder. Some patients are at high risk of sudden death and must be treated aggressively in this regard. Pharmacologic therapy to improve diastolic filling, reduce LV outflow obstruction, and possibly decrease myocardial ischemia is the primary means of relieving the signs and symptoms of HCM. Surgery to remove the area of hypertrophy causing outflow tract obstruction is considered in the 5% of patients who have both marked outflow tract obstruction and severe symptoms unresponsive to medical therapy.

Medical therapy. β blockers and calcium channel blockers are used to treat HCM. The beneficial effects of β blockers on dyspnea, angina pectoris, and exercise tolerance are likely due to the resulting decrease in heart rate, with consequent prolongation of diastole and lengthening of the time for passive ventricular filling. β blockers lessen myocardial oxygen requirements and decrease dynamic outflow tract obstruction during exercise by blunting sympathetic nervous system activity. Similarly, calcium channel blockers (e.g., verapamil, diltiazem) have beneficial effects on the symptoms of HCM because they improve ventricular filling and decrease myocardial ischemia. Patients who develop heart failure despite treatment with β blockers or calcium channel blockers may show improvement with the addition of a diuretic. Diuretic administration must be done very cautiously due to the requirement for relatively high ventricular filling pressures to achieve adequate cardiac output. In patients who remain symptomatic despite maximal therapy with β blockers or calcium channel blockers, disopyramide can be considered as second-line add-on therapy. Disopyramide has a negative inotropic effect therefore improving the LVOT obstruction and the heart failure symptoms. Atrial fibrillation often develops in patients with HCM and is associated with an increased risk of arterial thromboembolism, heart failure, and sudden death. Amiodarone is the most effective antidysrhythmic drug for prevention of paroxysms of atrial fibrillation in these patients. Long-term anticoagulation is indicated in those with recurrent or chronic atrial fibrillation.

Surgical therapy. The small subgroup of patients with HCM who have both large outflow tract gradients (≥50 mm Hg) and severe symptoms of heart failure despite maximal medical therapy are candidates for surgery. There are several surgical strategies. Surgical reduction of the outflow gradient is usually achieved by removing a small amount of cardiac muscle from the ventricular septum (septal myomectomy). Surgery abolishes or greatly reduces the LVOT gradient in most patients. Intraventricular systolic and end-diastolic pressures are markedly reduced, and these changes favorably influence LV filling and myocardial oxygen requirements. Similar results can be obtained by cardiac catheterization and selective alcohol injection into the septal perforator arteries. This maneuver causes ischemic injury followed by necrosis of the interventricular septum, which results in relief of the LVOT obstruction. Either procedure has the potential for the development of atrioventricular block, bundle branch block, or ventricular septal defect. More recently, a less invasive technique utilizing echocardiography-guided percutaneous intramyocardial septal radiofrequency ablation has shown promising results with lower complication rates. If patients remain symptomatic despite these therapies, a prosthetic mitral valve can be inserted in an attempt to counteract the systolic anterior motion of the mitral leaflet. Surgery seems to be less beneficial for older patients or those with atrial fibrillation. A pacemaker can be placed in an attempt to desynchronize the left ventricle during contraction to decrease outflow obstruction. However, this technique has suboptimal results and is currently reserved only for patients who are not surgical candidates or who are unwilling to undergo surgery. In patients deemed at intermediate or high risk of sudden cardiac death, placement of an ICD as a primary prevention method is indicated.

Prognosis

In patients with the nonobstructive form of HCM, the disease is usually benign and the majority remain asymptomatic. The overall annual mortality of patients with HCM is approximately 1%. However, in patients with the most advanced forms of disease (i.e., "burned-out" state), the annual mortality rises to 11%. The subset of patients at high risk of sudden death (family history of sudden death or history of malignant ventricular dysrhythmias) has a mortality rate of 5% per year.

Management of Anesthesia

Management of anesthesia in patients with HCM is directed toward minimizing LVOT obstruction. Any drug or event that decreases myocardial contractility or increases preload or afterload will improve LVOT obstruction. Conversely, sympathetic stimulation, hypovolemia, and vasodilation worsen LVOT obstruction (see Table 10.10). Intraoperatively, patients with HCM may develop severe hypotension, myocardial ischemia, acute heart failure, and supraventricular or ventricular tachydysrhythmias. Previously unrecognized HCM may become manifest intraoperatively as unexplained hypotension or development of a systolic murmur in association with acute hemorrhage or drug-induced vasodilation.

Preoperative evaluation and management. Patients already diagnosed with this disease should undergo an updated cardiac evaluation before elective surgery. Such evaluation should include a 12-lead ECG and an echocardiogram. Patients taking β blockers or calcium channel blockers should continue these medications throughout the perioperative period. For patients with an ICD, the device should be turned off immediately before surgery, an external defibrillator should be readily available in the operating room, and the device should be reactivated immediately in the recovery room.

A more challenging task is detecting patients with HCM in whom the diagnosis has not yet been made. These patients are often young and appear healthy. Every patient should be asked preoperatively about any possible cardiac symptoms or a family history of cardiac disease or sudden death. The presence of a systolic murmur should raise suspicion of a possible diagnosis of HCM. If the ECG shows abnormalities, cardiologic evaluation is prudent.

In patients with HCM, preoperative administration of medication to allay anxiety and its associated activation of the sympathetic nervous system may be advisable. Expansion of intravascular volume during the preoperative period may also be useful in minimizing LVOT obstruction and the adverse hemodynamic effects of positive pressure ventilation.

Intraoperative management. Regional or general anesthesia can be selected for patients with HCM so long as the anesthesiologist is aware of the main pathophysiologic mechanisms that trigger LVOT obstruction and has developed an anesthetic plan tailored to meet these specific needs.

Induction of anesthesia with an intravenous drug is acceptable, but the importance of avoiding sudden decreases in systemic vascular resistance and increases in heart rate and contractility must be kept in mind. A modest degree of direct myocardial depression is acceptable. Administration of a volatile anesthetic or β-adrenergic antagonist before direct laryngoscopy can blunt the sympathetic response typically evoked by tracheal intubation. Positive pressure ventilation can significantly decrease preload and predispose a hypovolemic patient to dynamic LVOT obstruction. To help avoid this, smaller tidal volumes and higher respiratory rates should be used, and positive end-expiratory pressure (PEEP) should be avoided if possible. Preload reduction and severe hypotension due to LVOT obstruction can also be encountered when abdominal insufflation is performed for laparoscopic surgery. The surgeon should be advised about this possibility, and the abdomen should be insufflated slowly.

Anesthesia should be maintained with drugs that produce mild depression of myocardial contractility and have minimal effects on preload and afterload. A volatile anesthetic in a moderate dose is often used for this purpose.

Invasive monitoring of blood pressure may be helpful. TEE during surgery and anesthesia is particularly useful in patients with HCM because of the unique pathophysiology of this disorder. Note that neither CVP monitoring nor PAP monitoring can diagnose LVOT obstruction or systolic anterior motion of the mitral valve leaflet, nor do these monitoring techniques give an accurate assessment of LV filling in patients with HCM.

Hypotension that occurs in response to a decrease in preload or afterload should be treated with an α-adrenergic agonist such as phenylephrine. Drugs with β-adrenergic agonist activity, such as ephedrine, dopamine, and dobutamine, are contraindicated because the drug-induced increase in myocardial contractility and heart rate increases LVOT obstruction. Prompt replacement of blood loss and careful titration of intravenous fluids is important for maintaining preload and blood pressure. However, aggressive fluid replacement may result in pulmonary edema secondary to diastolic dysfunction. Vasodilators should *not* be used to lower blood pressure; the decrease in systemic vascular resistance will accentuate LVOT obstruction.

Maintenance of normal sinus rhythm is very important because adequate LV filling is dependent on left atrial contraction. Patients who develop intraoperative supraventricular tachydysrhythmias should undergo immediate pharmacologic or electrical cardioversion. A cardioverter-defibrillator must be readily available in the operating room. β blockers such as metoprolol and esmolol are indicated to slow persistently elevated heart rates.

Parturient patients. Pregnancy is usually well tolerated in patients with HCM despite the pregnancy-induced decrease in systemic vascular resistance and the risk of impaired venous return due to aortocaval compression. Parturient women with HCM may present major anesthetic challenges because events such as labor pain, which produces catecholamine release, and bearing down (Valsalva maneuver) may increase LVOT obstruction. There is no evidence that regional anesthesia increases complication rates in parturient patients with HCM undergoing vaginal delivery. Epidural anesthesia has been successfully administered to these patients. Maintenance of euvolemia or slight hypervolemia is helpful. Should hypotension unresponsive to fluid administration occur as a result of regional anesthesia, phenylephrine should be used to increase afterload. Oxytocin must be administered carefully because of its vasodilating properties and the compensatory tachycardia it causes and because of the abrupt inflow of large amounts of blood into the central circulation as a consequence of uterine contraction.

Pulmonary edema has been observed in parturient women with HCM after delivery, a finding that emphasizes the delicate balance in fluid requirements of these patients. Treatment of pulmonary edema may include phenylephrine if hypotension is present and esmolol to slow the heart rate, prolong diastolic filling time, and decrease myocardial contractility, all of which will decrease LVOT obstruction. Diuretics and nitrates *cannot* be used to treat pulmonary edema in this setting. They worsen the situation by provoking further LVOT obstruction.

Postoperative management. Patients with HCM must be vigilantly monitored in the recovery room or intensive care unit in the immediate postoperative period. All factors that stimulate sympathetic activity (e.g., pain, shivering, anxiety, hypoxia, hypercarbia) must be eliminated. Maintenance of euvolemia and prompt treatment of hypotension are crucial.

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is a primary myocardial disease characterized by LV or biventricular dilatation, biatrial dilation, decreased ventricular wall thickness, and systolic dysfunction in the absence of abnormal loading conditions or coronary artery disease. The etiology of DCM is unknown, but it may be genetic or associated with infection (e.g., coxsackievirus B), drugs, toxins, or immune mediators. There is a familial transmission pattern in 30% to 50% of cases, usually of an autosomal dominant form. Many types of secondary cardiomyopathies have features of dilated cardiomyopathy. These include the cardiomyopathies associated with alcohol abuse, cocaine abuse, the peripartum

state, pheochromocytoma, infectious diseases (human immunodeficiency virus infection), uncontrolled tachycardia, Duchenne muscular dystrophy, thyroid disease, chemotherapeutic drugs, radiation therapy, hypertension, coronary artery disease, and valvular heart disease. Black men have an increased risk of developing dilated cardiomyopathy. Overall, DCM is the most common type of cardiomyopathy, the third most common cause of heart failure, and the most common indication for cardiac transplantation.

Signs and Symptoms

The initial manifestation of DCM is usually heart failure. Chest pain on exertion that mimics angina pectoris occurs in some patients. Ventricular dilatation may be so dramatic that functional mitral and/or tricuspid regurgitation occurs. Supraventricular and ventricular dysrhythmias, conduction abnormalities, and sudden death are common. Systemic embolization due to formation of mural thrombi in dilated and hypokinetic cardiac chambers is also common.

Diagnosis

The ECG often shows ST-segment and T-wave abnormalities and left bundle branch block. Dysrhythmias are common and include premature ventricular beats and atrial fibrillation. Chest radiography may show enlargement of all four cardiac chambers, with LV dilatation the principal morphologic feature.

Echocardiography typically reveals dilatation of all four cardiac chambers, again predominantly the left ventricle, as well as global hypokinesis. Regional wall motion abnormalities may be seen in dilated cardiomyopathy but do not necessarily imply the presence of coronary disease. Mural thrombi can be detected, and valvular regurgitation due to annular dilatation is a common finding. Severe functional mitral regurgitation has been associated with twofold increased risk of mortality in patients with DCM.

Cardiac magnetic resonance imaging (MRI) displaying a large extent of late gadolinium enhancement (LGE) is highly suggestive of remodeling via cardiac fibrosis. Pronounced myocardial midwall LGE is associated with higher hospitalization and mortality rates related to heart failure in patients with DCM.

Laboratory testing should be performed to eliminate other causes of cardiac dilation such as hyperthyroidism. Coronary angiography is typically unremarkable; however, right-sided heart catheterization reveals high PCWP, high systemic vascular resistance, and low cardiac output. Endomyocardial biopsy is *not* recommended.

Treatment

Treatment of DCM includes general supportive measures such as adequate rest, weight control, a low-sodium diet, fluid restriction, abstinence from tobacco and alcohol, and decreased physical activity during periods of cardiac decompensation. Cardiac rehabilitation, if possible, will improve general conditioning.

The medical management of DCM is similar to that of chronic heart failure. Patients with DCM are at risk of systemic and pulmonary embolization secondary to thrombosis from activation of the coagulation cascade due to blood stasis. The risk of cardiac embolization is greatest in patients with severe LV dysfunction, atrial fibrillation, a history of thromboembolism, or echocardiographic evidence of intracardiac thrombus. Anticoagulation with warfarin, dabigatran (direct thrombin inhibitor), rivaroxaban, or apixaban (factor Xa inhibitors) is often instituted in patients with DCM and symptomatic heart failure.

Asymptomatic nonsustained ventricular tachycardia is common. However, suppression of this dysrhythmia with drug therapy does not improve survival. Prophylactic placement of an ICD decreases the risk of sudden death by 50%. It is recommended in patients with heart failure (class II–III) and LVEF less than 35% on guideline-directed medical therapy.

In patients with DCM and severe functional mitral regurgitation, studies evaluating the impact of placing a transcatheter MitraClip device have produced conflicting results. While in the MITRA-FR trial the 1-year mortality and hospitalization rates did not differ between the group managed with MitraClip and medical therapy versus just medical therapy, in the COAPT trial patients receiving the MitraClip device experienced significantly lower mortalities and hospitalization rates at 2 years.

DCM remains the principal indication for cardiac transplantation in adults and children. Patients most likely to benefit from a heart transplant are those who were previously active, younger than 60 years of age, who have intractable symptoms of heart failure despite optimal medical therapy.

Prognosis

Symptomatic patients with DCM referred to tertiary care medical centers have a 5-year mortality rate of 50%. Involvement of both the right and left ventricles worsens their overall prognosis. Hemodynamic abnormalities that predict a poor prognosis include an ejection fraction lower than 25%, a PCWP above 20 mm Hg, a cardiac index of less than 2.5 L/min/m^2, systemic hypotension, pulmonary hypertension, and increased CVP. Alcoholic cardiomyopathy is largely reversible if complete abstinence from alcohol is maintained.

Management of Anesthesia

Since DCM is a cause of heart failure, the anesthetic management of these patients is the same as previously described. Regional anesthesia may be an alternative to general anesthesia in selected patients with DCM; however, anticoagulant therapy may limit this option.

Stress Cardiomyopathy

Stress cardiomyopathy, also known as apical ballooning syndrome, takotsubo cardiomyopathy, or broken heart syndrome, is a temporary cardiac condition characterized by LV apical hypokinesis with ischemic ECG changes but unobstructed coronary arteries at cardiac catheterization. There is a temporary disruption of cardiac contractility in the LV apex while the rest of the heart has normal or even enhanced contractility. The apical ballooning seen on echocardiography resembles a Japanese octopus trap, thus the name "takotsubo." The most

common symptoms according to the International Takotsubo Registry study include chest pain and dyspnea causing concern among patients that they are experiencing a heart attack. Stress is determined to be the main factor in the development of this cardiomyopathy. The stressor can be either a physical event (e.g., acute asthma, surgery, chemotherapy, stroke) or an emotional event. The condition more commonly occurs in women than in men.

Diagnosis, Treatment, and Prognosis

Diagnostic criteria for confirming apical ballooning syndrome include transient LV systolic dysfunction, absence of obstructive coronary disease, new ECG abnormalities, and the absence of pheochromocytoma or myocarditis. Treatment is supportive. However, since the disease process involves a high catecholamine state, inotropes should be avoided, and instead negative inotropes such as β blockers or calcium channel blockers should be used. Intraaortic balloon counterpulsation has also been demonstrated to be a successful treatment option. Prognosis is generally favorable, and most patients have complete recovery within 2 months with a 10% chance of recurrence.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy is a rare form of dilated cardiomyopathy of unknown cause that arises during the peripartum period (third trimester of pregnancy up until 5 months postdelivery). There appears to be a genetic predisposition toward this disease. The estimated incidence of peripartum cardiomyopathy is 1 in 3000 to 1 in 4000 parturients and occurs in women with no prior history of heart disease. The incidence is noted to be higher in South Africa, at 1:1000, and as high as 1:300 in Haiti. Postpartum cardiomyopathy may be related to diet and lifestyle. Risk factors include hypertension, obesity, prior toxin exposure (e.g., cocaine), multiparity, age older than 30 years, multifetal pregnancy, preeclampsia, long-term oral tocolytic therapy, and black ethnicity. Other causes may include viral myocarditis, an abnormal immune response to pregnancy, and maladaptive responses to the hemodynamic stresses of pregnancy.

Signs and Symptoms

The signs and symptoms of peripartum cardiomyopathy are those of heart failure: dyspnea, fatigue, and peripheral edema. However, these signs and symptoms are common in the final trimester of many pregnant women, and there are no specific criteria for differentiating subtle symptoms of heart failure from normal late pregnancy. Clinical conditions that may mimic heart failure, such as amniotic fluid or pulmonary embolism, should be excluded when considering the diagnosis of peripartum cardiomyopathy.

Diagnosis

The diagnosis of peripartum cardiomyopathy is based on three clinical criteria: development of heart failure in the period surrounding delivery, absence of another explainable cause of heart failure, and LV systolic dysfunction with an LVEF generally lower than 45%. Studies that can assist in this diagnosis include ECG, BNP levels, chest radiography, echocardiography, cardiac MRI, cardiac catheterization, and endomyocardial biopsy.

Treatment

The goal of treatment is to alleviate the symptoms of heart failure. Diuretics and vasodilators can be used. ACE inhibitors are teratogenic but can be useful following delivery. During pregnancy, vasodilation is accomplished with hydralazine and nitrates. Intravenous immunoglobulin may also have a beneficial effect. Thromboembolic complications are not uncommon, and anticoagulation is often recommended. Patients in whom conservative therapy fails may be treated with mechanical circulatory support or even heart transplantation.

Prognosis

The mortality rate of peripartum cardiomyopathy ranges from 25% to 50% and typically occurs within 3 months of delivery. Higher mortality rates have been noted in black patients. Death is usually a result of progression of heart failure or sudden death related to cardiac dysrhythmias or thromboembolic events. The prognosis appears to depend on the degree of normalization of LV size and function within 6 months of delivery.

Management of Anesthesia

Anesthesia management in women with peripartum cardiomyopathy requires assessment of cardiac status and careful planning of the analgesia and/or anesthesia required for delivery. Regional anesthesia may provide a desirable decrease in afterload.

Secondary Cardiomyopathies With Restrictive Physiology

Secondary cardiomyopathies with restrictive physiology are due to systemic diseases that produce myocardial infiltration and severe diastolic dysfunction. The most common of these is caused by amyloidosis. Other systemic diseases such as hemochromatosis, sarcoidosis, and carcinoid may produce a similar type of cardiomyopathy. The diagnosis should be considered in patients who have heart failure but no evidence of cardiomegaly or systolic dysfunction. The condition results from increased stiffness of the myocardium caused by the deposition of abnormal substances. The severe diastolic dysfunction leads to markedly increased filling pressures and the development of atrial enlargement. This predisposes the patients to develop atrial fibrillation, which further impairs the ventricular filling. Although the systolic function is usually normal, the stroke volume is decreased due to inadequate filling. Consequently, patients have low to normal blood pressure and can develop orthostatic hypotension. Cardiomyopathies with restrictive physiology must be differentiated from constrictive pericarditis, which has a similar physiology. A clinical history of pericarditis makes the diagnosis of constrictive pericarditis more likely.

Signs and Symptoms

Because cardiomyopathies with restrictive physiology can affect both ventricles, symptoms and signs of both LV and RV failure

may be present. In advanced stages of this disease, all the signs and symptoms of heart failure are present, but there is no cardiomegaly. Amyloid cardiomyopathy often presents with thromboembolic complications. Atrial fibrillation is common. Cardiac conduction disturbances are particularly common in amyloidosis and sarcoidosis, often leading to heart block or ventricular dysrhythmias, resulting in sudden death.

Diagnosis

The ECG may demonstrate conduction abnormalities. The chest radiograph may show signs of pulmonary congestion and/or pleural effusion, but cardiomegaly is absent. Laboratory tests should be used as needed to diagnose the systemic disease responsible for the cardiac infiltration.

Echocardiography will demonstrate significant diastolic dysfunction and normal systolic function. Atria are enlarged due to high atrial pressures, but ventricular size remains normal. The ventricle may appear speckled, a characteristic sign of amyloid deposition. Various echocardiographic criteria can differentiate secondary cardiomyopathy with restrictive physiology from constrictive pericarditis. Endomyocardial biopsy can help elucidate the cause of an infiltrative cardiomyopathy.

Treatment and Prognosis

Symptomatic treatment is similar to that for diastolic heart failure, which includes administration of diuretics to treat pulmonary and systemic venous congestion. Excessive diuresis may decrease ventricular filling pressures and cardiac output and result in hypotension and hypoperfusion. The development of atrial fibrillation with loss of the "atrial kick" may substantially worsen diastolic dysfunction, and a rapid ventricular response may further compromise cardiac output. Maintenance of normal sinus rhythm is extremely important. Stroke volume tends to be fixed in the presence of cardiomyopathy with restrictive physiology, therefore bradycardia may precipitate acute heart failure. Significant bradycardia or severe conduction system disease may require implantation of a cardiac pacemaker. With cardiac sarcoidosis, malignant ventricular dysrhythmias are common and may necessitate insertion of an ICD. Anticoagulation may be needed in patients with atrial fibrillation and/or low cardiac output. The prognosis of secondary cardiomyopathy with restrictive physiology is very poor.

Management of Anesthesia

Management of anesthesia for patients with restrictive cardiomyopathy follows the same principles as that for patients with cardiac tamponade. Because stroke volume is relatively fixed, it is important to maintain sinus rhythm and to avoid any significant decrease in heart rate. Maintenance of venous return and intravascular fluid volume is equally essential to maintain an acceptable cardiac output.

Cor Pulmonale

Cor pulmonale is RV enlargement (hypertrophy and/or dilatation) that may progress to right-sided heart failure. Diseases that induce pulmonary hypertension, such as COPD, restrictive lung disease, and respiratory insufficiency of central origin (e.g., obesity-hypoventilation syndrome), cause cor pulmonale. It can also result from idiopathic pulmonary artery hypertension—that is, pulmonary hypertension that occurs in the absence of left-sided heart disease, myocardial disease, congenital heart disease, or any other clinically significant respiratory, connective tissue, or chronic thromboembolic disease. The most common cause of cor pulmonale is COPD and is more prevalent in male patients over the age of 50.

Pathophysiology

The main pathophysiologic determinant of cor pulmonale is pulmonary hypertension. Chronic alveolar hypoxia is the most important factor in this process. Acute hypoxia, such as seen in exacerbations of COPD or during sleep in patients with obesity-hypoventilation syndrome, results in pulmonary vasoconstriction. Chronic alveolar hypoxia promotes pulmonary vasculature remodeling and an overall increase in PVR. Even mild hypoxemia may result in vascular remodeling. The elevated pulmonary resistance increases the workload for the right ventricle, and over time causes RV hypertrophy with eventual RV failure.

Signs and Symptoms

Symptoms of cor pulmonale may be obscured by the coexisting lung disease. Clinical signs occur late in the course of the disease, the most prominent being peripheral edema. As RV function deteriorates, dyspnea increases, and effort-related syncope can occur. Accentuation of the pulmonic component of the second heart sound, a diastolic murmur due to incompetence of the pulmonic valve, and a systolic murmur due to tricuspid regurgitation connote severe pulmonary hypertension. Evidence of overt RV failure consists of increased jugular venous pressure and hepatosplenomegaly.

Diagnosis

The ECG may show signs of RA and RV hypertrophy. RA hypertrophy is suggested by peaked P waves in leads II, III, and aVF ("P pulmonale"). Right axis deviation and a partial or complete right bundle branch block are also often seen. A normal-appearing ECG, however, does not exclude the presence of pulmonary hypertension.

Radiographic signs of cor pulmonale include an increase in the width of the right pulmonary artery and a decrease in pulmonary vascular markings in the lung periphery ("pruning"). On a lateral chest radiograph, RV enlargement is indicated by a decrease in the retrosternal space.

TEE can provide quantitative estimates of PAP, assessment of the size and function of the right atrium and ventricle, and evaluation of the presence and severity of tricuspid or pulmonic regurgitation. The presence of pericardial effusion or RV dysfunction are associated with poor prognosis. TTE is often difficult to perform in patients with COPD because the hyperinflated lungs impair transmission of the ultrasound waves. However, speckle tracking can be used to perform RV strain analysis.

Right heart catheterization measures the PAP and the PCWP. In the setting of cor pulmonale, the PAP is elevated (>19 mm Hg) and the PCWP is low or normal.

Treatment

Treatment of cor pulmonale is aimed at reducing the workload of the right ventricle by decreasing PAP and PVR. If the pulmonary artery vasoconstriction has a reversible component, as may occur during an acute exacerbation of COPD, this goal can be achieved by returning the Pao_2, $Paco_2$, and arterial pH to normal. Oxygen supplementation to maintain the Pao_2 above 60 mm Hg (oxygen saturation >90% by pulse oximetry) is useful in both the acute and long-term treatment of right-sided heart failure. Long-term oxygen therapy decreases the mortality of cor pulmonale and improves cognitive function and quality of life.

Diuretics may be used to treat right-sided heart failure that does not respond to correction of hypoxia or hypercarbia. Diuretics must be administered very carefully because diuretic-induced metabolic alkalosis, which encourages CO_2 retention, may aggravate ventilatory insufficiency by depressing the effectiveness of CO_2 as a stimulus to breathing. Diuresis can also increase blood viscosity and myocardial work. Pulmonary vasodilators such as sildenafil, bosentan, and ambrisentan have been shown to improve the symptoms of cor pulmonale and reduce RV mass as well as RV remodeling. Additionally, calcium channel blockers such as nifedipine and diltiazem have been successfully used to produce pulmonary vasodilation.

When cor pulmonale is progressive despite maximum medical therapy, transplantation of one or two lungs or a heart-lung transplantation will provide dramatic relief of cardiorespiratory failure.

Prognosis

The prognosis of patients with cor pulmonale is dependent on the disease responsible for initiating the pulmonary hypertension. Patients with COPD in whom arterial oxygenation can be maintained at near-normal levels and whose pulmonary hypertension is relatively mild have a favorable prognosis, whereas prognosis is poor in patients with severe irreversible pulmonary hypertension.

Management of Anesthesia

The overall anesthetic goal in patients with cor pulmonale is to avoid any factors that increase PAP: hypoxia, hypercarbia, acidosis, hypovolemia. It is important to maintain optimal RV function by increasing RV inotropy and decreasing its afterload. The anesthetic management includes preoperative optimization and intraoperative and postoperative prevention of deterioration. Preoperative preparation of patients with cor pulmonale is directed toward (1) eliminating and controlling acute and chronic pulmonary infection, (2) reversing bronchospasm, (3) improving clearance of airway secretions, (4) expanding collapsed or poorly ventilated alveoli, (5) maintaining hydration, and (6) correcting any electrolyte imbalances. Preoperative measurement of arterial blood gases will provide guidelines for perioperative management.

Induction of general anesthesia can be accomplished using any available method or drug. Adequate depth of anesthesia should be present before endotracheal intubation because this stimulus can elicit reflex bronchospasm in lightly anesthetized patients.

Anesthesia is typically maintained with a balanced anesthetic. Volatile anesthetics are effective bronchodilators but at high concentration they can reduce systemic blood pressure and worsen pulmonary hypertension. Large doses of opioids should be avoided because they can contribute to prolonged postoperative ventilatory depression.

Positive pressure ventilation improves oxygenation, presumably because of better ventilation/perfusion matching. Humidification of inhaled gases helps maintain hydration, liquefaction of secretions, and mucociliary function.

In situations of severe right heart failure intravenous milrinone can be used to increase inotropy and decrease PVR. Other inhaled pulmonary vasodilators that can be used in the intraoperative setting for acute right heart failure include nitic oxide, epoprostenol, iloprost, treprostinil, and prostacyclin.

Intraoperative monitoring of patients with cor pulmonale is influenced by the complexity of the surgery. Intraarterial catheters are recommended as they permit frequent blood draws for arterial blood gases. A CVC or PAC may be useful depending on the surgery. Trend values of right atrial pressure can provide some information about RV function. Direct measurement of PAP helps determine the time to treat pulmonary hypertension and the response to treatment. TEE is an alternative method for monitoring RV function and fluid status. Patients may have an implantable PAP measurement sensor (CardioMEMS HF System, Abbott) that allows for monitoring of their pulmonary pressures; however, this has not been adapted to be used during surgery.

Regional anesthesia can be used in appropriate situations in patients with cor pulmonale, but regional anesthesia is best avoided for operations that require a high level of sensory and motor block because loss of function of the accessory muscles of respiration may be very deleterious in patients with pulmonary disease. In addition, any decrease in systemic vascular resistance in the presence of fixed pulmonary hypertension can produce very significant systemic hypotension.

The respiratory and cardiovascular status of a patient with cor pulmonale must be carefully monitored in the postoperative period, and any factors that exacerbate pulmonary hypertension (e.g., hypoxia, hypercarbia) must be avoided/treated. Oxygen therapy should be maintained as long as needed.

KEY POINTS

- Heart failure is a complex pathophysiologic state in which the heart is unable to fill with or eject blood at a rate appropriate to meet tissue requirements. Heart failure is characterized by specific symptoms (dyspnea and fatigue) and signs (circulatory congestion or hypoperfusion).
- Heart failure is associated with significant morbidity and mortality, which imposes a great financial burden on the healthcare system.
- Heart failure with reduced ejection fraction (HFrEF) is commonly due to obstructive ischemic heart disease. Heart failure with preserved ejection fraction (HFpEF) is increasing in prevalence and primarily the result of poor lifestyle choices and comorbidities (e.g. diabetes, smoking, obesity).
- Management of acute heart failure includes the use of loop diuretics in combination with vasodilators, positive inotropic drugs, and/or insertion of mechanical devices.
- Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac disorder. Its pathophysiology is related to the development of left ventricular outflow tract (LVOT) obstruction and ventricular dysrhythmias that can cause sudden death.
- Factors that induce LVOT obstruction in HCM include hypovolemia, tachycardia, an increase in myocardial contractility, and a decrease in afterload. Outflow tract obstruction can be managed by maintaining hydration, increasing afterload (phenylephrine), and decreasing heart rate and myocardial contractility (β blockers or calcium channel blockers).
- Dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy and the second most common cause of heart failure.
- Cor pulmonale is RV enlargement (hypertrophy and/or dilatation) that may progress to right-sided heart failure. It is caused by diseases that promote development of pulmonary hypertension.
- The most important pathophysiologic determinant of the development of pulmonary hypertension and cor pulmonale in patients with chronic lung disease is alveolar hypoxia. The best available treatment to improve the prognosis in these patients is long-term oxygen therapy.

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11

Pericardial Disease and Cardiac Trauma

Ruma Bose, Mario Montealegre-Gallegos

OUTLINE

INTRODUCTION

Pericardial diseases have a varied clinical presentation, ranging from chronic or subacute to acute and potentially life threatening. These pathologies often present urgently to the operating room, and their perioperative management poses unique challenges for the anesthesiologist. The hemodynamic compromise resulting from some of these conditions (e.g., tamponade) often requires emergent management. Routine perioperative interventions, such as positive pressure ventilation, may have an adverse impact on hemodynamics. Therefore safe anesthetic care of patients with pericardial disease requires a thorough understanding of the pathophysiology and associated hemodynamic changes.

PERICARDIAL STRUCTURE AND FUNCTION

The word *pericardium* derives from the Greek word *perikardion* (*peri* around, about | *kardia* heart). The pericardium is a protective fibroserous sac that envelopes the heart and portions of the great vessels. It is composed of two intimately related layers, the serosa (inner layer) and the fibrosa (outer). The serosa or serous pericardium is composed of a visceral layer of epicardium and a parietal layer; the space in between the two is the pericardial cavity. Under physiologic conditions, the pericardial cavity is filled with approximately 10 to 50 mL of pericardial fluid, a plasma ultrafiltrate. The parietal serous pericardium is adjacent to the fibrous pericardium (Fig. 11.1).

The normal pericardium is approximately 0.8 to 1 mm in thickness but may vary depending on the anatomic region. Pericardial reflections around the great vessels and pulmonary veins form a U-shaped oblique sinus behind the left atrium and between the inferior vena cava and the pulmonary veins, and a transverse sinus between the aorta and pulmonary artery and the dome of the left atrium and superior vena cava. These potential spaces may accommodate a small amount of pericardial fluid and are important to compensate for changes in intrapericardial pressure during the cardiac cycle. Lymphatic drainage of pericardial fluid occurs via the tracheal, bronchial, anterior, and posterior mediastinal lymph nodes.

Histologically, the pericardium is composed of a dense parallel array of collagen layers interspaced with short elastin fibers. This structure is responsible for the viscoelastic mechanical properties of the pericardium. Conceptually, it is useful to visualize the pericardium as having two different resistances to mechanical stress. Small effusions stretch only the elastic fibers, while the expansion produced by larger, high-pressure effusions is opposed by the resistance of the more rigid collagen fibers. This results in the characteristic steep J shape of the pericardial pressure-volume relationship curve (Fig. 11.2).

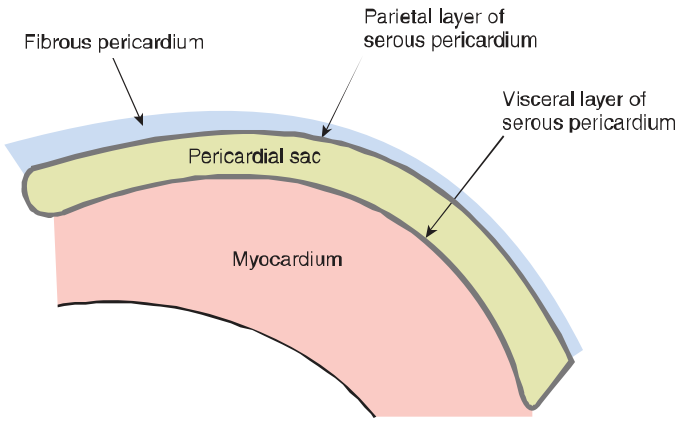

Fig. 11.1 Anatomy of the pericardium and pericardial space.

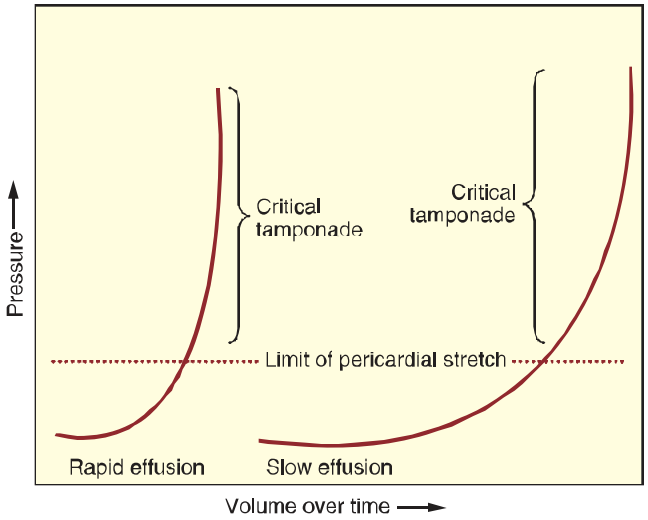

Fig. 11.2 Pericardial pressure-volume curves are shown in which the intrapericardial volume increases slowly or rapidly over time. On the left curve, rapidly increasing pericardial fluid quickly exceeds the limit of pericardial stretch, which causes a steep increase in pericardial pressure. On the right curve a slower rate of pericardial filling takes longer to exceed the limit of pericardial stretch because there is more time for the pericardium to stretch and compensatory mechanisms to become activated. (From Spodick DH. Acute cardiac tamponade. *N Engl J Med.* 2003;349:684–690. Copyright 2003 Massachusetts Medical Society, with permission.)

The stiffness of the pericardium is higher than that of the cardiac muscle. Therefore the pericardium allows for equalization of the compliance of both ventricles, maximizing diastolic ventricular interaction. As an example, the intrapericardial pressure follows the changes in intrathoracic pressure during respiration. The negative intrathoracic pressure during inspiration increases right ventricular filling. The interventricular septum accommodates this increase in right ventricular filling pressures by shifting leftward, therefore impairing left ventricular filling and causing a transient decrease in cardiac output and systemic blood pressure. This phenomenon is also known as ventricular interdependence. As we will discuss later, these physiologic changes are exaggerated when intrapericardial pressures are elevated and manifest clinically as pulsus paradoxus (Fig. 11.3).

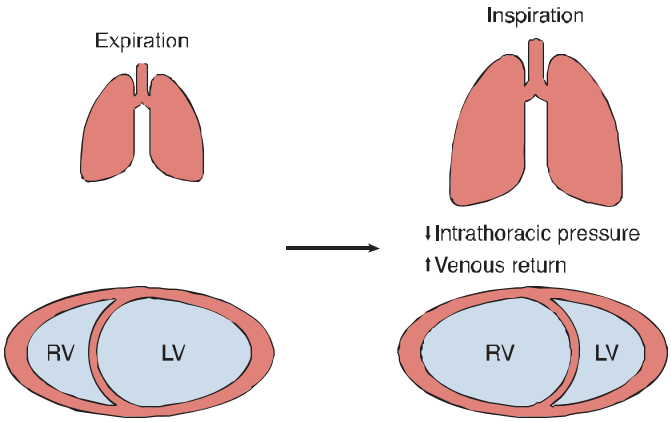

Fig. 11.3 Effect of intrathoracic pressure on ventricular filling. The decrease in intrathoracic pressure during inspiration increases in venous return to the right ventricle. This increase in right ventricular volume shifts the interventricular septum toward the left, causing a decrease in left ventricular filling and consequently in systemic cardiac output and arterial blood pressure. Pulsus paradoxus is an exaggeration of this phenomenon, which occurs in patients with cardiac tamponade. *LV,* Left ventricle; *RV,* right ventricle.

CONGENITAL ABNORMALITIES

The pericardium is not essential for sustaining life, and congenital partial or complete absence of the pericardium can occur. Partial absence of pericardium is most frequently left sided. Most of these abnormalities are clinically silent, but in some cases they can result in herniation, ischemia, or strangulation of cardiac structures and sudden death.

Pericardial cysts are the most common congenital pericardial disorder (Fig. 11.4). They are most commonly incidental findings on chest imaging, but occasionally may present with respiratory symptoms, dyspnea, arrhythmias, and compression

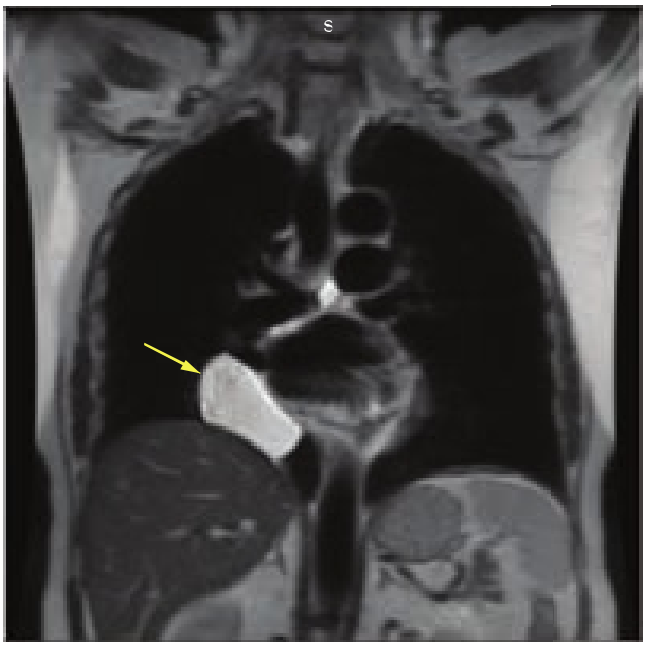

Fig. 11.4 Magnetic resonance imaging coronal plane across the chest demonstrating contrast enhancement due to a pericardial cyst *(arrow).*

of surrounding structures or may become infected. In cases that need intervention, surgical excision via video-assisted thoracoscopic surgery is preferred due to the high incidence of recurrence with percutaneous drainage (~30%).

PERICARDITIS

Pericarditis, the most common pericardial disorder, is an inflammatory syndrome of the pericardium that may or may not be accompanied by pericardial effusion. Pericarditis is responsible for approximately 5% of chest pain evaluations in the emergency department that are not attributed to myocardial infarction.

Pericarditis is classified based on the duration and recurrence of signs and symptoms. The symptoms of acute pericarditis usually last 2 to 4 weeks, incessant pericarditis 1 to 3 months, and chronic pericarditis more than 3 months. Recurrent pericarditis is defined as a recurrence of symptoms after a 4- to 6-week symptom-free period. Acute pericarditis has multiple etiologies, but it is often idiopathic (Table 11.1).

Diagnosis

Diagnosis of pericarditis requires at least two of four criteria: pleuritic chest pain, a pericardial friction rub, diffuse ST-segment elevation or PR depression on electrocardiogram (ECG) (Fig. 11.5), and a new or worsening pericardial effusion. ECG changes occur due to inflammation of the superficial myocardium. The chest pain of acute pericarditis can mimic coronary artery disease. Some clinical features may help differentiate between these two etiologies, including the absence of reciprocal

TABLE 11.1 Selected Etiologies of Pericarditis and Pericardial Effusions

Idiopathic

Infectious

Viral: coxsackie, adenovirus, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, hepatitis B, echovirus

Bacterial: *Mycobacterium tuberculosis* (endemic in developing countries), *Streptococcus* sp., *Staphylococcus* sp., *Mycoplasma pneumoniae, Borrelia burdogferi, Haemophilus influenzae*

Fungal: *Histoplasma capsulatum, Coccidioides immitis*

Neoplasic

Primary tumors: mesothelioma, sarcoma

Metastatic tumors: breast, lung, lymphoma, leukemia, melanoma

Radiation induced

Postcardiac Injury

Trauma

Postinfarction (Dressler syndrome)

Postpericardiotomy

Medication Induced

Procainamide, hydralazine, isoniazic, cyclosporine

Autoimmune

Churg-Strauss syndrome, Wegener granulomatosis, dermatomyositis, rheumatoid arthritis, sarcoidosis, scleroderma, ankylosing spondylitis

Metabolic Disorders

Uremia, gout, myxedema

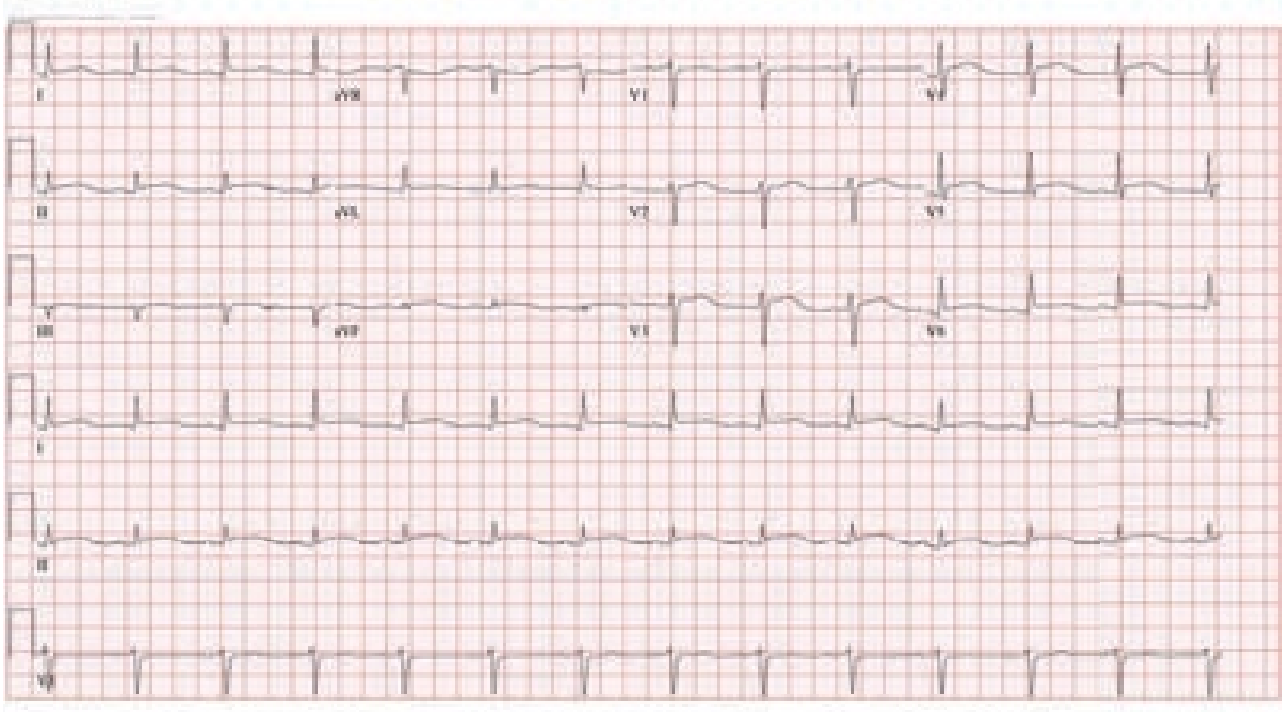

Fig. 11.5 Electrocardiogram of a patient with acute pericarditis. Diffuse ST-segment elevations and PR-segment depressions are seen.

TABLE 11.2 Differentiation of Acute Pericarditis and Myocardial Ischemia

Clinical Finding	Myocardial Ischemia	Pericarditis
Duration of symptoms	Minutes to hours	Hours to days
Pain	Retrosternal pressure, no relief with positional changes and no changes with respiration	Retrosternal, stabbing or sharp, relief with leaning forward, worsened with inspiration
Pain relief with nitroglycerin	Yes	No
Pericardial friction rub	Absent	Present
PR-segment depression	Absent	Present
ST-segment shape	Convex upward	Concave upward
Reciprocal ST-segment changes	Present	Absent

ST-segment depressions with pericarditis (Table 11.2). The diagnosis of acute pericarditis can be further supported by elevation of inflammatory markers such as C-reactive protein or erythrocyte sedimentation rate, leukocytosis, and evidence of pericardial inflammation on computerized tomography (CT) or magnetic resonance imaging (MRI).

Some elevation of troponin T and I can be seen as markers of myocardial injury. Troponin levels are not prognostic in these cases. Several factors are associated with increased morbidity in acute pericarditis (Table 11.3).

Pericardial inflammation results in edema, thickening of the parietal pericardium, and exudative pericardial effusion. Up to 15% of cases of acute pericarditis can be associated with myocarditis, which may result in a modest elevation of cardiac biomarkers with normal (myopericarditis) or depressed (perimyocarditis) left ventricular function.

Cardiac imaging modalities such as transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) can identify increased echogenicity of the pericardium and help evaluate complications such as effusion, constrictive pericarditis, or associated regional wall motion abnormalities. In general, larger effusions are associated with a higher risk of complications. Cardiac MRI with late gadolinium enhancement can also provide morphologic and hemodynamic information. In the absence of disease, the pericardium is not vascularized. Pericarditis causes neovascularization of the pericardium that can be detected by late gadolinium enhancement.

TABLE 11.3 Major Factors Associated With Severe Illness in Acute Pericarditis

Fever ≥ 38°C
Cardiac tamponade
Large effusion size (measuring ≥ 20 mm on TTE)
Subacute onset
Lack of response to NSAIDs

NSAIDs, Nonsteroidal antiinflammatory drugs; *TTE*, transthoracic echocardiography

Treatment

Treatment of the underlying etiology of pericarditis is not always possible given the large proportion of patients in which it is idiopathic. Drugs such as colchicine and nonsteroid antiinflammatories (NSAIDs) are the mainstay of treatment for pericarditis and work by reducing inflammation. Besides managing inflammation, NSAIDs also provide symptomatic relief. The use of these drugs is often limited by their contraindications and adverse effects (Table 11.4). There is some evidence that colchicine alone or combined with NSAIDs may reduce the recurrence of pericarditis. Corticosteroids may also be useful in

TABLE 11.4 Empirical Pharmacologic Treatment of Acute Pericarditis

Drug	Mechanism of Action	Dose	Treatment Course	Adverse Effects
Colchicine	Antiinflammatory action, interference with granulocyte function by inhibiting tubulin polymerization	0.5mg q12 or q24 h	3 months, taper over 2–3 weeks	Nausea and vomiting Abdominal pain Diarrhea Myopathy Neutropenia Aplastic anemia Neutropenia
Aspirin	Nonsteroid antiinflammatory drug, inhibits cyclooxygenase therefore decreasing production of proinflammatory mediators	750–1000 mg q8h	Treat for 1–2 weeks, then taper over 3–4 weeks	Dyspepsia Gastrointestinal bleeding Antiplatelet effects Acute kidney injury Bronchospasm
Ibuprofen	Nonsteroid antiinflammatory drug, inhibits cyclooxygenase therefore decreasing production of proinflammatory mediators	600–800 mg q8h	Treat for 1–2 weeks, then taper over 2–4 weeks	Similar to aspirin

decreasing inflammation but are associated with an increased risk of relapse after discontinuation of therapy. Other drugs, such as interleukin-1 inhibitors, methotrexate, azathioprine, mycophenolate, and intravenous immunoglobulin have also been used for treatment of recurrent pericarditis. Surgical pericardiectomy is indicated in patients with refractory chest pain.

Due to an increased risk of sudden death and cardiac arrest, restriction of physical activity is advised in patients with pericarditis at least until inflammatory markers have returned to normal and the pain has subsided.

POSTCARDIAC INJURY SYNDROMES

Postcardiac injury syndromes are a group of inflammatory pleuropericardial syndromes. Among these conditions, the ones most frequently encountered by the anesthesiologist are postinfarction pericarditis (Dressler syndrome), postpericardiotomy syndrome occurring after cardiac surgery, and traumatic pericarditis. The initial damage to pericardial tissue is believed to trigger an autoimmune response after an asymptomatic latent period. The diagnosis is suspected in patients who, after an initial injury, present with unexplained fever, pleuritic chest pain, pericardial rub, and elevated inflammatory markers.

Early pericarditis can occur after large transmural myocardial infarctions (1–3 days), although this is uncommon in the current era of percutaneous coronary interventions. Dressler syndrome is a late postinfarction pericarditis that usually occurs 1 to 8 weeks after the initial event. It is frequently accompanied by an effusion, although tamponade is rare. Since it is frequently associated with chest pain, it can mimic postinfarction angina.

Postpericardiotomy syndrome presents primarily as acute pericarditis in patients who have undergone cardiac surgery, with an incidence of 10% to 40%. It is more frequent in the pediatric population. Interestingly, it is rare in patients receiving immunosuppressant drugs after cardiac transplantation, which suggests an autoimmune mechanism. Although it is frequently benign, it is important to distinguish between postpericardiotomy syndrome and myocardial ischemia. Patients with postpericardiotomy syndrome are at an increased risk of reoperation for tamponade and have increased hospital length of stay.

Pericarditis can also occur after accidental or iatrogenic cardiac trauma, such as after percutaneous coronary interventions and electrophysiology procedures.

The treatment of postcardiac injury syndromes is similar to that of other forms of pericarditis. Empiric NSAIDs and colchicine are frequently prescribed and are notably less effective than in other forms of pericarditis. There are some data demonstrating the efficacy of colchicine in prevention of postpericardiotomy syndrome; however, a high incidence of gastrointestinal side effects may limit its utility.

PERICARDIAL EFFUSION AND TAMPONADE

Etiology

Pericardial fluid can accumulate in the pericardial sac with virtually any form of pericardial disease. Pathologic processes that result in inflammation of the pericardium generally produce exudative pericardial effusions. Idiopathic effusions or those secondary to viral infection are frequently small and asymptomatic, whereas patients in which the effusion is secondary to bacterial processes or tuberculosis may appear septic and critically ill. Pericardial effusions can occur with primary malignant disease of the heart, or more commonly secondary to metastatic tumors, such as melanoma, lymphoma, breast, and lung cancer. Malignant disease is a frequent cause of tamponade in nonsurgical patients. Besides increased production and accumulation of pericardial fluid, effusions can also occur due to decreased reabsorption. This mechanism explains pericardial effusions that occur secondary to an increase in systemic venous pressure, such as in patients with congestive heart failure or pulmonary hypertension. The effusions in these cases are most frequently transudative.

Pathophysiology

As we reviewed previously, besides the normal volume of pericardial fluid (10–50 mL), the pericardial space can accommodate only a small quantity of additional fluid mainly through expansion of the pericardial sinuses (pericardial reserve volume). Because the pericardium is relatively noncompliant and fluid is noncompressible, accumulation of pericardial fluid may result in an increase in intrapericardial pressure and compression of cardiac cavities.

Cardiac tamponade occurs when circumferential or localized intrapericardial fluid collections exceed the pericardial reserve volume causing cardiac chamber collapse. It can also occur when localized effusions constrain cardiac filling sufficiently to impact hemodynamics.

Diagnosis

Pericardial effusions can be categorized by their duration as acute, subacute, or chronic (lasting ≥ 3 months). The presence or absence of symptoms in a patient with a pericardial effusion depends on its size and duration of fluid accumulation. Rapid accumulation of volumes as small as 100 mL may result in symptoms and may cause tamponade within minutes. This may occur after iatrogenic cardiac injury, postsurgical bleeding, or trauma. In contrast, large volumes of up to 2000 mL can be accumulated in chronic pericardial effusions with little to no symptomatology.

Pericardial effusions can be discovered as a serendipitous finding during routine chest x-ray imaging or echocardiogram in asymptomatic patients (Fig. 11.6). The classic symptoms of pericardial effusion include shortness of breath, orthopnea, cough, and chest pain. Additionally, local compression of the recurrent laryngeal nerve may cause hoarseness, and compression of the phrenic nerve may cause hiccups. Dysphagia may occur due to compression of the esophagus, which is located posterior to the left atrium. Nonspecific symptoms such as fever, malaise, weakness, anorexia, or sinus tachycardia may be associated with the primary cause of the effusion. Typically, patients feel more comfortable when leaning forward. Right upper quadrant pain may be present secondary to hepatic congestion.

When tamponade is not present, the physical examination is usually unremarkable. Subtle clinical findings include muffled heart sounds and difficulty palpating the point of maximal impulse.

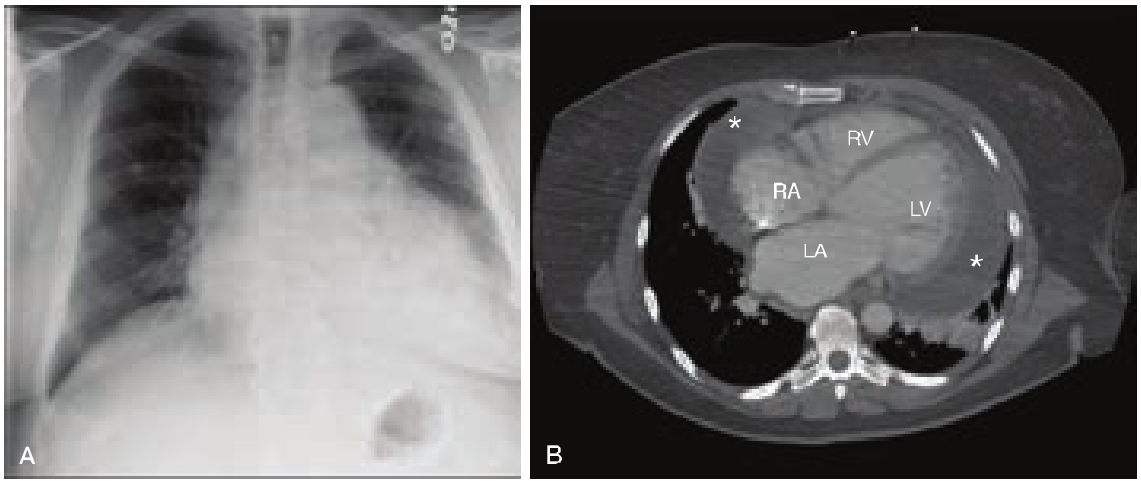

Fig. 11.6 (A) Chest x-ray on a patient after cardiac surgery demonstrates an enlarged cardiac silhouette due to a large pericardial effusion. (B) Computerized tomography scan demonstrating a large circumferential pericardial effusion (*stars*). *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

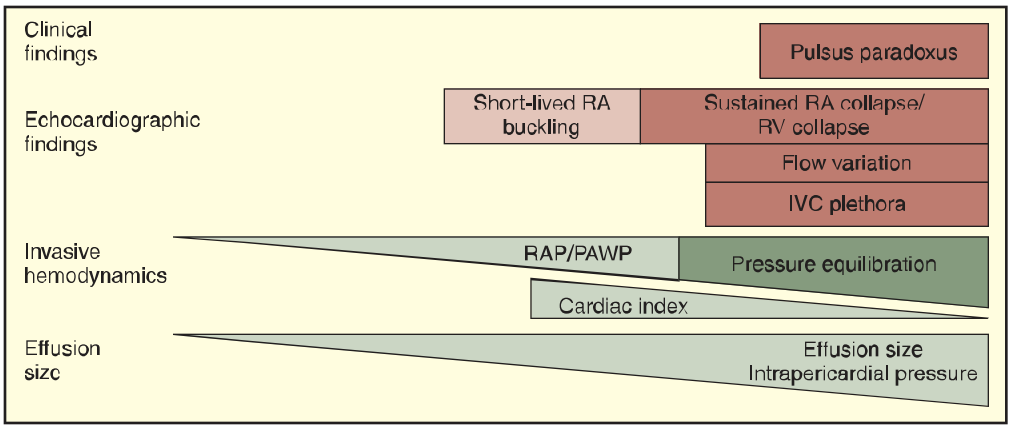

Fig. 11.7 Subacute pericardial tamponade is a spectrum of hemodynamic abnormalities. A common timeline for different findings is shown, although a wide variation is possible. *IVC,* Inferior vena cava; *PAWP,* pulmonary arterial wedge pressure; *RA,* right atrium; *RAP,* right atrial pressure; *RV,* right ventricle. (From Argulian E, Messerli F. Misconceptions and facts about pericardial effusion and tamponade. *Am J Med.* 2013;126:858–861.)

Tamponade can cause a spectrum of symptoms, including dyspnea, tachypnea, sinus tachycardia, and symptoms and signs of hypoperfusion. Frequently, the patient is tachycardic, and the central venous pressure is almost always elevated. The low stroke volume associated with tamponade results in a low systemic blood pressure, which in association with an increased sympathetic tone and elevated peripheral vascular resistance manifests as a thready pulse on physical examination. Of note, the clinical findings of tamponade are of varying severity rather than an all-or-none phenomenon (Fig. 11.7).

As reviewed previously, an exaggerated respiratory variation in right atrial filling is responsible for some of the clinical signs of tamponade. Under normal physiologic conditions the negative intrathoracic pressure during inspiration causes increased venous return to the right heart. The increased right ventricular filling shifts the interventricular septum leftward, decreasing left ventricular filling, systemic stroke volume, and blood pressure. During tamponade, this respiratory variation is exaggerated due to the decreased compliance of the ventricles encased in a high-pressure pericardial sac. Notable on examination is distension of the jugular veins on inspiration due to increased jugular venous pressure associated with impaired right ventricular filling (Kussmaul sign). A third of patients with tamponade present with Beck's triad, a combination of muffled heart sounds, increased jugular venous pressure, and hypotension.

Pulsus paradoxus is an exaggeration of ventricular interdependence in patients with tamponade. It is defined as a decrease of greater than 10 mm Hg of the systolic blood pressure during spontaneous inspiration.

The ECG may demonstrate low QRS voltages and a cyclical alteration in the QRS voltage (electrical alternans) due to a damping effect of the pericardial fluid and an oscillating heart (Fig. 11.8).

Echocardiography is the imaging modality of choice for the diagnosis of pericardial effusion. CT and MRI are less readily available and rarely indicated.

Echocardiographic Imaging in Pericardial Effusion and Tamponade

Echocardiography is the most accurate and practical method for confirming the presence of a pericardial effusion. Furthermore, it can be used as a point-of-care modality to confirm or exclude

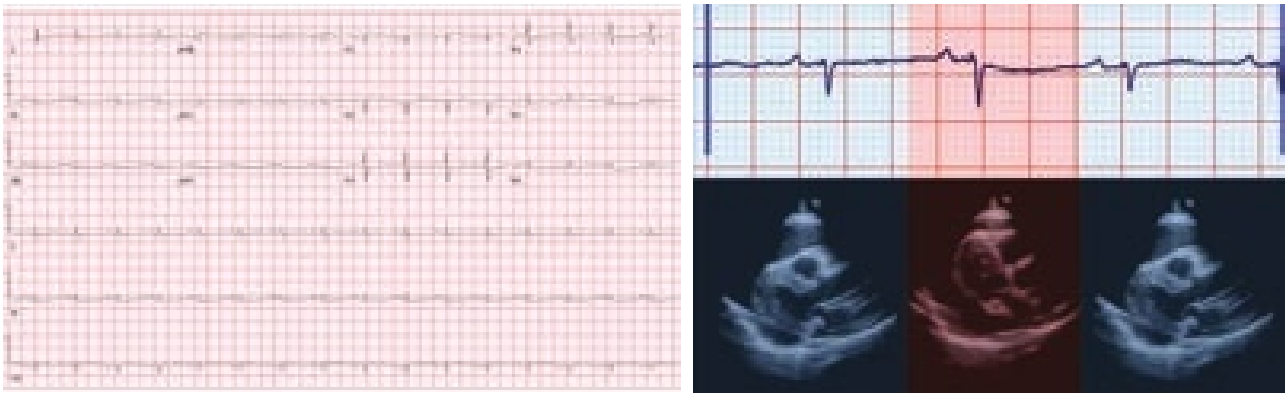

Fig. 11.8 Electrocardiographic changes in pericardial effusion. (A) Electrocardiogram with low voltages, particularly on the limb leads. (B) Electrical alternans occurs due to swinging motion of the heart in patients with large effusions. As the heart approaches the anterior chest wall the QRS voltage increases, the opposite occurs as the heart is positioned away from the anterior chest wall.

the diagnosis in patients with acute hemodynamic instability. Although tamponade is a clinical diagnosis, echocardiography can be used to evaluate tamponade-induced hemodynamic changes and to establish disease severity.

After confirming the presence of a pericardial effusion using echocardiographic imaging, a simple linear measurement can further classify it by size as small (< 10 mm), moderate (10–20 mm), or large (> 20 mm) (Fig. 11.9). It can also differentiate between circumferential or localized effusions.

Echocardiographic features of tamponade include decreased left ventricular systolic and diastolic dimensions due to impaired filling, a plethoric (dilated) inferior vena cava with minimal respiratory variation, abnormal interventricular septal motion (right-to-left diastolic shift), and a swinging motion of the heart. Echocardiography can also be used to evaluate cardiac chamber collapse due to increased intrapericardial pressures (Fig. 11.10). Initial collapse usually occurs during the portion of the cardiac cycle when the intracardiac chamber pressure is lowest. Right atrial collapse starting early during

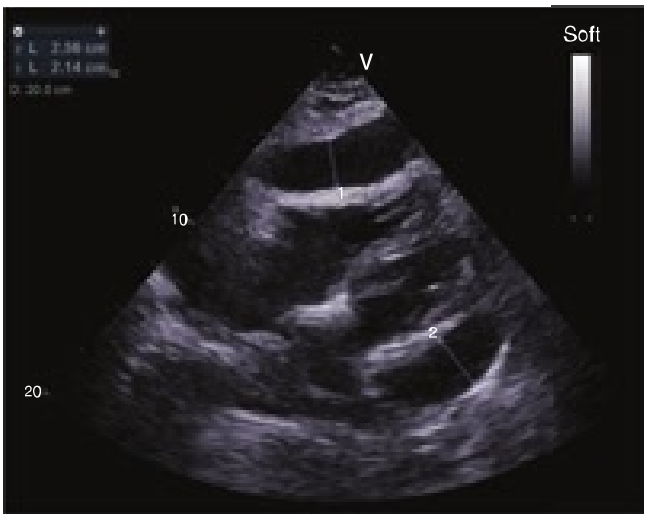

Fig. 11.9 Subcostal four-chamber view on transthoracic echocardiography demonstrating a large pericardial effusion (measuring > 20 mm in diastole).

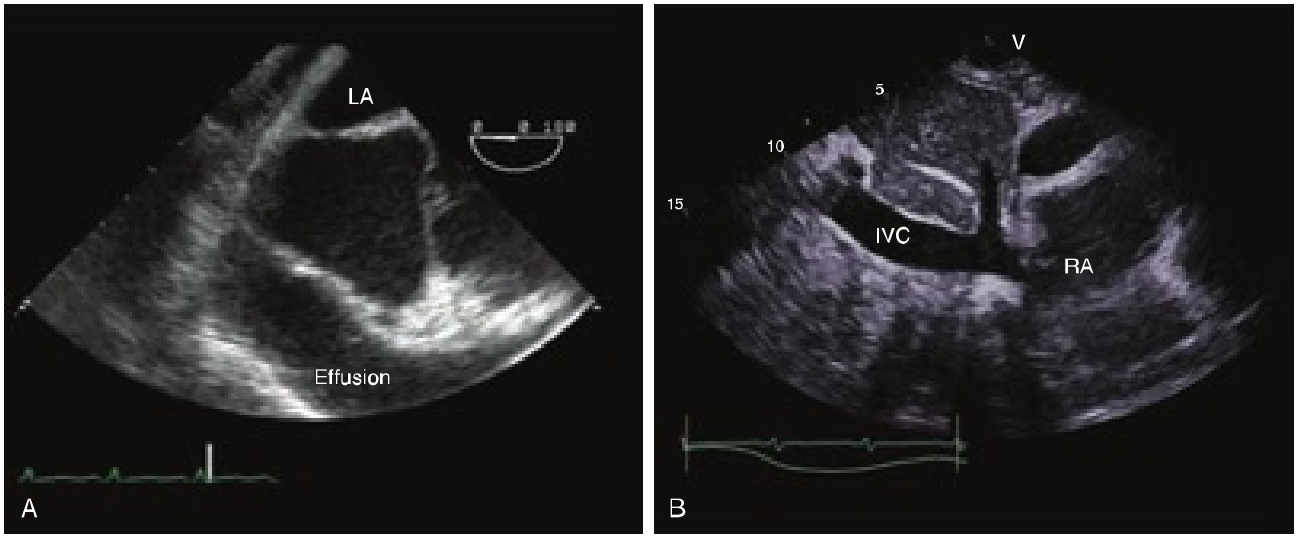

Fig. 11.10 (A) Transesophageal echocardiography, midesophageal four-chamber view with focus on the right atrium. Collapse of the right atrium during ventricular systole can be visualized. (B) Subcostal inferior vena cava view on transthoracic echocardiography on a patient with cardiac tamponade. A dilated, plethoric inferior vena cava is seen. *IVC*, Inferior vena cava; *LA*, left atrium; *RA*, right atrium.

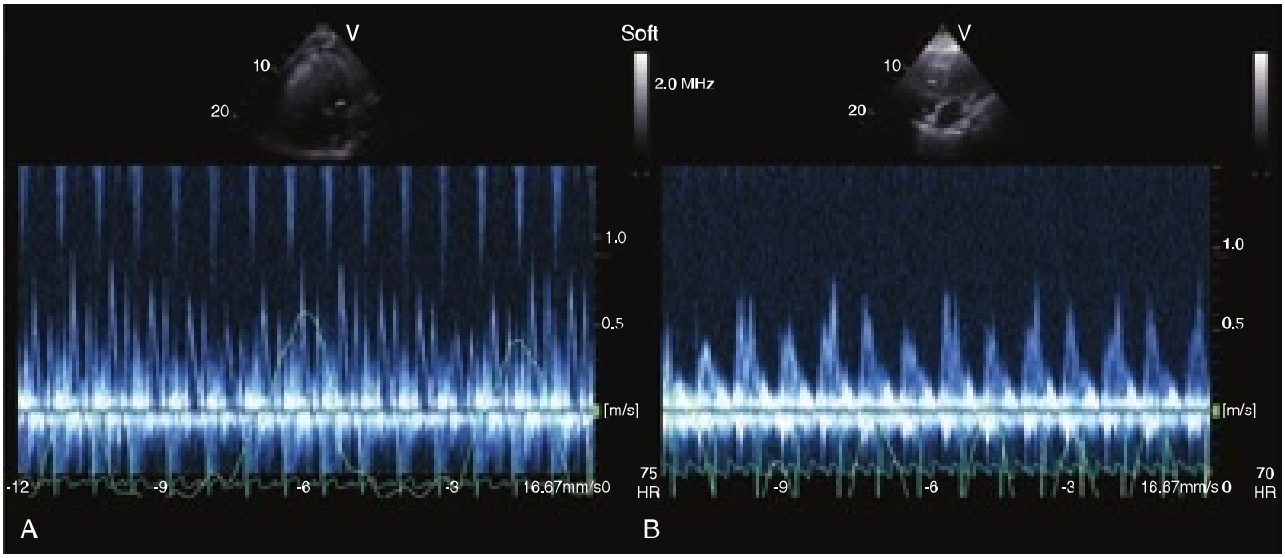

Fig. 11.11 Apical four-chamber view on transthoracic echocardiography with Doppler interrogation across the mitral (A) and tricuspid (B) valves. A large variability during respiration can be seen in both inflow patterns, suggesting the presence of tamponade.

ventricular systole and lasting more than one-third of the cardiac cycle is a highly sensitive and specific sign of tamponade. Early diastolic collapse of the right ventricle is also highly sensitive and specific. Isolated left atrial or left ventricular collapse is rare but can be seen with localized effusions or in patients with tamponade and severe pulmonary hypertension.

Doppler echocardiography can also be used to confirm the exaggerated phasic respiratory variations in transmitral (↑130%) and transtricuspid (↓60%) inflows that occur in patients with tamponade (Fig. 11.11).

HEMOPERICARDIUM

Bleeding into the pericardial sac can occur after trauma, myocardial infarction with rupture of the left ventricular free wall, and as a complication of cardiac surgery or interventional procedures.

Postoperative bleeding is a relatively common complication of cardiac surgery, and it requires reoperation in 2% to 8% of cases. Patients requiring surgical exploration for bleeding after cardiac surgery have an increased morbidity and mortality, longer length of stay, and increased resource utilization.

Despite routine placement of mediastinal drains after cardiac surgery, some patients with postprocedural bleeding can develop tamponade. Importantly, postprocedural bleeding after cardiac surgery can compromise cardiac function in the absence of a circumferential effusion. Localized hematomas that compress the atria or ventricles can cause obstructive shock and tamponade physiology (Fig. 11.12). Tamponade occurring early (<24 h) after cardiac surgery is usually due to surgical bleeding or coagulopathy. Hemodynamic monitoring and increased postoperative vigilance in the intensive care unit are essential for early detection. Tamponade should be suspected in patients with a decreasing chest tube output after an initial period of bleeding, with increasing inotrope and vasopressor requirement, and with elevated right-sided filling pressures. Late tamponade

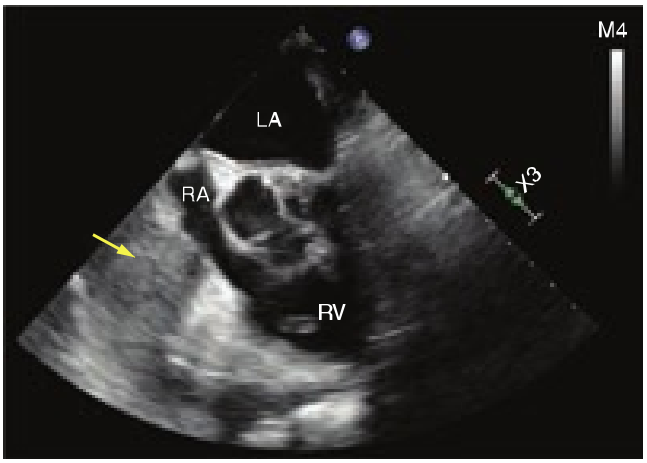

Fig. 11.12 Micesophageal right ventricular inflow and outflow view in a patient with postsurgical bleeding after cardiac surgery. A localized hematoma (hemopericardium) can be seen compressing the right atrium (arrow).

(>5–7 days) is multifactorial, and postpericardiotomy syndrome is frequently implicated. Late tamponade can be more problematic since it can occur after hospital discharge.

Treatment

Although mild cardiac tamponade can be managed conservatively with close observation in some patients, most cases should be decompressed. Emergent decompression is recommended in high-risk patients (Table 11.5). Decompression can be performed through pericardiocentesis or surgical drainage. Removal of even a small amount of pericardial fluid can result in a dramatic decrease in intrapericardial pressure. Furthermore, it allows for analysis of the fluid, which can clarify the etiology of the pericardial effusion.

In unstable patients, pericardiocentesis is performed emergently under sedation. Echocardiographic or fluoroscopic guidance is frequently used to assist pericardiocentesis.

TABLE 11.5 European Society of Cardiology Working Group on Myocardial and Pericardial Diseases Proposed Criteria for Triage of Cardiac Tamponade

Pathologies that always require urgent surgical management:
Type A aortic dissection
Ventricular free wall rupture after myocardial infarction
Severe chest trauma
Iatrogenic hemopericardium not amenable to percutaneous control of bleeding
For other pathologies a score can be calculated for clinical decision making. A score of ≥6 requires urgent pericardiocentesis. In patients with a score of <6, pericardiocentesis can be postponed for up to 48 hours if clinically stable.
The score is calculated as follows:

Etiology
Malignant disease: 2
Tuberculosis: 2
Recent radiotherapy: 1
Recent viral infection: 1
Recurrent effusion, previous pericardiocentesis: 1
Chronic terminal renal failure: 1
Immunodeficiency or immunosuppression: 1
Hypothyroidism or hyperthyroidism: -1
Systemic autoimmune disease: -1

Clinical Presentation
Dyspnea or tachypnea: 1
Orthopnea: 3
Hypotension: 0.5
Progressive sinus tachycardia: 1
Oliguria: 1
Pulsus paradoxus: 2
Pericardial chest pain: 0.5
Friction rub: 0.5
Rapid worsening of symptoms: 2
Slow evolution of disease: -1

Imaging
Cardiomegaly on chest x-ray: 1
Electrical alternans: 0.5
Low voltages on ECG: 1
Circumferential effusion ≥20 mm: 3
Moderate effusion: 1
Small effusion: -1
Right atrial collapse: 1
Right ventricular collapse: 1.5
Left ventricular collapse: 2
Plethoric, noncollapsible IVC: 1.5
Mitral or tricupid inflow variation: 1
Swinging heart: 1

ECG, Electrocardiogram; *IVC*, inferior vena cava.
Modified from Adler Y, Charron P, Imazio M, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the task force for the diagnosis and management of pericardial diseases of the European Society of Cardiology (ESC). Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2015;36(42):2921–2964. doi:10.1093/eurheartj/ehv318.

A surgical pericardiostomy, also known as a pericardial window, is a partial resection of the pericardium that allows drainage of fluid to the pleural or peritoneal cavity. When compared to pericardiocentesis, surgical approaches yield a lower recurrence rate. There are several approaches to the procedure, including subxiphoid, video-assisted thoracoscopic, and anterior thoracotomy. The subxiphoid approach can be performed under local anesthesia in a supine or head-up position. In contrast, thoracotomy and video-assisted thoracoscopic approaches are more often performed under general anesthesia with or without lung isolation.

Management of Anesthesia

In hemodynamically unstable patients, fluid therapy and inotropes can be used as temporizing measures while awaiting transport to the interventional suite or operating room. However, these measures should not delay definitive management.

The anesthetic management of patients with tamponade can be quite challenging (Fig. 11.13). First and foremost, the surgical team should be aware that general anesthesia and positive pressure ventilation in the presence of a hemodynamically significant cardiac tamponade can result in life-threatening hypotension. Hypotension can be the result of peripheral vasodilation and decreased myocardial contractility due to general anesthetics. Additionally, the increase in intrathoracic pressure associated with positive pressure ventilation can severely impair venous return.

Pericardiocentesis performed under local anesthesia is preferred for the initial management of hemodynamically unstable patients with tamponade. After the hemodynamic status is improved by the percutaneous pericardiocentesis, general anesthesia and positive pressure ventilation can be instituted to permit surgical exploration and more definitive treatment of the cardiac tamponade (Table 11.6).

When it is not possible to relieve cardiac tamponade before induction of anesthesia, it is essential to maintain adequate cardiac output and perfusion. The main goals of anesthetic management are avoiding myocardial depression, hypovolemia, arterial vasodilation, and bradycardia. Ideally, invasive arterial monitoring and adequate venous access should be established prior to induction, although surgical intervention should not be delayed in unstable patients. Inotrope and vasopressor boluses and infusions should be available. The goal is to maintain inotropy and chronotropy with minimal decrease in afterload. Prior to induction, the surgical area can be prepped and draped, and the surgeon should be present in the operating room if rapid intervention is needed.

Ketamine is an ideal agent for the induction and maintenance of anesthesia due to its sympathomimetic effects and preservation of respiratory drive. Positive pressure ventilation can result in life-threatening hypotension due to reduction in preload. If spontaneous ventilation is not adequate, then optimizing preload and minimizing inspiratory pressures can mitigate the effects of positive pressure ventilation. Fluid overload is not tolerated well by these patients, and cautious hydration with titrated fluid boluses should be considered. TEE is useful for intraoperative monitoring and interventional guidance.

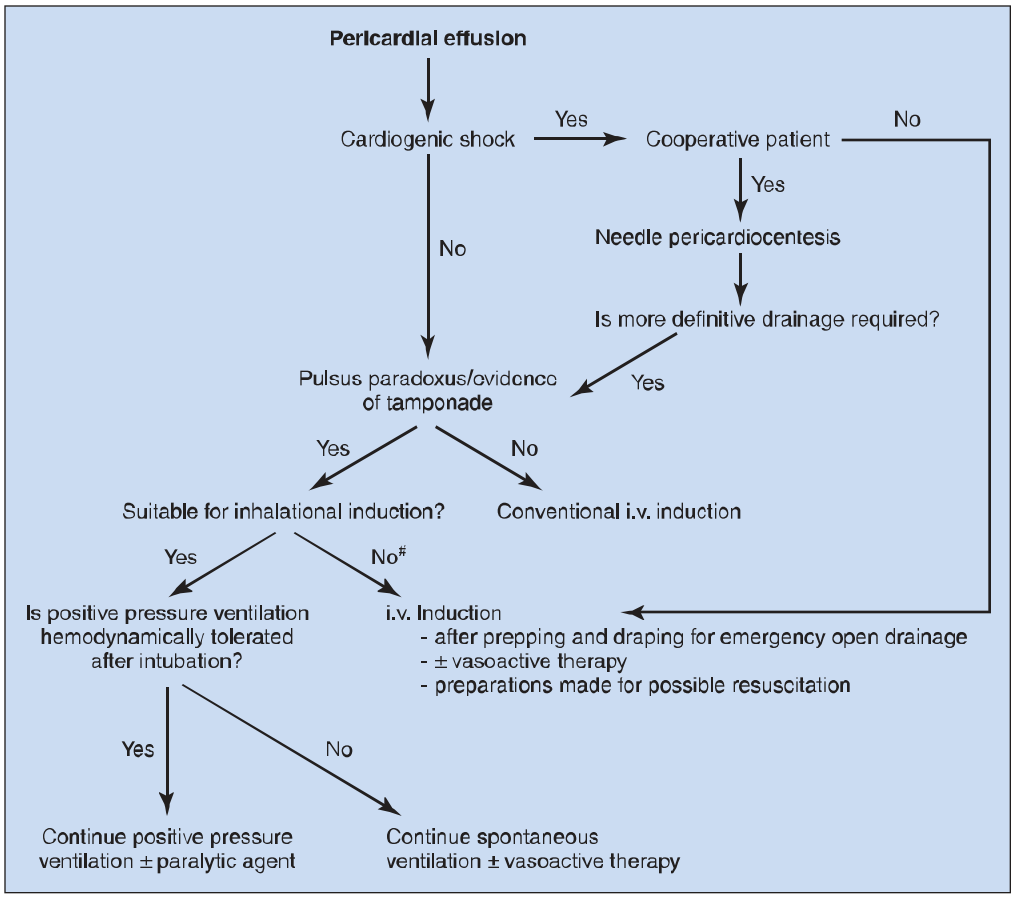

Fig. 11.13 Management strategies for patients with significant pericardial effusion/tamponade. In the absence of overt cardiogenic shock, anesthetic management of patients for pericardial effusion drainage relies on the determination of the hemodynamic significance of the effusion. When tamponade is not present, a conventional intravenous *(i.v.)* induction can proceed. If there is significant tamponade, consideration can be given to an inhalational induction unless specific contraindications exist. Use of positive pressure ventilation versus spontaneous ventilation will be based on the hemodynamic tolerance to either mode of ventilation. The need for vasoactive therapy should be anticipated regardless of the anesthetic technique chosen. #, Conditions that might preclude inhalational induction include significant aspiration risk, significant obesity, severe orthopnea, or an uncooperative patient. (From Grocott HP, Gulati H, Srinathan S, et al. Anesthesia and the patient with pericardial disease. *Can J Anaesth*. 2011;58:952–966.)

TABLE 11.6 Anesthetic Management of Tamponade

Prior to surgery	• Large-bore intravenous access • Preinduction arterial line if possible • Fluid therapy to maintain preload • Maintain heart rate with catecholamines, atropine • Correct metabolic acidosis
Before decompression	• Consider pericardiocentesis prior to induction in unstable patients • Surgeon present in the room prior to induction • Prep and drape surgical site before induction • Ketamine intravenous induction or inhaled induction • Maintain spontaneous ventilation or if not possible minimize inspiratory pressure • Vasopressors and inotropes ready • Lung isolation with double lumen tube or bronchial blocker might be needed for thoracoscopic or thoracotomy approach
After decompression	• Be prepared to manage hypertension • Monitor for acute heart failure or hypotension as a consequence of pericardial decompression syndrome

Several hemodynamic alterations can occur after release of tamponade. Frequently there is a significant change in arterial blood pressure from hypotension to marked hypertension. The anesthesiologist must be prepared for this change, and appropriate treatment must be started quickly, especially in cases of tamponade due to an aortic dissection or aneurysm. In some patients, however, sudden release of pericardial compression can precipitate acute heart failure and pulmonary edema with severe hypotension (i.e., pericardial decompression syndrome). Although the mechanisms for pericardial decompression syndrome are not fully known, it is thought that rapid expansion of right heart chambers can result in a decrease in left ventricular filling and systemic hypotension.

CONSTRICTIVE PERICARDITIS

Constrictive pericarditis is a condition resulting from fibrosis of the pericardium due to chronic pericardial inflammation or organization of a pericardial effusion. Tuberculosis is the most prevalent cause for constrictive pericarditis in developing

countries. Other etiologies of constrictive pericarditis are infectious processes (bacterial and viral), postpericardiotomy syndrome, rheumatologic diseases, mediastinal radiation, malignancies (Hodgkin lymphoma and breast cancer), asbestosis, sarcoidosis, uremia, and medication induced. Constrictive pericarditis is classified into transient, effusive, and chronic based on the duration of the disease processes. Each of these categories has different prognostic implications.

Pathophysiology

Constrictive pericarditis is characterized by a decrease in pericardial compliance due to fibrosis and thickening of the pericardium. This decreased compliance results in an impairment of cardiac chamber filling. The thickened pericardium also isolates the cardiac chambers from the intrathoracic pressure changes during the respiratory cycle. The pulmonary veins are extrapericardial, so inspiratory decreases in pulmonary venous pressures lead to reduced left-sided preload. As a result, the interventricular septum shifts to the left, increasing right ventricular filling during inspiration.

Diagnosis

The classic presentation of constrictive pericarditis is that of right heart failure with preserved systolic function. Fatigue, dyspnea, ascites, and abdominal distension are common. Physical examination demonstrates an elevated jugular venous pressure and a positive Kussmaul sign. A pericardial knock can sometimes be auscultated. Pulsus paradoxus has been reported in some cases due to diminished left heart filling during inspiration.

Laboratory findings are nonspecific and include elevation in inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate. Other diagnostic tests can support or rule out etiologies. These include renal function tests, thyroid-stimulating hormone (TSH), antinuclear antibody (ANA), extractable nuclear antigen (ENA), antineutrophil cytoplasmic antibody (ANCA), and viral polymerase chain reaction (PCR). Pericardial fluid can be tested for acid-fast bacilli, bacterial culture, PCR, and cytology.

Diagnostic imaging includes chest x-ray and echocardiography. Chest x-ray shows pericardial calcification in a third of cases. Echocardiography demonstrates respiratory variation of ventricular filling, ventricular interdependence, and usually a preserved systolic function.

Cardiac MRI is an adjuvant test that provides morphologic and hemodynamic information. It determines the degree of inflammation, degree of myocardial involvement, and hemodynamic impact of constrictive pericarditis.

CT is recommended in patients requiring cardiac surgery to define cardiac and mediastinal anatomy. Cardiac catheterization is recommended only for patients where the noninvasive diagnostic modalities are inconclusive (Table 11.7).

Clinically, it is important to differentiate constrictive pericarditis and restrictive cardiomyopathy. The two diseases are similar in presentation in terms of physical and ECG findings (low voltage, atrial fibrillation, nonspecific ST changes) (Table 11.8).

TABLE 11.7 Diagnosis of Constrictive Pericarditis

Symptoms
- Fatigue
- Dyspnea
- Weight loss
- Abdominal pain

Physical exam
- Increased jugular venous pressure
- Kussmaul sign
- Pulsus paradoxus
- Pericardial knock
- Ascites

Echocardiography
- Increased respiratory variation in transmitral inflow
- Restrictive ventricular filling pattern on Doppler exam
- Decreased lateral mitral annulus excursion compared to the medial mitral annulus (annulus reversus)
- Respiration-related ventricular septal shift
- Dilation of the inferior vena cava
- Expiratory diastolic hepatic flow reversal

Chest x-ray
- Pericardial calcification

Computerized tomography
- Pericardial calcification
- Pericardial thickening 4 mm

Cardiac catheterization
- Square root sign: dip and plateau configuration of ventricular pressure during diastole
- Majority of ventricular filling occurs during early diastole and is followed by a prolonged diastasis
- Near-equalization of right and left heart filling pressures
- Exaggerated decrease in systemic blood pressure during inspiration

TABLE 11.8 Differentiation Between Constrictive Pericarditis and Restrictive Cardiomyopathy

	Constrictive Pericarditis	Restrictive Cardiomyopathy
Murmur	Rare	Tricuspid regurgitation, mitral regurgitation
Pericardial knock	–	–
Pericardial calcification	–	–
Pericardial thickening	–	–
Mitral inflow respiratory variation	–	–
Atrial enlargement		

Treatment

Antiinflammatory agents in combination with medical management specific to the underlying etiology are the cornerstone of treatment for constrictive pericarditis. Pericardiectomy is recommended in cases that do not show favorable response to medical management.

Patients with severe constrictive pericarditis have a fixed cardiac output. Therefore, perioperative hemodynamic goals are to prevent deterioration of right heart function, maintain preload,

and avoid bradycardia. Additionally, avoiding hypoxemia and hypercarbia mitigates a rise in pulmonary artery pressures.

Radical pericardiectomy is indicated for patients with refractory symptoms. Prior chest radiation, renal failure, pulmonary hypertension, reduced left ventricular ejection fraction, and hyponatremia are poor prognostic factors in patients undergoing pericardiectomy.

Effusive-constrictive pericarditis occurs when constrictive pericarditis coexists with pericardial effusion and symptoms are not relieved by drainage of pericardial fluid. This is more common in tuberculosis and hemopericardium, and further management requires visceral pericardiectomy.

Management of Anesthesia

Hemodynamic goals of anesthetic management include maintaining adequate venous return by avoiding hypovolemia and using cautious preoperative hydration; maintaining normal sinus rhythm and avoiding bradycardia and significant decreases in afterload; avoiding positive pressure ventilation when possible, minimizing inspiratory pressure, minimizing positive end-expiratory pressure, and prolonging expiratory time; and optimizing right heart function.

Invasive monitoring with Swan-Ganz catheter is recommended for intracardiac pressure monitoring and guiding therapeutic interventions. Intraoperative TEE is indicated to monitor cardiac function and measure chamber sizes. It can also allow evaluation of tricuspid regurgitation, which is an important prognostic factor after pericardiectomy.

Surgical manipulation during pericardiectomy can result in phrenic nerve injury, and some recommend avoidance of neuromuscular paralysis to monitor its function. Postoperative presentation of diaphragmatic palsy ranges from asymptomatic to respiratory failure requiring mechanical ventilation. Additionally, significant blood loss requiring transfusion can occur during pericardiectomy. Arrythmias can occur due to manipulation of the heart and surrounding structures. Intraoperative arrythmias can significantly impact ventricular filling and require prompt treatment. Abrupt decreases in afterload should be avoided. Recovery of cardiac function after pericardiectomy is often delayed postoperatively, therefore these patients often require close postoperative monitoring in the intensive care unit.

CARDIAC TRAUMA

Trauma is the third leading cause of death in the United States. Of all trauma-related deaths, up to 25% are related to cardiothoracic injuries. The most common cause of blunt cardiac trauma is motor vehicle accidents. The most common causes of penetrating cardiac trauma are gunshot and stab wounds.

Blunt Cardiac Injuries

Blunt cardiac injury may be responsible for up to 20% of motor vehicle collision-related deaths. In these patients, severe cardiac injury may result in a prehospital mortality of up to 95%. It results in a wide spectrum of clinical manifestations ranging from mild and asymptomatic to severe injuries that can cause death within minutes. The main mechanisms of injury are rapid deceleration of the chest as it impacts the steering wheel and shear forces on internal thoracic structures. In addition to motor vehicle collisions, explosions can also result in blunt cardiac injury as the pressure wave originating from the blast causes tissue disruption and vascular tearing.

Diagnosis

Blunt chest trauma can result in myocardial contusions, aortic dissection or tear, and sternal fractures. Occasionally there may be serious cardiovascular injury despite the lack of obvious external signs of trauma. Therefore, cardiac injury must be suspected in any patient with chest trauma even if there are no obvious external signs of injury.

The right ventricle is more susceptible to injury due to its anterior location in the chest, immediately behind the sternum. Blunt cardiac trauma can result in a wide range of problems, including myocardial concussion, ventricular rupture, disruption of valves or the conduction system, or injury to the coronary arteries.

Myocardial concussion is usually asymptomatic and is defined as a new regional wall motion abnormality without elevation of cardiac biomarkers. In contrast, cardiac contusions represent myocardial cellular injury leading to necrosis and presenting with elevated cardiac biomarkers. Hemopericardium and tamponade can also occur. Ventricular rupture is most frequently fatal, but occasionally patients may present with tamponade.

The symptoms of myocardial contusion include chest pain and palpitations. The chest pain can resemble angina pectoris, but it is not relieved by nitroglycerin. Heart failure is uncommon in patients with myocardial contusion.

The presence of chest pain and ECG changes, especially in young patients, should prompt questions regarding recent chest trauma that might have seemed trivial at the time of its occurrence. A wide spectrum of electrical abnormalities may occur in patients with blunt cardiac trauma. Diffuse ST-segment or T-wave abnormalities are frequently noted in trauma patients in general, even in the absence of myocardial contusion.

The most common rhythm abnormality with myocardial contusion is new-onset right bundle branch block. Tachyarrhythmias and bradyarrhythmias, including heart block (due to atrioventricular node dysfunction), can also be present. Approximately 25% to 30% of patients will need some pharmacologic or electrical intervention for arrhythmias.

Elevation in cardiac biomarkers occurs in patients with myocardial contusion. Of note, creatine kinase (CK) and CK-MB are unreliable, as they are difficult to interpret in patients with concomitant noncardiac muscle injuries. Troponin I and T elevation is more specific for cardiac injury. When combined with normal serial ECG, the absence of troponin elevation can rule out significant cardiac injury within 8 hours of presentation.

Cardiac contusion can be recognized by TTE or TEE, which can demonstrate ventricular regional wall motion abnormalities, valvular regurgitation, or pericardial effusion. These wall motion abnormalities usually resolve within a few days.

Treatment

In patients with ventricular rupture and tamponade, early diagnosis and surgical intervention can be lifesaving. Treatment of a myocardial contusion is directed toward improving the symptoms and anticipating possible complications. Life-threatening dysrhythmias can occur within the first 24 to 48 hours after injury. Severely contused hearts may also require hemodynamic support. Patients with a severe myocardial contusion may have other injuries that require emergent surgical intervention. Invasive hemodynamic monitoring is prudent in this situation. Anesthetic drugs that depress myocardial function should be avoided. A cardioverter-defibrillator and medications for dysrhythmia management should be immediately available.

Commotio Cordis

Commotio cordis (from Latin *commotio* = agitation, *cordis* = heart) is an electrical disturbance of the heart that results in sudden death and usually occurs secondary to a fairly low-impact trauma to the chest. It commonly occurs in athletes when a projectile (punch, kick, baseball, hockey puck, lacrosse ball) strikes the chest during ventricular repolarization. This period is usually around 20 to 40 ms of the upslope of the T wave. A focused mechanical injury during this small window of time could stretch cardiac fibers and cause an unsynchronized impulse, a mechanical R-on-T phenomenon that can trigger ventricular fibrillation. The essential treatment for commotio cordis is defibrillation. Because of this, the syndrome must be recognized, and rapid defibrillation must be available. Public awareness programs and the availability of automatic external defibrillators and rapid-response teams at sporting events are already making an impact on the survival of individuals sustaining this injury.

Penetrating Cardiac Trauma

The incidence of penetrating cardiac trauma has increased over the past several years. Penetrating cardiac injury has a mortality of greater than 70%. The most frequent causes are stab wounds and gunshot injuries. The right ventricle is the most common site of injury with penetrating cardiac trauma due to its anterior position in the chest. Injuries to the left ventricle can also be seen, but they are almost always lethal. Death in patients with penetrating cardiac trauma is usually due to hemorrhagic shock and cardiac tamponade.

TABLE 11.9 Traumatic Aortic Injuries

Grade of Severity	Injury	Description
Grade 1	Laceration	Intimal tear
Grade 2	Intramural hematoma	Intramural hematoma or large intimal flap
Grade 3	Pseudoaneurysm	Rupture contained by the adventitia
Grade 4	Rupture or complete transection	Injury traverses the three layers of the vessel wall

Aortic Injuries

Blunt or penetrating chest trauma can result in a spectrum of aortic injuries (Table 11.9). Most injuries are caused by blunt trauma due to head-on motor vehicle collisions. The portion most susceptible to injury is the isthmus (between the left subclavian origin and ligamentum arteriosum). This section of the aorta is susceptible to deceleration injuries due to tethering by the ligamentum arteriosum.

Diagnosis

There are no specific signs or symptoms for aortic injury. Therefore a high degree of suspicion aids with the diagnosis in patients who present after falls from heights or high-speed motor vehicle collisions. Clinical findings may include hypotension, altered mental status, external signs of trauma, and chest pain. A discrepancy in blood pressure measurement between both arms and decreased or absent pulses in the lower extremities can also occur.

Imaging studies may show nonspecific findings, such as widening of the mediastinum or tracheal displacement on chest x-ray. CT angiogram is the investigational modality of choice for aortic trauma.

Treatment

Aortic trauma is a surgical emergency, and mortality depends on early diagnosis and intervention. Hemodynamically unstable patients should be taken immediately to the operating room. Close monitoring without intervention may be indicated for patients with intimal hemorrhage without laceration. In contrast, surgical repair is required for intramural hematomas, pseudoaneurysms, and rupture.

KEY POINTS

- The pericardial cavity is filled with approximately 10-50mL of fluid under normal conditions.
- Pericarditis is the most common pericardial disorder. It may or may not be accompanied by pericardial effusion and it is a common cause of non-ischemic chest pain.
- Pericarditis diagnosis requires at least two of these four criteria: pleuritic chest pain, pericardial friction rub, diffuse ST-segment elevation or PR depression on the ECG, and new or worsening pericardial effusion.
- Postcardiac injury syndromes include postinfarction pericarditis, postpericardiotomy syndrome after cardiac surgery, and traumatic pericarditis. These conditions result after damage to pericardial tissue triggers an autoimmune response with an inflammatory reaction.
- Dressler's syndrome (postinfarction pericarditis) may mimic postinfarction angina.
- Cardiac tamponade can be caused by rapid accumulation of small amounts of pericardial fluid accumulation.
- Large pericardial effusions that accumulate over a prolonged period of time may result in little or no symptomatology but can also result in cardiac tamponade in some patients.

- Echocardiography is the most accurate and practical method for confirming the presence of a pericardial effusion.
- Echocardiographic features of tamponade include decreased left ventricular end systolic and end diastolic dimensions, plethoric inferior vena cava with minimal respiratory variation, large respiratory variation in transmitral and transtricuspid inflows, right atrial systolic collapse, and right ventricular diastolic collapse.
- Localized hematomas (hemopericardium) that occur after cardiac surgery or trauma can result in cardiac tamponade, even if a circumferential effusion is not present.
- Tamponade after cardiac surgery should be suspected in patients with decreased chest tube and mediastinal drain output after an initial period of bleeding, with increasing inotropic and vasopressor requirement.
- General anesthesia and positive pressure ventilation can result in life threatening hypotension in patients with hemodynamically significant cardiac tamponade.
- Blunt cardiac and aortic trauma results in high morbidity and mortality, and the diagnosis of these conditions requires a high degree of suspicion

RESOURCES

Adler Y, Charron P, Imazio M, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the task force for the diagnosis and management of pericardial diseases of the European Society of Cardiology (ESC). Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2015;36(42):2921–2964. doi:10.1093/eurheartj/ehv318.

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12

Vascular Disease

Loreta Grecu

OUTLINE

DISEASES OF THE THORACIC AND ABDOMINAL AORTA

Aneurysms, dissections, and occlusive disease are the main pathologies that can affect arterial vessels. Whereas occlusive disease is more likely to occur in peripheral arteries, the aorta and its major branches are affected by two abnormalities that may be present simultaneously or occur at different stages of the same disease process—aneurysms (more common) and dissections (Fig. 12.1 and Table 12.1). Although there can be some overlap, a clear distinction between these entities is critical, as approach and treatment may be very different. For example, an ascending aortic dissection is a catastrophic event that requires immediate surgical intervention and carries a mortality of 1%–2% per hour for the first 48 hours, with overall mortality between 27% and 58%. That is a very different clinical situation from aortic aneurysms that are primarily treated medically, with surgical intervention needed only when they reach a certain threshold diameter.

An aneurysm is a dilatation of all three layers of an artery, which appears ballooned in a certain region, such as the ascending or descending portions of the thoracic or abdominal aorta. The most common definition is a 50% increase in diameter compared with normal, or greater than 3 cm in diameter. Arterial diameter depends on age, gender, and body habitus. Aneurysms may occasionally produce symptoms because of compression of surrounding structures, but rupture with exsanguination is the most dreaded complication since only about 25% of patients who experience rupture of an abdominal aortic aneurysm survive (Fig. 12.2).

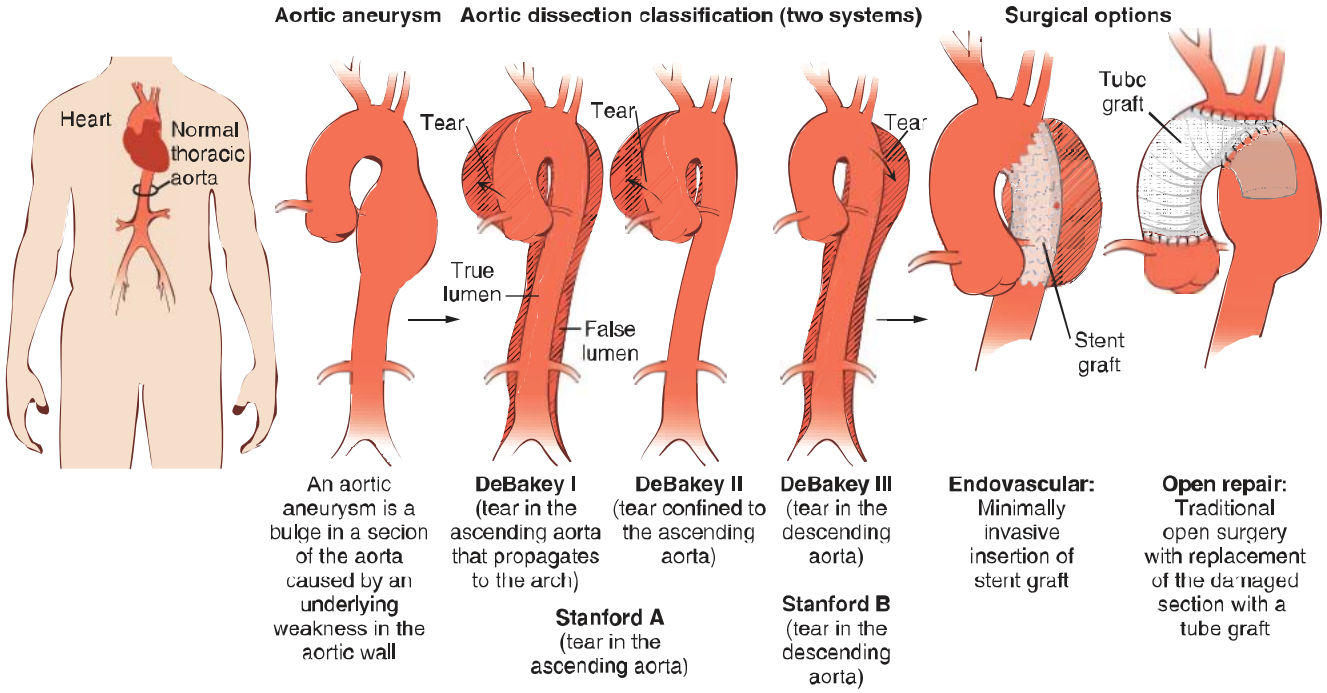

Fig. 12.1 Overview of thoracic aneurysms and dissections. (Adapted from Goldfinger JZ, Halperin JL, Marin ML, et al. Thoracic aortic aneurysms and dissection. *J Am Coll Cardiol.* 2014;64:1725–1739.)

TABLE 12.1 Comparison Between Aortic Aneurysms and Dissections

	Aortic Aneurysm	Aortic Dissection
Definition	Dilatation of all three aortic layers	Blood entry into the media
False lumen	No	Yes
Predisposing factors	HTN, atherosclerosis, age, male, smoking, family history of aneurysm	HTN, atherosclerosis, preexisting aneurysm, inflammatory diseases, collagen diseases, family history of aortic dissection, aortic coarctation, bicuspid aortic valve, Turner syndrome, CABG, previous aortic valve replacement, cardiac catheterization, crack cocaine use, trauma
Symptoms	May be asymptomatic or present with pain mostly due to compression of adjacent structures or vessels	Severe sharp pain in the posterior chest or back pain
Diagnosis	CXR, echocardiography, CT, MRI, angiography	For patients in unstable condition, echocardiography; after patient's condition is medically stabilized, imaging can include CT, CXR, aortography, MRI, echocardiography.
Management	Elective surgical repair, whether thoracic or abdominal, for diameter >6 cm or rapidly enlarging aneurysms with >10-mm growth over 6 mo for thoracic and diameter of >5.5 cm or >5-mm increase for abdominal; endovascular repair recommended owing to better patient outcomes, especially in patients at high risk, although no randomized trial data exist.	*Type A dissection:* Acute surgical emergency; as accurate diagnosis is made, patient will require acute medical management to decrease blood pressure and aortic wall stress. *Type B dissection:* If uncomplicated, medical management can be pursued.

CABG, Coronary artery bypass grafting; *CT*, computed tomography; *CXR*, chest x-ray; *HTN*, hypertension; *MRI*, magnetic resonance imaging.

Dissection of an artery occurs when blood enters the medial layer. The media of large arteries is made up of organized lamellar units that decrease in number with distance from the heart. The initiating event of an aortic dissection is a tear in the intima. Blood surges through the intimal tear into an extraluminal channel called the false lumen. Blood in the false lumen can reenter the true lumen anywhere along the course of the dissection. The origins of aortic branch arteries arising from the area involved in the dissection may be compromised and the aortic valve rendered incompetent. This sequence of events occurs over minutes to hours. A delay in diagnosis or treatment can be fatal (Fig. 12.3).

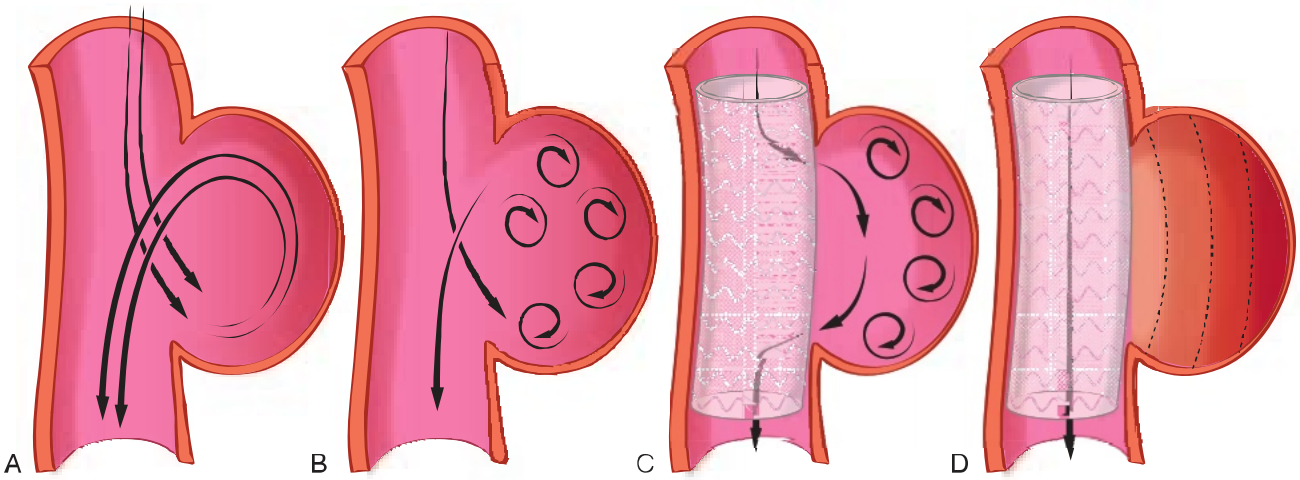

Fig. 12.2 A, Blood flow through a saccular aneurysm. B, Saccular aortic aneurysm with increased flow velocity. C, Saccular aortic aneurysm treated with a multilayer stent that decreases the flow velocity into the aneurysm. D, Saccular aneurysm that is now excluded from blood flow circulation. (Adapted from Buck DB, van Herwaarden JA, Schermerhorn ML, et al. Endovascular treatment of abdominal aortic aneurysms. *Nat Rev Cardiol.* 2014;11:112–123.)

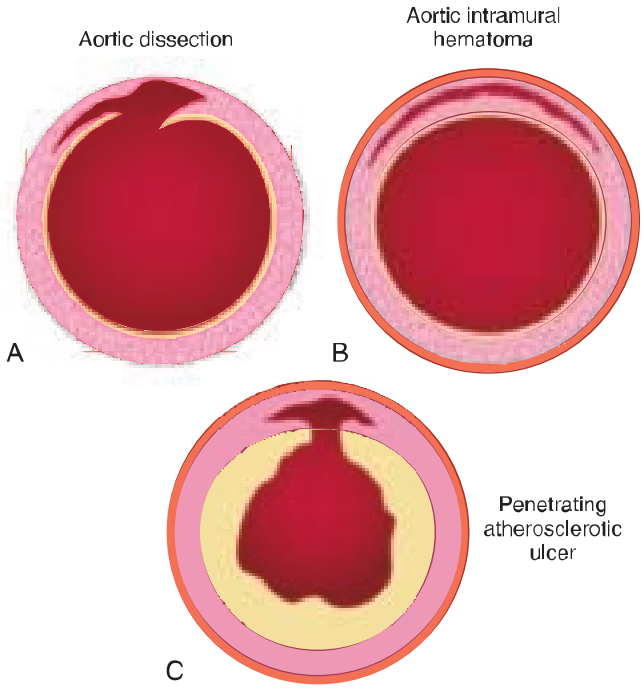

Fig. 12.3 Acute aortic syndromes. A, Classic aortic dissection. B, Aortic intramural hematoma. C, Penetrating atherosclerotic ulcer. (Adapted from Braverman AC. Diseases of the aorta. In: Mann DL, Zipes DP, Libby P, et al., eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.* 10th ed. Philadelphia: Elsevier; 2015:1277.)

ANEURYSMS AND DISSECTIONS OF THE THORACIC AND ABDOMINAL AORTA

Incidence

The incidence of descending thoracic aneurysms is 5.9 to 10.4 per 100,000 person-years, and rupture occurs at a rate of 3.5 per 100,000 person-years. Although it is commonly accepted that the threshold for repair is a diameter of 6 cm or larger, one must be aware of the possibility of synchronous aneurysms involving the ascending aorta or arch, which occur in approximately 10% of patients. Dissection of the aorta can originate anywhere along the length of the aorta, but the most common points of origin are in the thorax, in the ascending aorta just above the aortic valve, and just distal to the origin of the left subclavian artery near the insertion of the ligamentum arteriosum.

Etiology

The most frequently implicated factors in the development of aortic aneurysmal disease are hypertension, atherosclerosis, older age, male sex, family history of aneurysmal disease, and smoking. Causes of aortic dissection are deceleration injuries resulting from blunt trauma and use of crack cocaine, and iatrogenic dissection may occur secondary to aortic cannulation, including cardiac catheterization, cross clamping, aortic manipulation, or arterial incision for surgical procedures such as aortic valve replacement, bypass grafting, or aneurysm operations. Systemic hypertension is a factor that can be implicated in both genetic and nongenetic causes. Aortic dissection is more common in men, but there is also an association with pregnancy. Approximately half of all aortic dissections in women younger than age 40 occur during pregnancy, usually in the third trimester.

Causes of aneurysmal diseases are degenerative due to breakdown of the collagen and elastin in the aortic wall, infectious, and genetic. Thoracic aortic aneurysms and dissections associated with known genetic syndromes are well described. These include both conditions affecting large arteries, such as the aorta, and those involving the microvasculature. Four major inherited disorders are known to affect major arteries: Marfan syndrome, Ehlers-Danlos syndrome, bicuspid aortic valve, and nonsyndromic familial aortic dissection. Although it was once believed that mutant connective tissue proteins corrupted

proteins from the normal allele (dominant negative effect) in combination with normal wear and tear, it is now known that matrix proteins, in addition to showing specific mechanical properties, have important roles in the homeostasis of the smooth muscle cells that produce them. Matrix proteins play a key metabolic function because of their ability to sequester and store bioactive molecules and participate in their precisely controlled activation and release. In the inherited disorders associated with aortic dissection, loss of this function (biochemical rather than mechanical) is thought to alter smooth muscle cell homeostasis. The end result is a change in matrix metabolism that causes structural weakness in the aorta.

Marfan syndrome is one of the most prevalent hereditary connective tissue disorders. Its inheritance pattern is autosomal dominant. Marfan syndrome is caused by mutations in the fibrillin-1 gene. Fibrillin is an important connective tissue protein in the capsule of the ocular lens, arteries, lung, skin, and dura mater. Fibrillin mutations can result in disease manifestations in each of these tissues. Because fibrillin is an integral part of elastin, recognition of the mutations in fibrillin led to the assumption that the clinical manifestations of Marfan syndrome in the aorta were secondary to an inherent weakness of the aortic wall exacerbated by aging. However, histologic studies of the aortas of Marfan syndrome patients also demonstrate abnormalities in matrix metabolism that can result in matrix destruction.

Although the genetics of thoracic aortic aneurysm disease in patients with Marfan syndrome are well documented, less is known about familial patterns of aneurysm occurrence not associated with any particular collagen or vascular disease. Up to 19% of people with thoracic aortic aneurysm and dissection do not have syndromes traditionally considered to predispose them to aortic disease. However, these individuals often have several relatives with thoracic aortic aneurysm disease, which suggests a strong genetic predisposition.

Bicuspid aortic valve is the most common congenital anomaly resulting in aortic dilation/dissection. It occurs in 1% of the general population. Histologic studies show elastin degradation in the aorta just above the aortic valve. Echocardiography shows that aortic root dilatation is common even in younger patients with bicuspid aortic valve. Bicuspid aortic valve clusters in families and is found in approximately 9% of first-degree relatives of affected individuals.

Nonsyndromic familial aortic dissection and aneurysm is found in approximately 20% of patients referred for repair of thoracic aneurysm or dissection. Affected families do not meet the clinical criteria for Marfan syndrome and do not have biochemical abnormalities in type III collagen, as in Ehlers-Danlos syndrome. In most of these families the inheritance pattern appears to be dominant with variable penetrance. At least three chromosomal regions have so far been mapped in families with nonsyndromic thoracic aortic aneurysm disease. The specific biochemical abnormalities predisposing to thoracic aortic aneurysm disease remain to be identified.

Abdominal aortic aneurysms have traditionally been viewed as resulting from atherosclerosis. This atherosclerosis involves several highly interrelated processes, including lipid disturbances, platelet activation, thrombosis, endothelial dysfunction, inflammation, oxidative stress, vascular smooth muscle cell activation, altered matrix metabolism, remodeling, and genetic factors. Atherosclerosis represents a response to vessel wall injury caused by processes such as infection, inflammation, increased protease activity within the arterial wall, genetically regulated defects in collagen and fibrillin, and mechanical factors. A familial component has also been identified, because 12% to 19% of first-degree relatives (usually men) of a patient with an abdominal aortic aneurysm will develop an aneurysm. Specific genetic markers and biochemical changes that produce this pathologic condition remain to be elucidated.

Factors that disrupt the normal integrity of the aortic wall or significant increases in shear tension may induce the occurrence of dissections. Examples of conditions associated with aortic dissection are hypertension, genetically triggered aortic disease (see earlier), bicuspid aortic valve, tetralogy of Fallot, atherosclerosis, penetrating atherosclerotic ulcer, trauma, intraaortic balloon pump, aortic/vascular surgery, coronary artery bypass graft, giant cell arteritis, aortitis, syphilis, pregnancy, and weightlifting.

Classification

Aortic aneurysms can be classified morphologically as either fusiform or saccular. In fusiform aneurysm there is a uniform dilatation involving the entire circumference of the aortic wall, whereas a saccular aneurysm is an eccentric dilatation of the aorta that communicates with the main lumen by a variably sized neck. Aneurysms can also be classified based on the pathologic features of the aortic wall (e.g., atherosclerosis or cystic medial necrosis).

Arteriosclerosis is the primary lesion associated with aneurysms in the infrarenal abdominal aorta, thoracoabdominal aorta, and descending thoracic aorta. Aneurysms affecting the ascending aorta are primarily the result of lesions that cause degeneration of the aortic media, a pathologic process termed *cystic medial necrosis.*

Aneurysms of the thoracoabdominal aorta may also be classified according to their anatomic location. Two classifications widely used for aortic dissection are the DeBakey and Stanford classifications (Fig. 12.4; also see Fig. 12.1). The DeBakey classification includes types I to III. In type I, the intimal tear originates in the ascending aorta, and the dissection involves the ascending aorta, arch, and variable lengths of the descending thoracic and abdominal aorta. In DeBakey type II, the dissection is confined to the ascending aorta. In type III, the dissection is confined to the descending thoracic aorta (type IIIa) or extends into the abdominal aorta and iliac arteries (type IIIb). The Stanford classification describes thoracic aneurysms as type A or B. Type A includes all cases in which the ascending aorta is involved by the dissection, with or without involvement of the arch or descending aorta. Type B includes all cases in which the ascending aorta is not involved.

Signs and Symptoms

Many patients with thoracic aortic aneurysms are asymptomatic at the time of presentation, and the aneurysm is detected

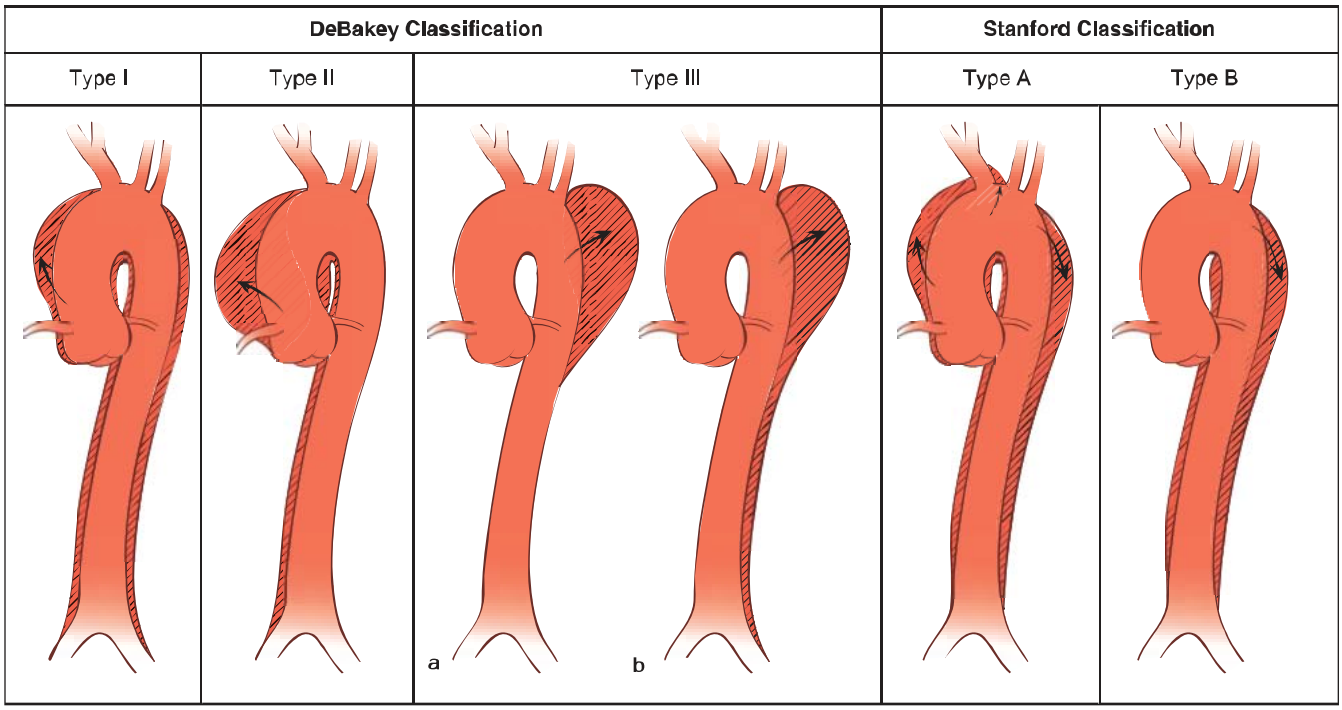

Fig. 12.4 The two most widely used classifications of aortic dissection: DeBakey and Stanford classifications. In DeBakey type I dissection the intimal tear usually originates in the proximal ascending aorta, and the dissection involves the ascending aorta and variable lengths of the aortic arch and descending thoracic and abdominal aorta. In DeBakey type II the dissection is confined to the ascending aorta. In DeBakey type III the dissection is confined to the descending thoracic aorta (type IIIa) or extends into the abdominal aorta and iliac arteries (type IIIb). Stanford type A dissection includes all cases in which the ascending aorta is involved by the dissection, with or without involvement of the arch or the descending aorta. Stanford type B includes cases in which the ascending aorta is not involved. (Data from Kouchoukos NT, Dougenis D. Surgery of the thoracic aorta. *N Engl J Med*. 1997;336:1876–1888. Copyright 1997 Massachusetts Medical Society.)

during testing for other disorders. Symptoms resulting from thoracic aneurysm typically reflect impingement of the aneurysm on adjacent structures. Hoarseness results from stretching of the left recurrent laryngeal nerve. Stridor is due to compression of the trachea. Dysphagia is due to compression of the esophagus. Dyspnea results from compression of the lungs. Plethora and edema result from compression of the superior vena cava. Patients with ascending aortic aneurysms associated with dilatation of the aortic valve annulus may have signs of aortic regurgitation and congestive heart failure.

Acute, severe, sharp pain in the anterior chest, neck, or between the shoulder blades is the typical presenting symptom of thoracic aortic dissection. The pain may migrate as the dissection advances along the aorta. Patients with aortic dissection often appear as if they are in shock (vasoconstricted), yet the systemic blood pressure may be quite elevated. Patients who have severe hypotension or even shock at presentation have a worse prognosis. Hypotension at presentation is more common with proximal dissections. Other symptoms and signs of acute aortic dissection, such as diminution or absence of peripheral pulses, reflect occlusion of branches of the aorta and may be followed by inadequate treatment because of falsely low blood pressure measurements. Neurologic complications of aortic dissection may include stroke caused by occlusion of a carotid artery, ischemic peripheral neuropathy associated with ischemia of an arm or a leg, and paraparesis or paraplegia caused by impairment of the blood supply to the spinal cord. Myocardial infarction (MI) may reflect occlusion of a coronary artery. Gastrointestinal ischemia may occur. Renal artery obstruction is manifested by an increase in serum creatinine concentration. Retrograde dissection into the sinus of Valsalva with distortion of aortic valve, aortic insufficiency, and even rupture into the pericardial space leading to cardiac tamponade is a major cause of death. Approximately 90% of patients with acute dissection of the ascending aorta who are not treated surgically die within 3 months.

Abdominal aortic aneurysms are usually detected as asymptomatic pulsatile abdominal masses.

Diagnosis

Widening of the mediastinum on chest radiograph may be diagnostic of a thoracic aortic aneurysm. However, enlargement of the ascending aorta may be confined to the retrosternal area, so the aortic silhouette can appear normal. Computed tomography (CT) and magnetic resonance imaging (MRI) can be used to diagnose thoracic aortic disease, but in acute aortic dissection the diagnosis is most rapidly and safely made using echocardiography with color Doppler imaging (Fig. 12.5). Although transthoracic echocardiography (TTE) is the mainstay in evaluation of the heart, including evaluation for complications

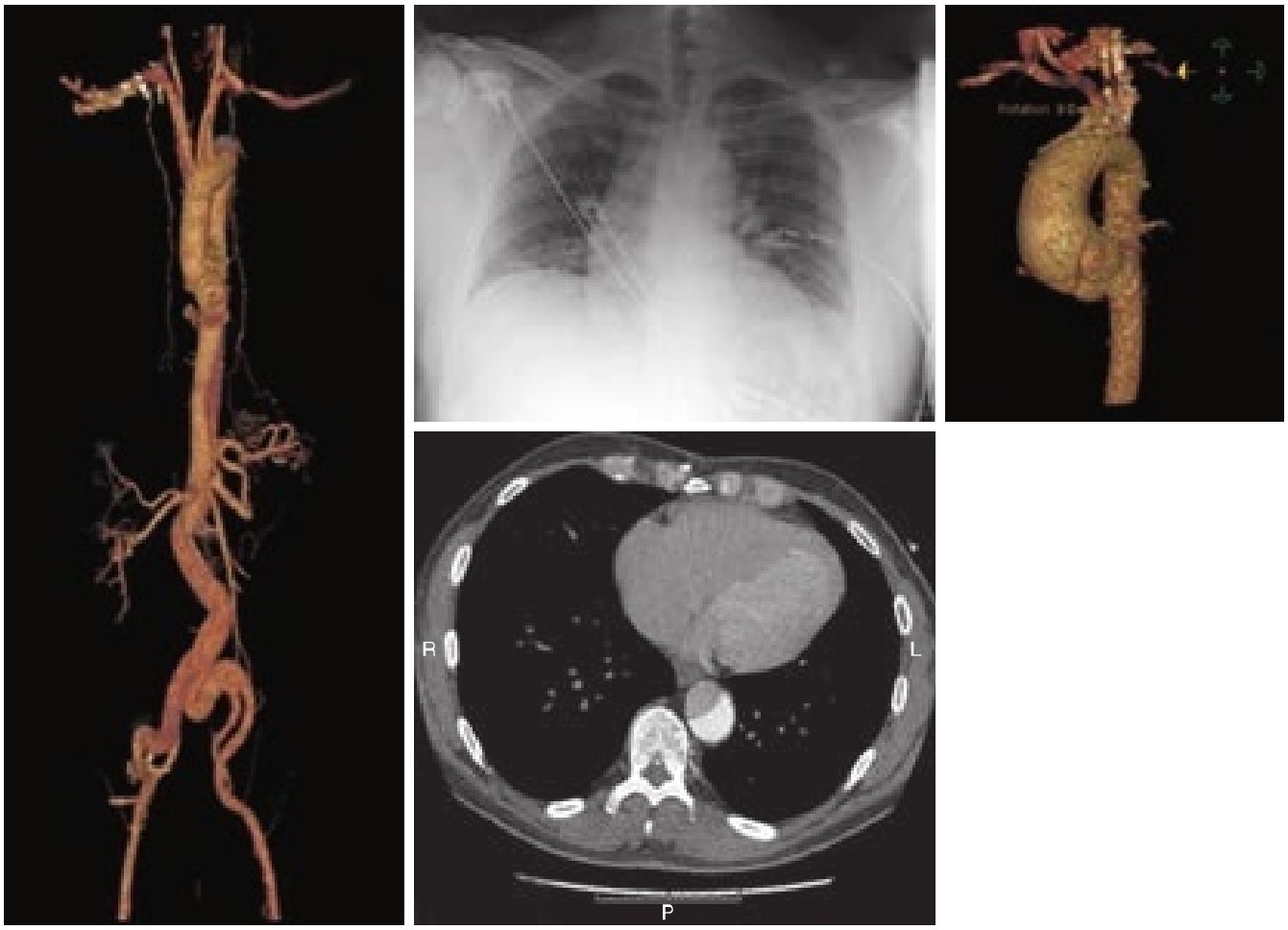

Fig. 12.5 (Clockwise from left) Tomographic reconstruction of a type B aortic dissection, chest radiography showing enlarged mediastinum, and type A aortic dissections seen on image reconstruction as well as with contrast computed tomography scanning.

of dissection like aortic insufficiency, pericardial effusions, and impaired regional left ventricular function, it is of somewhat limited value in assessment of the distal ascending, transverse, and descending aorta. Transesophageal echocardiography (TEE), on the other hand, plays an essential role in diagnosing aortic dissection because it is both highly sensitive and specific (98% and 95%, respectively), has the advantage of using portable equipment, and can be performed as a single study, especially in patients in unstable condition. Angiography of the aorta may be required for patients undergoing elective surgery on the thoracic aorta so that the complete extent of the dissection and the location of all compromised aortic branches can be defined.

Abdominal ultrasonography is a very sensitive test for the detection of abdominal aortic aneurysms. CT is also very sensitive and is more accurate than ultrasonography in estimating aneurysm size.

Improvements in CT technology, such as the advent of helical CT and CT angiography, have increased the role of CT imaging in the evaluation and treatment of abdominal aortic aneurysms. Helical CT provides excellent three-dimensional anatomic detail and is particularly useful for evaluating the feasibility of endovascular stent graft repair of the aneurysm. In addition to radiation exposure, a disadvantage of CT scanning includes the utilization of a contrast substance with potential for worsening renal function.

MRI is useful for accurate measurement of aneurysm size and evaluation of relevant vascular anatomy without the need for the use of ionizing radiation or contrast medium.

Medical Management of Aortic Aneurysms

Medical management of an aortic aneurysm focuses on decreasing its expansion rate and thus potentially avoiding its evolution toward dissection and/or rupture. Careful management of blood pressure, hyperlipidemia, and smoking cessation are essential. Avoidance of strenuous exercise, stimulants such as cocaine, and overall stress are important aspects of long-term care of these patients. The most commonly used agents are β blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers, as well as statins for lipid control. In addition, patients with known aneurysms should be followed at regular intervals to evaluate for possible continued expansion of their aneurysm and subsequent need for surgical intervention.

Preoperative Evaluation

Because myocardial ischemia or infarction, respiratory failure, renal failure, and stroke are the principal causes of morbidity and mortality associated with surgery of the thoracic aorta, preoperative assessment of the function of the corresponding organ systems is needed. Assessment for the presence of myocardial ischemia, previous MI, valvular dysfunction, and heart failure is important in performing risk stratification and planning maneuvers for risk reduction. A preoperative percutaneous coronary intervention or coronary artery bypass grafting may be indicated in some patients with ischemic heart disease.

Preoperative evaluation of cardiac function might include exercise or pharmacologic stress testing with or without echocardiography or radionuclide imaging. Severe reductions in vital capacity and FEV_1 (forced expiratory volume in the first second of expiration), as well as abnormal renal function, may mitigate against abdominal aortic aneurysm resection or significantly increase the risk of elective aneurysm repair.

Cigarette smoking and the presence of chronic obstructive pulmonary disease (COPD) are important predictors of respiratory failure after thoracic aortic surgery. Spirometric tests of lung function and arterial blood gas analysis may better define this risk. Reversible airway obstruction and pulmonary infection should be treated with bronchodilators, antibiotics, and chest physiotherapy. Smoking cessation is highly desirable.

The presence of preoperative renal dysfunction is the single most important predictor of the development of acute renal failure after surgery on the thoracic aorta. Preoperative hydration and avoidance of hypovolemia, hypotension, low cardiac output, and nephrotoxic drugs during the perioperative period are important to decrease the likelihood of postoperative renal failure.

Duplex imaging of the carotid arteries or angiography of the brachiocephalic and intracranial arteries may be performed preoperatively in patients with a history of stroke or transient ischemic attacks (TIAs). Patients with severe stenosis of one or both common or internal carotid arteries could be considered for carotid endarterectomy before elective surgery on the thoracic aorta.

Indications for Surgery

As noted earlier, the mainstay of treatment for aortic aneurysm is medical management, so thoracic aortic aneurysm repair is an elective procedure, and surgery is contemplated only when aneurysm size exceeds a diameter of 5.5 cm. This size limit may be decreased somewhat for patients with a significant family history, a previous diagnosis of any of the hereditable diseases that affect blood vessels, or an aneurysm growth rate of 10 mm or more per year. A number of important technical advances have decreased the risk of surgery on the thoracic aorta, including the use of adjuncts such as distal aortic perfusion, profound hypothermia with circulatory arrest, monitoring of evoked potentials in the brain and spinal cord, and cerebrospinal fluid (CSF) drainage, as well as the rapid increase in endovascular procedures for aortic repairs.

The recommendation for surgery for abdominal aortic aneurysms larger than 5.5 cm in diameter is based on clinical studies indicating that the risk of rupture within a 5-year period is 25% to 41% for aneurysms larger than 5 cm. Smaller aneurysms are less likely to rupture, but patients with aneurysms less than 5 cm in diameter should be followed with serial ultrasonography. However, these recommendations are only guidelines. Each patient must be evaluated for the presence of risk factors for accelerated aneurysm growth and rupture, such as tobacco use and family history. If the abdominal aortic aneurysm expands by more than 0.6 to 0.8 cm per year, repair is usually recommended. Surgical risk and overall health are also part of the evaluation to determine the timing of aneurysm repair. Endovascular aneurysm repair is a valid alternative to surgical repair.

Rupture of Abdominal Aortic Aneurysm

The classic triad of hypotension, back pain, and a pulsatile abdominal mass is present in only about half of patients who have a ruptured abdominal aortic aneurysm. Renal colic, diverticulitis, and gastrointestinal hemorrhage may be confused with a ruptured abdominal aortic aneurysm.

Most abdominal aortic aneurysms rupture into the left retroperitoneum. Although hypovolemic shock may be present, exsanguination may be prevented by clotting and the tamponade effect of the retroperitoneum. Euvolemic resuscitation may be deferred until the aortic rupture is surgically controlled in the operating room, because euvolemic resuscitation and the resultant increase in blood pressure without surgical control of bleeding may lead to loss of retroperitoneal tamponade, further bleeding, hypotension, and death.

Patients in unstable condition who have a suspected ruptured abdominal aortic aneurysm require immediate operation and control of the proximal aorta without preoperative confirmatory testing or optimal volume resuscitation.

Aortic Dissections

Ascending and aortic arch dissection requires emergent or urgent surgery; however, descending thoracic aortic dissection is rarely treated with urgent surgery.

Type A dissection. The International Registry of Acute Aortic Dissection is a consortium of 21 large referral centers around the world. This registry's data have shown the in-hospital mortality rate of patients with ascending aortic dissection is approximately 27% in those who undergo timely and successful surgery. This is in contrast to an in-hospital mortality rate of 56% in those treated medically. Other independent predictors of in-hospital death include older age, visceral ischemia, hypotension, renal failure, cardiac tamponade, coma, and pulse deficits.

Long-term survival rates (i.e., survival at 1–3 years after hospital discharge) are 90% to 96% in the surgically treated group and 69% to 89% in those treated medically who survive initial hospitalization. Thus aggressive medical treatment and imaging surveillance of patients who for various reasons are unable to undergo surgery appear prudent.

Ascending aorta. All patients with acute dissection involving the ascending aorta should be considered candidates for surgery. The most commonly performed procedures are replacement of

the ascending aorta and aortic valve with a composite graft (Dacron graft containing a prosthetic valve) or replacement of the ascending aorta and resuspension of the aortic valve. In the last decade it appears that more centers perform valve-sparing surgical procedures that allow for reimplantation of the aortic valve.

Aortic arch. In patients with acute aortic arch dissection, resection of the aortic arch (i.e., the segment of aorta that extends from the origin of the innominate artery to the origin of the left subclavian artery) is indicated. Surgery on the aortic arch requires cardiopulmonary bypass, profound hypothermia, and a period of circulatory arrest. With current techniques, a period of circulatory arrest of 30 to 40 minutes at a body temperature of 15°C to 18°C can be tolerated by most patients. Focal and diffuse neurologic deficits are the major complications associated with replacement of the aortic arch. These occur in 3% to 18% of patients, and it appears that selective antegrade cerebral perfusion decreases but does not completely eliminate the morbidity and mortality associated with this procedure.

Type B dissection

Descending thoracic aorta. Patients with an acute but uncomplicated type B aortic dissection who have normal hemodynamics, no periaortic hematoma, and no branch vessel involvement at presentation can be treated with medical therapy. Such therapy consists of (1) intraarterial monitoring of systemic blood pressure and urinary output and (2) administration of drugs to control blood pressure and the force of left ventricular contraction. Short-acting β blockers such as esmolol and nitroprusside or nicardipine, and more recently clevidipine, are commonly used for this purpose. This patient population has an in-hospital mortality rate of 10%. Long-term survival rate with medical therapy only is approximately 60% to 80% at 4 to 5 years and 40% to 50% at 10 years.

Surgery is indicated for patients with type B aortic dissection who have signs of impending rupture (persistent pain, hypotension, left-sided hemothorax); ischemia of the legs, abdominal viscera, or spinal cord; and/or renal failure. Surgical treatment of distal aortic dissection is associated with a 29% in-hospital mortality rate.

Unique Risks of Surgery

Surgical approach. Classically the ascending aorta and aortic arch are approached via median sternotomy and require cardiopulmonary bypass. The descending thoracic aorta is repaired through a thoracotomy incision, and abdominal aneurysms are repaired via laparotomy. Endovascular repairs require groin incisions and have only minimal scars.

Surgical resection of thoracic aortic aneurysms can be associated with a number of serious, even life-threatening complications. There is the risk of spinal cord ischemia (anterior spinal artery syndrome) with resulting paraparesis or paraplegia. Cross clamping and unclamping the aorta introduces the potential for adverse hemodynamic responses such as myocardial ischemia and heart failure. Hypothermia, an important neuroprotective maneuver, can be responsible for the development of coagulopathy. Renal insufficiency or renal failure occurs in up to 30% of patients. Approximately 6% of patients will require hemodialysis. Pulmonary complications are common; the incidence of respiratory failure approaches 50%. Cardiac complications are the leading cause of mortality.

Anterior spinal artery syndrome. Cross clamping the thoracic aorta can result in ischemic damage to the spinal cord (see Fig. 12.2). The frequency of spinal cord injury ranges from 0.2% after elective infrarenal abdominal aortic aneurysm repair to 8% in elective thoracic aortic aneurysm repair to 40% in the setting of acute aortic dissection or rupture involving the descending thoracic aorta. Manifestations of anterior spinal artery syndrome include flaccid paralysis of the lower extremities and bowel and bladder dysfunction. Sensation and proprioception are spared.

Spinal cord blood supply. The spinal cord is supplied by one anterior spinal artery and two posterior spinal arteries. The anterior spinal artery begins at the fusion of branches of both vertebral arteries and relies on reinforcement of its blood supply by six to eight radicular arteries, the largest and most important of which is the great radicular artery of Adamkiewicz. Multiple levels of the spinal cord do not receive feeding radicular branches, which leaves watershed areas that are particularly susceptible to ischemic injury. These areas are in jeopardy during aortic occlusion or hypotension (Fig. 12.6). Damage can also result from surgical resection of the artery of Adamkiewicz (because the origin is unknown) or exclusion of the origin of the artery by the cross clamp. In this situation, not only is the anterior spinal artery blood flow reduced directly, but the potential for collateral blood flow to the spinal cord is also reduced because aortic pressure distal to the cross clamp is very low.

Risk factors. The risk of paraplegia during thoracic aortic surgery is determined by the interaction of four factors: (1) the decrease in spinal cord blood flow, (2) the rate of neuronal metabolism, (3) postischemia reperfusion injury, and (4) blood

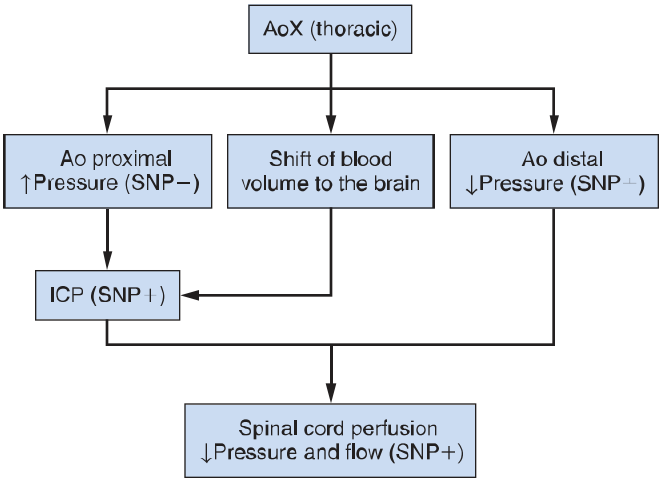

Fig. 12.6 Spinal cord blood flow and perfusion pressure during thoracic aortic occlusion, with or without sodium nitroprusside (SNP) infusion. The arrows represent the response to aortic cross clamping (AoX) per se. ↑, Increased; ↓, decreased; *Ao*, aorta; *ICP*, intracranial pressure; *SNP−*, the effects enhanced by SNP infusion; *SNP−*, the effects counteracted by SNP infusion. (Adapted from Gelman S. The pathophysiology of aortic cross-clamping and unclamping. *Anesthesiology.* 1995;82:1026–1060. © 1995, Lippincott Williams & Wilkins.)

flow after reperfusion. The duration of aortic cross clamping is critical in determining the risk of paraplegia. A brief period of thoracic aortic cross clamping (<30 minutes) is usually tolerated. If cross clamp time is more than 30 minutes, the risk of spinal cord ischemia is significant, and use of techniques for spinal cord protection is indicated. These include partial circulatory assistance (left atrium to femoral artery bypass), reimplantation of critical intercostal arteries when possible, CSF drainage, maintenance of proximal hypertension during cross clamping, reduction of spinal cord metabolism by moderate hypothermia (30°–32°C), including spinal cooling, avoidance of hyperglycemia, and the use of mannitol, corticosteroids, and/or calcium channel blockers.

There is debate regarding the incidence of spinal cord ischemia after endovascular repair. Although some studies report an incidence similar to open aortic surgery, others show a lower rate with endovascular repair. Nevertheless, the incidence seems to be directly correlated with the severity of aortic disease. The theoretical reason is that although the respective vessel may be taken out of circulation, with endovascular repair (as opposed to open repair) there is no dissection of other vessels that may represent important collateral flow, which ensures perfusion of the spinal cord.

Hemodynamic responses to aortic cross clamping. Thoracic aortic cross clamping and unclamping are associated with severe hemodynamic and homeostatic disturbances in virtually all organ systems because of the decrease in blood flow distal to the aortic clamp and the substantial increase in blood flow above the level of aortic occlusion. There is a substantial increase in systemic blood pressure and systemic vascular resistance (SVR), with no significant change in heart rate. A reduction in cardiac output usually accompanies these changes. Systemic hypertension is attributed to increased impedance to aortic outflow (increased afterload). In addition, there is blood volume redistribution caused by collapse and constriction of the venous vasculature distal to the aortic cross clamp. An increase in preload results. Evidence of this blood volume redistribution can be seen as an increase in filling pressures (central venous pressure, pulmonary capillary occlusion pressure, left ventricular end-diastolic pressure). Substantial differences in the hemodynamic response to aortic cross clamping can be seen at different levels of clamping: thoracic, supraceliac, and infrarenal. Changes in mean arterial pressure, end-diastolic and end-systolic left ventricular area and ejection fraction, and wall motion abnormalities may be assessed by TEE or pulmonary artery catheterization and are minimal during infrarenal aortic cross clamping but dramatic during intrathoracic aortic cross clamping. Some of these differences result in part from different patterns of blood volume redistribution. Preload may not increase if the aorta is clamped distal to the celiac artery because the blood volume from the distal venous vasculature may be redistributed into the splanchnic circulation. For the increase in afterload and preload to be tolerated, an increase in myocardial contractility and an autoregulatory increase in coronary blood flow are required. If coronary blood flow and myocardial contractility cannot increase, left ventricular dysfunction is likely. Indeed, echocardiography often indicates abnormal wall motion of the left ventricle during aortic cross clamping, which suggests the presence of myocardial ischemia. Hemodynamic responses to aortic cross clamping are blunted in patients with aortoiliac occlusive disease.

Pharmacologic interventions intended to offset the hemodynamic effects of aortic cross clamping, especially clamping of the thoracic aorta, are related to the effects of the administered drug on arterial and/or venous capacitance. For example, vasodilators such as nicardipine, nitroprusside, and nitroglycerin often reduce the clamp-induced decrease in cardiac output and ejection fraction. The most plausible explanation for this effect is a drug-induced decrease in SVR and afterload, and increased venous capacitance.

It is important, however, to recognize that perfusion pressures distal to the aortic cross clamp are decreased and are directly dependent on proximal aortic pressure (i.e., the pressure above the level of aortic clamping). Blood flow to tissues distal to aortic occlusion (kidneys, liver, spinal cord) occurs through collateral vessels or through a shunt. It decreases dramatically during aortic clamping. Blood flow to vital organs distal to the aortic clamp depends on perfusion pressure, not on cardiac output or intravascular volume.

Clinically, drugs and volume replacement must be adjusted to maintain distal aortic perfusion pressure even if that results in an increase in blood pressure proximal to the clamp. Strategies for myocardial preservation during and after aortic cross clamping include decreasing afterload and normalizing preload, coronary blood flow, and contractility. Modalities such as placement of temporary shunts, reimplantation of arteries supplying distal tissues (spinal cord), and hypothermia may influence the choice of drugs and end points of treatment.

Cross clamping of the thoracic aorta just distal to the left subclavian artery is associated with severe decreases (~90%) in spinal cord and renal blood flow, glomerular filtration rate, and urinary output. Infrarenal aortic cross clamping is associated with a large increase in renal vascular resistance and a decrease (~30%) in renal blood flow. Renal failure following aortic surgery is almost always due to acute tubular necrosis. Ischemia-reperfusion insults to the kidneys play a central role in the pathogenesis of this renal failure.

Cross clamping of the thoracic aorta is associated not only with a decrease in distal aortic/anterior spinal artery pressure but also with an increase in CSF pressure. Presumably, intracranial hypertension resulting from systemic hypertension above the clamp produces redistribution of blood volume and engorgement of the intracranial compartment (intracranial hypervolemia). This results in redistribution of CSF into the spinal fluid space and a decrease in the compliance of the spinal fluid space. CSF drainage may increase spinal cord blood flow and decrease the incidence of neurologic complications.

Pulmonary damage associated with aortic cross clamping and unclamping is reflected by an increase in pulmonary vascular resistance (particularly with unclamping of the aorta), an increase in pulmonary capillary membrane permeability, and development of pulmonary edema. The mechanisms involved may include pulmonary hypervolemia and the effects of various vasoactive mediators.

Aortic cross clamping is associated with formation and release of hormonal factors (caused by activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system) and other mediators (prostaglandins, oxygen free radicals, complement cascade). These mediators may aggravate or blunt the harmful effects of aortic cross clamping and unclamping. Overall, injury to the spinal cord, lungs, kidneys, and abdominal viscera is principally due to ischemia and subsequent reperfusion injury caused by the aortic cross clamp (local effects) and/or the release of mediators from ischemic and reperfused tissues (distant effects).

Hemodynamic responses to aortic unclamping. Unclamping of the thoracic aorta is associated with substantial decreases in SVR and systemic blood pressure. Cardiac output may increase, decrease, or remain unchanged. Left ventricular end-diastolic pressure decreases, and myocardial blood flow increases. Gradual release of the aortic clamp is recommended to allow time for volume replacement and to slow the washout of vasoactive and cardiodepressant mediators from ischemic tissues.

The principal causes of unclamping hypotension include (1) central hypovolemia caused by pooling of blood in reperfused tissues; (2) hypoxia-mediated vasodilation, which causes an increase in vascular capacitance in the tissues below the level of aortic clamping; and (3) accumulation of vasoactive and myocardial-depressant metabolites in these tissues. Vasodilation and hypotension may be further aggravated by the transient increase in carbon dioxide release and oxygen consumption in these tissues following unclamping. Correction of metabolic acidosis does not significantly influence the degree of hypotension following aortic unclamping.

Management of Anesthesia

Management of anesthesia in patients undergoing thoracic aortic aneurysm resection requires consideration of monitoring systemic blood pressure, neurologic function, and intravascular volume and planning the pharmacologic interventions and hemodynamic management that will be needed to control hypertension during the period of aortic cross clamping. Proper monitoring is more important than selection of anesthetic drugs in these patients.

Monitoring Blood Pressure

Surgical repair of a thoracic aortic aneurysm requires aortic cross clamping just distal to the left subclavian artery or between the left subclavian artery and the left common carotid artery. Therefore blood pressure monitoring must be via an artery in the right arm, since occlusion of the aorta can prevent measurement of blood pressure in the left arm. Monitoring blood pressure both above (right radial artery) and below (femoral artery) the aneurysm is less commonly done but may be useful. This approach permits assessment of cerebral, renal, and spinal cord perfusion pressure during cross clamping.

Blood flow to tissues below the aortic cross clamp is dependent on perfusion pressure rather than on preload and cardiac output. Therefore during cross clamping of the thoracic aorta, proximal aortic pressures should be maintained as high as the heart can safely withstand unless other modalities (e.g., temporary shunts, hypothermia) are implemented. A common recommendation is to maintain mean arterial pressure near 100 mm Hg above the cross clamp and above 50 mm Hg in the areas distal to the cross clamp.

Use of vasodilators to treat hypertension above the level of the aortic cross clamp must be balanced against the likelihood of a decrease in perfusion pressure in the tissues below the clamp. Indeed, nitroprusside may decrease spinal cord perfusion pressure both by decreasing distal aortic pressure and by increasing CSF pressure as a result of cerebral vasodilation (see Fig. 12.6). It is prudent to limit the use of drugs that decrease proximal aortic pressure and cause cerebral vasodilation. Use of temporary shunts to bypass the occluded thoracic aorta (proximal aorta–to–femoral artery or left atrium–to–femoral artery shunts) may be considered when attempting to maintain renal and spinal cord perfusion. Partial cardiopulmonary bypass is another option to maintain distal aortic perfusion.

Monitoring Neurologic Function

Somatosensory evoked potentials (SEPs) and electroencephalography (EEG) are monitoring methods for evaluating central nervous system viability during the period of aortic cross clamping. Unfortunately, intraoperative monitoring of SEPs is not completely reliable for detecting spinal cord ischemia during aortic surgery as it reflects dorsal column (sensory tract) function. Ischemic changes in anterior spinal cord function (motor tracts) are not detected. Monitoring of motor evoked potentials would indicate anterior spinal cord function but is impractical, since it prohibits use of neuromuscular blocking drugs. Spinal cooling with epidural instillation of iced saline during cross clamping in thoracic aneurysm surgery has been used successfully for many years in some institutions across the United States on the basis that lowering the spinal cord temperature directly will improve recovery of potentially poorly perfused tissues after reimplantation of patent critical intercostal vessels by the surgeon. Spinal drainage has been used to decrease pressure around the spinal cord and avoid ischemia in a confined space if the spinal cord dilates after adequate perfusion is reestablished. CSF pressure is also maintained at a value of less than 10 cm H_2O in the days immediately after surgery for the same reason—namely, that an increase in pressure in the spinal canal may decrease perfusion to the spinal cord and impair motor function. This method is used successfully in both open surgical procedures and endovascular repairs of the aorta (see later). Another method that can be useful is atriofemoral bypass to maintain distal aortic perfusion.

Monitoring Cardiac Function

During operations on the thoracic aorta, TEE can provide valuable information about the presence of atherosclerosis in the thoracic aorta, the competence of cardiac valves, ventricular function, adequacy of myocardial perfusion, and intravascular volume status. A pulmonary artery catheter provides data that may complement information obtained from TEE.

Monitoring Intravascular Volume and Renal Function

Optimization of systemic hemodynamics, including circulating blood volume, represents the most effective measure for protecting the kidneys from the ischemic effects produced by aortic cross clamping. Use of diuretics such as mannitol before aortic clamping may also be useful. Mannitol improves renal cortical blood flow and glomerular filtration rate.

Renal protection is achieved by direct instillation of renal preservation fluid (4°C lactated Ringer solution with 25 g mannitol/L and 1 g methylprednisolone/L) and can be administered directly by the surgeon into the renal artery.

Induction and Maintenance of Anesthesia

Induction of anesthesia and tracheal intubation must minimize undesirable increases in systemic blood pressure that could exacerbate an aortic dissection or rupture an aneurysm. Use of a double-lumen endobronchial tube permits collapse of the left lung and facilitates surgical exposure during resection of a thoracic aneurysm.

General anesthesia can be maintained with volatile anesthetics and/or opioids. General anesthesia may cause some reduction in cerebral metabolic rate, which may be particularly desirable during this surgery. The choice of neuromuscular blocking drug may be influenced by the dependence of a particular drug on renal clearance.

Management of anesthesia for resection of an abdominal aortic aneurysm requires consideration of commonly associated medical conditions in this patient group: ischemic heart disease, hypertension, COPD, diabetes mellitus, and renal dysfunction. Monitoring intravascular volume and cardiac, pulmonary, and renal function is essential during the perioperative period. An intraarterial catheter monitors systemic blood pressure continuously. If appropriate personnel and equipment are available, echocardiography can be very useful for evaluating the cardiac response to aortic cross clamping and unclamping and assessing left ventricular filling volume and regional and global myocardial function. Urine output is monitored continuously.

No single anesthetic drug or technique is ideal for all patients undergoing elective abdominal aortic aneurysm repair. Combinations of volatile anesthetics and/or opioids are commonly used, with or without nitrous oxide. Continuous epidural anesthesia combined with general anesthesia may offer advantages by decreasing overall anesthetic drug requirements, attenuating the increased SVR associated with aortic cross clamping, and facilitating postoperative pain management. Nevertheless there is no evidence that the combination of epidural anesthesia and general anesthesia decreases postoperative cardiac or pulmonary morbidity compared with general anesthesia alone in high-risk patients who undergo aortic surgery. Postoperative epidural analgesia may favorably influence the postoperative course, however. Administration of anticoagulants during abdominal aortic surgery raises the controversial issue of placement of an epidural catheter and the remote risk of epidural hematoma formation.

Patients undergoing thoracoabdominal aortic aneurysm repair usually experience significant fluid and blood losses. Administration of a combination of balanced salt and colloid solutions (and blood if needed) guided by appropriate monitoring of cardiac and renal function facilitates maintenance of adequate intravascular volume, cardiac output, and urine formation. Balanced salt and/or colloid solutions should be infused during aortic cross clamping to build up an intravascular volume reserve and thereby minimize unclamping hypotension. If urinary output is decreased despite adequate fluid and blood replacement, diuretic therapy with mannitol or furosemide might be considered. The efficacy of low-dose dopamine in preserving renal function during abdominal aortic aneurysm surgery is unproven.

Infrarenal aortic cross clamping and unclamping are significant events during abdominal aortic surgery. The anticipated consequences of abdominal aortic cross clamping include increased SVR (afterload) and decreased venous return (see earlier discussion). Often, myocardial performance and circulatory parameters remain acceptable after the aorta is clamped at an infrarenal level. An alteration in anesthetic depth or infusion of vasodilators may be necessary in some patients to maintain myocardial performance at acceptable levels.

Hypotension may occur when the aortic cross clamp is removed. Prevention of unclamping hypotension and maintenance of a stable cardiac output can often be achieved by volume loading to pulmonary capillary occlusion pressures higher than normal before the cross clamp is removed. Likewise, gradual opening of the aortic cross clamp may minimize the decrease in systemic blood pressure by allowing some pooled venous blood to return to the central circulation. The washout of acid metabolites from ischemic areas below the cross clamp when the clamp is released plays a much less important role than central hypovolemia, and sodium bicarbonate pretreatment does not reliably blunt unclamping hypotension. If hypotension persists for more than a few minutes after removal of the cross clamp, the presence of unrecognized bleeding or inadequate volume replacement must be considered. Echocardiography at this time may be particularly helpful in determining the adequacy of volume replacement and cardiac function.

Postoperative Management

Posterolateral thoracotomy is among the most painful of surgical incisions; major muscles are transected, and ribs are removed. In addition, chest tube insertion sites can be very painful. Amelioration of pain is essential to ensure patient comfort and facilitate coughing and maneuvers designed to prevent atelectasis. Pain relief is commonly provided by neuraxial opioids and/or local anesthetics. Intrathecal or epidural catheters providing intermittent or continuous infusion of analgesic medications can be adapted to provide an element of patient-controlled analgesia as well. Inclusion of local anesthetic drugs in these solutions may produce sensory and motor anesthesia and delay recognition of anterior spinal artery syndrome. Moreover, when a neurologic deficit is recognized, the epidural drug may be implicated as the cause of the paraplegia. If neuraxial analgesia is used in the period immediately after surgery, opioids are preferred over local anesthetics to prevent masking of anterior spinal artery syndrome.

Patients recovering from thoracic aortic aneurysm resection are at risk of developing cardiac, pulmonary, and renal failure during the immediate postoperative period. In the majority of clinical series, postoperative pulmonary complications are the most common, representing 25% to 45% of cases. Cerebrovascular accidents may result from air or thrombotic emboli that occur during surgical resection of the diseased aorta. Patients with coexisting cerebrovascular disease may be more vulnerable to development of new central nervous system complications. Spinal cord injury may manifest during the period immediately after surgery as paraparesis or flaccid paralysis. Delayed appearance of paraplegia (12 hours to 21 days postoperatively) has been associated with postoperative hypotension in patients with severe atherosclerotic disease in whom marginally adequate collateral circulation to the spinal cord is present.

Systemic hypertension is not uncommon and may jeopardize the integrity of the surgical repair and/or predispose to myocardial ischemia. The role of pain in the development of hypertension must be considered.

Patients recovering from abdominal aortic aneurysm repair are also at risk of developing cardiac, pulmonary, and renal dysfunction during the postoperative period. Assessment of graft patency and lower extremity blood flow is primary. Adequate pain control accomplished with either neuraxial opioids or patient-controlled analgesia is important in facilitating early tracheal extubation.

ENDOVASCULAR AORTIC ANEURYSM REPAIR

Recently, the management of aortic aneurysms has evolved with a propensity toward endovascular approaches in part based on patient preference. Only a few years back, the endovascular approach of placement of intraluminal stent grafts to treat patients with aneurysms of the descending thoracic and abdominal aorta was mainly reserved for the elderly and those with coexisting medical conditions such as hypertension, COPD, and renal insufficiency that would significantly increase the risks associated with conventional operative treatment. These devices have been approved for aneurysms above 5.5 cm as well as complicated type B dissections. Endovascular devices appear to improve initial hospital morbidity and mortality, although there is a higher risk for later complications and need for reinterventions. At 5-year follow-up the mortality advantage is less evident. Endovascular treatment of aortic aneurysms is achieved by transluminal placement of one or more stent graft devices across the longitudinal extent of the lesion. The prosthesis bridges the aneurysmal sac to exclude it from high-pressure aortic blood flow, thereby allowing for sac thrombosis around the stent and possible remodeling of the aortic wall. Endovascular repair offers the benefit of aneurysm exclusion without causing the significant physiologic changes that occur during cross clamping.

Currently, endovascular aneurysm repair of the intrathoracic aorta has been focused on the descending thoracic aorta (i.e., the portion distal to the left subclavian artery). Endovascular repair of the thoracic aorta poses several unique challenges compared with endovascular repair of the abdominal aorta. First, the hemodynamic forces are significantly more severe and place greater mechanical demands on thoracic endografts. The potential for device migration, kinking, and late structural failure is an important concern. Second, greater flexibility is required of thoracic devices to conform to the natural curvature of the proximal descending aorta and to lesions with tortuous morphology. Third, because larger devices are necessary to accommodate the diameter of the thoracic aorta, arterial access is more problematic. Fourth, as with conventional open thoracic aneurysm repair, paraplegia remains a potential complication of the endovascular approach, despite the absence of aortic cross clamping. Fifth, visceral and renal ischemia still can occur if the graft occludes the celiac axis.

Over the past decade, many endovascular devices to repair abdominal aortic aneurysms have been developed (Fig. 12.7; also see Fig. 12.2). Endovascular repair involves gaining access to the lumen of the abdominal aorta, usually via small incisions over the femoral vessels. Although each device has unique features, all use the same basic structural design and are composed of a metal stent covered with fabric. There are two types of devices: unibody and modular. The unibody type comes in one piece and is easier to deploy but requires contralateral occlusion and bypass grafting. Modular devices are composed of more than one piece, and the components are deployed through both groin areas. The great variability in patient anatomy makes it difficult to find a single graft that will be adequate to cover an aneurysm; thus most surgeons use multipart grafts that interlock and provide a better fit.

The literature on thoracic stent grafting consists mostly of reports of small to medium-sized case series with short- to medium-term follow-up. All these studies show a common pattern of outcomes. Overall, successful device deployment is achieved in 85% to 100% of cases, and perioperative mortality ranges from 0% to 14%, falling within or below elective surgery mortality rates of 5% to 20%. Outcomes have improved over time with accumulated technical expertise, technologic advances in the devices, and improved patient selection criteria. Current reported experience with thoracic stent grafting demonstrates successful deployment in 87% of cases, 30-day mortality of 1.9% to 2.1% in elective cases, and paraplegia and endoleak rates of 4% to 9%. Survival at 1, 5, and 8 years is 82%, 49%, and 27%, respectively. Therefore mortality at 3 or 4 years is nearly identical in patients receiving stent grafts and in those undergoing open aneurysm repair. Other authors describe an approximately 98% rate of freedom from aneurysm rupture at 9 years in a cohort of 817 patients undergoing stenting, but a high rate of death (47% survival at 8 years) from comorbid medical diseases, especially cardiovascular events, even though patients were evaluated preoperatively with stress testing, and revascularization was performed if needed. There are no randomized studies comparing endovascular repair with the open procedure. Nevertheless, the overall trend is that endovascular procedures are associated with lower perioperative mortality, and the endovascular approach offers patients shorter hospital stay, quicker rehabilitation, and longer average number of months lived resulting from the decrease in preoperative mortality. Even if the results of the open procedure are

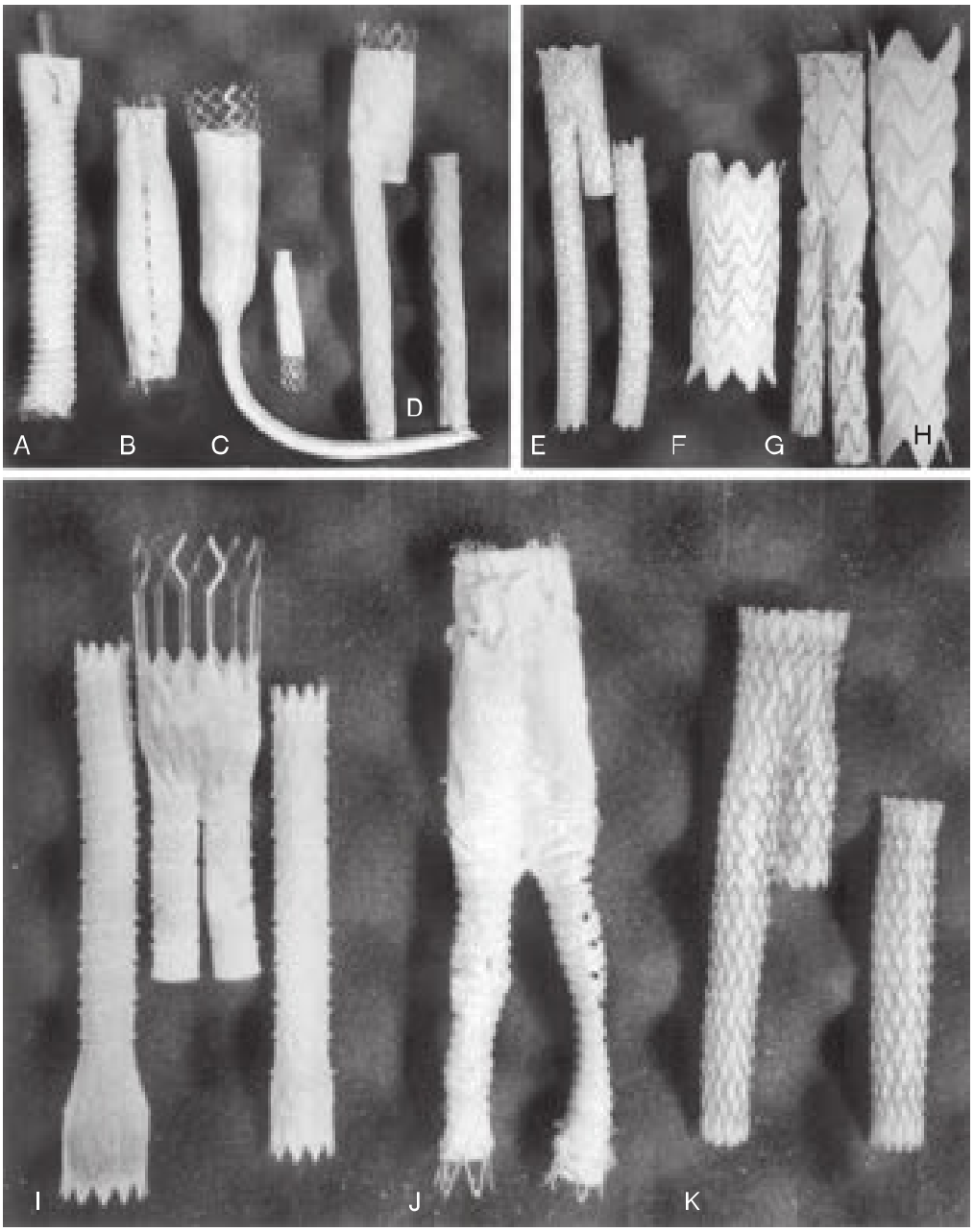

Fig. 12.7 Endovascular stent graft devices. A, Parodi graft. B, Endovascular Technologies endograft. C, Investigator endoscopic stent graft. D, Boston Scientific Vanguard stent graft. E, W.L. Gore excluder stent graft. F, W.L. Gore thoracic stent graft. G, Medtronic/World Medical Talent abdominal aortic stent graft. H, Medtronic/World Medical Talent thoracic aortic stent graft. I, Teramed/Cordis abdominal aortic stent graft. J, Guidant Ancure stent graft. K, Medtronic AneuRx stent graft. (From Marin ML, Hollier LH, Ellozy SH, et al. Endovascular stent graft repair of abdominal and thoracic aortic aneurysms: a ten-year experience with 817 patients. *Ann Surg.* 2003;238:586–595.)

more durable, it is associated with major postoperative complications. Therefore with the development of new types of grafts, the endovascular approach will most probably become the primary method of aortic aneurysmal repair when anatomic conditions are optimal.

Complications

Complications associated with endografts include endoleaks, vascular injury during graft deployment, inadequate fixation and sealing of the graft to the wall (i.e., risk of graft migration), stent frame fractures, and breakdown of graft material. After the graft has been deployed, the aneurysm eventually will thrombose and decrease in diameter.

Device migration is one of the most common causes of a need for secondary intervention because if such migration is left unmanaged, it may lead to endoleaks, aneurysm expansion, and rupture.

Reinterventions are part of late complications and, although minor, are more common after endovascular repair (9% of cases) than after open repair (1.7%); however, repeat laparotomy and

hospitalizations are more common after open surgical repair (9.7% vs 4.1%). Most practitioners do not consider the requirement for a secondary intervention to represent a failure. Nevertheless, patients must be aware that they will require lifelong surveillance.

Although endovascular repair does not require a period of aortic clamping, the possibility of spinal cord ischemia still exists because of exclusion of important intercostal arteries. There is no role for epidural cooling, but spinal drainage may offer some benefits in individuals at high risk. These may include patients with prior aortic repair (usually infrarenal), those with aortic dissections, and those with stable aortic ruptures. In patients in unstable condition the drain may be placed postoperatively.

Consideration of the risk of intraabdominal ischemia is an important aspect, especially when the celiac artery is occluded by the graft. Under development are bifurcated grafts that will be used in the near future to achieve aneurysm exclusion with preservation of flow to important vessels (e.g., celiac and renal arteries) when aneurysms involve their origins.

Anesthetic Management

General or regional anesthesia is acceptable for endovascular aneurysm repair. Monitoring consists of, at a minimum, intravascular blood pressure and urine output monitoring. The potential need for conversion to an open aneurysm repair must always be kept in mind. Large-bore intravenous access and availability of blood are still important concerns. Spinal drain placement is a consideration for thoracic aneurysm repair after discussion with the surgeon. Maintenance of euvolemia and normotension is important.

Administration of heparin and verification of activated clotting time are still mainstays, as in any other vascular procedure.

Postoperative Management

Postoperative management depends on numerous physiologic and procedural variables. Commonly, patients undergoing higher thoracic aortic repair will be cared for in an intensive care unit until all perioperative concerns have been resolved, including the possibility of ischemia, acidosis, ongoing respiratory failure, and cardiac problems. Patients undergoing lower abdominal aortic repair still must be followed closely, with particular attention to the development or worsening of renal dysfunction, even if transitory due to intravenous dye administration.

REBOA (RESUSCITATIVE ENDOVASCULAR BALLOON OCCLUSION OF THE AORTA)

The REBOA tool is controversial due to continued efforts to better select patients as well as in deciding the ideal timing of inflation. It is mainly used to expand options for a dying patient. In certain circumstances, such as acute exsanguinating trauma with noncompressible hemorrhage, the options are limited to REBOA, aortic occlusion through thoracotomy, or continued chest compression. These options are made more difficult if the patient is far away from a hospital setting, such as in a helicopter or military theater. The studies are contradictory at best, with some strong supporters with good results, especially from the military, while others emphasize complications. These include blood vessel or balloon rupture, and difficulty of insertion that is somewhat mitigated by using lower-diameter sheaths (7 Fr). Ischemia due to prolonged inflation may be somewhat corrected by development of partial REBOA; the latter is avoiding complete and prolonged vessel occlusion by keeping a slight deflation of the balloon or considering an intermittent occlusion. Other possible complications include accessing the wrong vascular tree, retroperitoneal hematoma, arterial dissection, and organ and limb ischemia with increased lactic acidosis. However, we must analyze the benefits, such as being a less invasive tool that would permit earlier control of profound hemorrhage, while decreasing the need for blood products, brain injury, and possibly prolonging life at the brink of cardiovascular collapse.

CAROTID ARTERY DISEASE AND STROKE

Cerebrovascular accidents (strokes) are characterized by sudden neurologic deficits resulting from ischemic or hemorrhagic events. Carotid artery disease is an important contributor to stroke risk. Anesthesiologists frequently manage anesthesia in patients with carotid disease, both for carotid surgery and for other surgical procedures.

Epidemiology and Risk Factors

Approximately 3% of US adults have experienced a stroke. It is the leading cause of disability and the third leading cause of death in this country. Strokes are classified as either ischemic (most commonly thrombotic or embolic in origin) or hemorrhagic (secondary to vascular malformation, trauma, or coagulopathy). Approximately 87% of all strokes are ischemic. TIAs are a subset of self-limited ischemic strokes and present as a sudden focal neurologic deficit that resolves within 24 hours. TIAs often herald an impending ischemic stroke, and individuals experiencing TIAs have a 10 times greater risk of subsequent stroke than age- and sex-matched populations.

Neurologic deficits following intracranial arterial occlusion are often extensive, reflecting the large areas of brain supplied by the major arteries and their branches. Six months after an ischemic stroke, fully one-quarter of survivors older than age 65 will be institutionalized.

Major risk factors for stroke are listed in Table 12.2. Although anesthesiologists may play a role in educating patients with modifiable health risk factors such as smoking or hypertension, the anesthetic management of patients who have already developed cerebrovascular disorders, including advanced carotid disease, is a common challenge for the specialty.

Cerebrovascular Anatomy

Blood supply to the brain (20% of cardiac output) is brought through the neck via two pairs of blood vessels: the internal carotid arteries and the vertebral arteries, which join into the basilar artery (Fig. 12.8). These vessels join in the circle of

TABLE 12.2 Factors Predisposing to Stroke

Inherited Risk Factors
Age
Prior history of stroke
Family history of stroke
Black race
Male gender
Sickle cell disease

Modifiable Risk Factors
Elevated blood pressure
Smoking
Diabetes
Carotic artery disease
Atrial fibrillation
Heart failure
Hypercholesterolemia
Obesity or physical inactivity

Willis to form major intracranial blood vessels (anterior cerebral arteries, middle cerebral arteries, posterior cerebral arteries). Occlusion of a specific major intracranial artery results in a constellation of predictable clinical neurologic deficits.

The major branches of the vertebral arteries are the arteries to the spinal cord and the posteroinferior cerebellar arteries that supply the inferior cerebellum and lateral medulla. Occlusion of the vertebral arteries or basilar artery results in signs and symptoms that depend on the level of the infarction. The basilar artery terminates by dividing into two posterior cerebral arteries that supply the medial temporal lobe, occipital lobe, and parts of the thalamus.

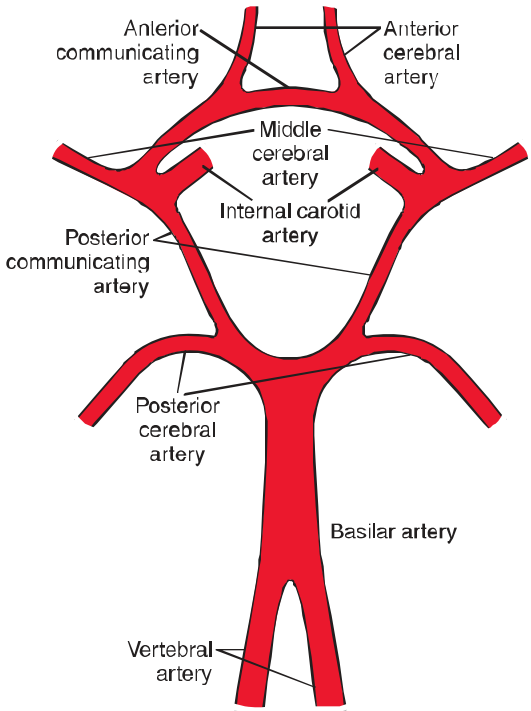

Fig. 12.8 Cerebral circulation and the circle of Willis. Cerebral blood supply comes from the vertebral arteries (arising from the subclavian arteries) and the internal carotid arteries (arising from the common carotid arteries).

Diagnostic Tests

Conventional angiography can demonstrate acute vascular occlusion from a thrombus or embolus lodged in the vascular tree. The vasculature can also be visualized noninvasively by CT angiography and magnetic resonance angiography. In addition to identifying ischemic stroke, these modalities can also identify aneurysms or arteriovenous malformations that may be precipitants for hemorrhagic stroke. Transcranial Doppler ultrasonography can provide indirect evidence of major vascular occlusion and offers the advantage of real-time bedside monitoring in patients undergoing thrombolytic therapy.

In the evaluation of ischemic stroke or TIA, auscultation of the carotid arteries may identify a bruit. Carotid ultrasonography can quantify carotid stenosis and may rarely identify a dissection. Carotid stenosis most commonly occurs at the bifurcation of the internal and external carotid arteries because of the tendency for turbulent flow at this branch point. Even in the presence of known carotid stenosis, workup of an intracranial embolic event includes evaluation for cardiac sources of emboli such as intraluminal thrombi (secondary to heart failure or atrial fibrillation), valvular vegetations, or paradoxical emboli in the setting of a patent foramen ovale.

Treatment of Stroke

The US Food and Drug Administration (FDA) has approved intravenous administration of recombinant tissue plasminogen activator (tPA) within 3 hours of stroke onset once the diagnosis of ischemic stroke is established and in the absence of contraindications. The American Heart Association has subsequently expanded that recommended window to 4.5 hours. In qualifying patients, the number needed to treat with recombinant tPA for one additional favorable outcome is approximately 10. Some stroke centers with access to interventional neuroradiology may offer intraarterial thrombolysis or endovascular clot removal, particularly in cases of persistent thrombus. Recent clinical trials have brought about a paradigm shift in managing strokes secondary to large vessel occlusion with endovascular evacuation of clot, showing benefit up to 8.5 hours after the initial event. Advances made with these suction systems have improved recanalization with acceptable rates of symptomatic intracerebral hemorrhage.

Regardless of thrombolytic efforts, the importance of avoiding hypoxia is paramount, as are the control of glycemic derangements, hyperthermia, hypotension, severe hypertension, and unstable dysrhythmias. Specific hemodynamic goals for patients with acute stroke undergoing thrombolysis or neuroradiologic procedures depend on a variety of patient-specific factors, but the overarching need to preserve or restore perfusion of at-risk brain tissue is universal. Outside the acute setting, medical management of strokes in general overlaps with the medical management of carotid stenosis discussed in the next section.

Carotid Endarterectomy

Surgical treatment of symptomatic carotid artery stenosis greatly decreases the risk of stroke compared with medical

management in men with severe carotid stenosis (70–99% luminal stenosis) and modestly reduces stroke risk in those with 50% to 69% luminal narrowing. Strokes and TIAs caused by carotid stenosis occur as a result of atheroembolic phenomena or hemodynamically significant pressure drops across the stenosis in the absence of sufficient collateral cerebral blood flow.

The advisability of surgical treatment for asymptomatic carotid disease varies based on the expected periprocedural risk and associated patient comorbid conditions. The absolute risk reduction in stroke is small (~1% per year for the first few years) but is higher with longer-term follow-up. A suggested guideline has been to recommend surgery for asymptomatic carotid disease only for patients and at centers for which the expected periprocedural complication rates are 3% or less. In patients forgoing surgical treatment, optimal medical therapy includes smoking cessation, antiplatelet therapy, aggressive blood pressure control, physical activity, and both dietary and pharmacologic lipid-lowering strategies. Hypoglycemic medications for diabetic patients, as well as ACE inhibitors, are beneficial. The current recommendations for surgical intervention are within a short period of time after significant events such as transient ischemic attacks or stroke, namely within 48 hours vs 7 days.

Preoperative Evaluation

In addition to undergoing a neurologic evaluation, patients scheduled for carotid endarterectomy should be examined for significant comorbid conditions, particularly cardiovascular disease. Perioperative MI is a major cause of morbidity and mortality following carotid endarterectomy, and predisposing coronary artery disease (CAD) is highly prevalent among patients with cerebrovascular occlusive disease. The reported incidence of perioperative MI in this population depends on the threshold and method of surveillance but was 2.3% among symptomatic patients who underwent endarterectomy in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). A follow-up trial, CREST-2, is underway to compare the outcomes in patients with asymptomatic carotid stenosis.

Chronic essential hypertension is a common finding in patients with cerebrovascular disease. It is useful to establish the usual range of blood pressure for each patient preoperatively to provide a guide for acceptable perfusion pressures during anesthesia and surgery. Intraoperative stability of chronically elevated blood pressure may be critical for maintenance of collateral blood flow through the stenotic cranial vasculature, especially during cross clamping of the carotid artery. The effect of a change in head position on cerebral function should also be ascertained. Extreme head rotation, flexion, or extension in patients with coexisting vertebral or carotid artery disease could lead to angulation or compression of the artery. Recognition of this response preoperatively allows hazardous head positions to be avoided while patients are anesthetized.

Patients with known severe CAD and severe carotid occlusive disease present a clinical dilemma. A staged surgical approach in which carotid endarterectomy is performed first could result in significant morbidity or mortality from cardiac causes. On the other hand, performing coronary revascularization first is associated with a high incidence of stroke. Insufficient evidence exists to make general guidelines, and the timing of surgical procedures should instead be individualized based on the severity and symptomatic profile of each patient.

Management of Anesthesia

Anesthetic management for carotid endarterectomy mandates careful control of heart rate, blood pressure, pain, and stress responses so organ perfusion is maintained in patients with a high preoperative risk of cardiac and cerebral ischemic events. At the conclusion of surgery, the goal should be to awaken the patient sufficiently for a neurologic examination.

Carotid endarterectomy can be performed under regional or general anesthesia. Regional anesthesia via cervical plexus blockade allows a patient to remain awake to facilitate neurologic assessment during carotid artery cross clamping. During establishment of the block, care should be taken to avoid vascular puncture that would obscure the surgical field or could dislodge microemboli. Appropriate sedation during surgical preparation and draping allows many otherwise anxious patients to tolerate the procedure quite well when a regional anesthetic technique under regional blockade is used. If general anesthesia is selected, the focus should be on maintenance of hemodynamic stability and prompt emergence to allow immediate assessment of neurologic status in the operating room.

Appropriate blood pressure management is important during carotid endarterectomy and is made more crucial because of the abnormal cerebral autoregulation present in many of these patients. Elevated blood pressure during cross clamping may facilitate collateral blood flow but after surgery may predispose to hematoma formation. Vasopressors or vasodilators are often needed to maintain an appropriate perfusion pressure during the various stages of the procedure. Surgical manipulation of the carotid sinus may cause marked alterations in heart rate and blood pressure. Carotid sinus infiltration with local anesthetic for controlling blood pressure lability has been anecdotal and yet to be proven effective.

It is generally accepted that changes in regional cerebral blood flow associated with changes in $Paco_2$ are unpredictable in these patients. Therefore maintenance of normocarbia is generally recommended.

Monitoring usually includes placement of an intraarterial catheter. As with any major vascular surgery, patients with poor left ventricular function and/or severe CAD might require a central venous or pulmonary artery catheter or TEE, but this is rarely necessary. The hemodynamic goals for cerebral and coronary perfusion are similar, and achievement of these goals will benefit both organ systems. If central venous cannulation is pursued, particular care must be taken during contralateral jugular venous access attempts to prevent inadvertent arterial or venous puncture, which could cause a hematoma that compromises collateral blood flow during carotid cross clamping.

When carotid endarterectomy is performed under general anesthesia, monitoring for cerebral ischemia, hypoperfusion, and cerebral emboli should be strongly considered. The principal reason to monitor cerebral function is to identify patients who would benefit from use of a carotid artery shunt during carotid cross clamping; another is to guide hemodynamic management

in patients who require increased cerebral perfusion pressure. The standard EEG is a sensitive indicator of inadequate cerebral perfusion during carotid cross clamping. Perioperative neurologic complications correlate with intraoperative EEG changes indicating cerebral ischemia. However, the utility of EEG monitoring during carotid endarterectomy is limited by several factors: (1) EEG may not detect subcortical or small cortical infarcts, (2) false-negative results are not uncommon (patients with previous strokes or TIAs have a high incidence of false-negative test results), and (3) the EEG can be affected not only by cerebral ischemia but also by changes in temperature, blood pressure, and depth of anesthesia. SEP monitoring can detect specific changes produced by decreased regional cerebral blood flow, but it can be difficult to determine whether these changes are due to anesthesia, hypothermia, changes in blood pressure, or cerebral ischemia. Stump pressure (internal carotid artery back pressure) is a poor indicator of the adequacy of cerebral perfusion. Transcranial Doppler ultrasonography allows continuous monitoring of blood flow velocity and the occurrence of microembolic events. It can be used to determine the need for shunt placement, to recognize shunt malfunction, and to manage postoperative hyperperfusion.

In situations in which general anesthesia is chosen and cerebral perfusion monitoring is unavailable, an alternative approach is to insert shunts in all patients, but placement of the shunt can itself predispose to an increased embolic load. Overall, awake neurologic assessment is the simplest, most cost-effective, and most reliable method of cerebral function monitoring during carotid endarterectomy.

Postoperative Management and Complications

In the period immediately after carotid endarterectomy, patients must be observed for cardiac, airway, and neurologic complications. These include hypertension or hypotension, myocardial ischemia or infarction, development of significant soft tissue edema or a hematoma in the neck, and the onset of neurologic signs and symptoms that signal a new stroke or acute thrombosis at the endarterectomy site.

Hypertension is frequently observed during the immediate postoperative period, often in patients with coexisting essential hypertension. The increase in blood pressure often peaks at 2 to 3 hours after surgery and may persist for 24 hours. Hypertension should be treated to avoid the hazards of cerebral edema, myocardial ischemia, and hematoma formation. The incidence of new neurologic deficits is increased threefold in patients who are hypertensive postoperatively. Continuous infusion of short-acting drugs such as nitroprusside, nitroglycerin, or clevidipine and the use of longer-acting drugs such as hydralazine or labetalol are options for blood pressure control. The mechanism of this postoperative hypertension may be related to altered activity of the carotid sinus or loss of carotid sinus function resulting from denervation during surgery.

Hypotension is also commonly observed during the period immediately after surgery. This hypotension can be explained based on carotid sinus hypersensitivity. The carotid sinus, previously shielded by atheromatous plaque, is now able to perceive blood pressure oscillations more clearly and goes through a period of hyperresponsiveness to these stimuli. Hypotension resulting from carotid sinus hypersensitivity is usually treated with vasopressors such as phenylephrine. It typically resolves within 12 to 24 hours.

Nerve dysfunction is possible after carotid endarterectomy, but most injuries are transient. Patients should be examined for evidence of hypoglossal, recurrent laryngeal, or superior laryngeal nerve injury. Such injury may produce difficulty swallowing or protecting the airway and could result in aspiration.

Carotid body denervation can also occur after carotid artery surgery and impair cardiac and ventilatory responses to hypoxemia. This can be clinically significant after bilateral carotid endarterectomy or with administration of narcotics.

Endovascular Treatment of Carotid Disease

The technique of carotid artery stenting continues to evolve as an alternative to carotid endarterectomy. The major complication of carotid stenting is stroke as a result of microembolization of atherosclerotic material into the cerebral circulation during the procedure. Embolic protection devices for use during carotid stenting have been developed, but the technology has so far failed to reduce endovascular stroke risk to that seen with the surgical approach. Nevertheless, endovascular approaches carry a lower risk of MI, and if embolic protection devices are improved, stenting may one day reemerge as a more widespread alternative to surgery.

Data comparing surgical and endovascular approaches come from several studies. The CREST results demonstrated an increased risk of stroke and decreased risk of MI in endovascular treatment compared with endarterectomy, but the investigators also found that periprocedural stroke was more devastating to quality of life than MI. The Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE) trial also showed increased rates of ischemic stroke or death within 30 days after an endovascular repair compared with a surgical procedure. As a result of this evidence, surgical endarterectomy for symptomatic carotid stenosis remains the recommended treatment for most patients. A new technique that appears to have similar incidence of strokes as the open endarterectomy, transcarotid artery revascularization (TCAR), shows promising results, although further data are needed before making a final determination.

PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease results in compromised blood flow to the extremities. Chronic impairment of blood flow to the extremities is most often due to atherosclerosis, whereas arterial embolism is most likely to be responsible for acute arterial occlusion (Table 12.3). Vasculitis may also be responsible for compromised peripheral blood flow.

Chronic Arterial Insufficiency

The most widely accepted definition of peripheral arterial insufficiency is an ankle-brachial index (ABI) less than 0.9. The ABI is calculated as the ratio of the systolic blood pressure at the ankle to the systolic blood pressure in the brachial artery.

TABLE 12.3 Peripheral Vascular Diseases

- Chronic peripheral arterial occlusive disease (atherosclerosis)
  - Distal abdominal aorta or iliac arteries
  - Femoral arteries
  - Subclavian steal syndrome
  - Coronary-subclavian steal syndrome
- Acute peripheral arterial occlusive disease (embolism)
- Systemic vasculitis
  - Takayasu arteritis
  - Thromboangiitis obliterans
  - Wegener granulomatosis
  - Temporal arteritis
  - Polyarteritis nodosa
- Other vascular syndromes
  - Raynaud phenomenon
  - Kawasaki disease

An ABI below 0.9 correlates extremely well with angiogram-positive disease.

The characteristics of peripheral atherosclerosis resemble those of atherosclerosis seen in the aorta, coronary arteries, and extracranial cerebral arteries. The prevalence of peripheral atherosclerosis increases with age, exceeding 70% in individuals older than age 75. Peripheral arterial disease has been estimated to reduce quality of life in approximately 2 million symptomatic Americans, and millions more without claudication are likely to experience peripheral arterial disease–associated impairment. Among patients who have claudication, 80% have femoropopliteal stenosis, 40% have tibioperoneal stenosis, and 30% have lesions in the aorta or iliac arteries.

Atherosclerosis is a systemic disease. Consequently, patients with peripheral arterial disease have a three to five times overall greater risk of cardiovascular ischemic events such as MI, ischemic stroke, and death than do those without this disease. Critical limb ischemia is associated with very high intermediate-term morbidity and mortality, due mostly to a high incidence of cardiovascular events in these patients. Associated cardiovascular ischemic events are much more frequent than actual ischemic limb events.

Risk Factors

Risk factors associated with development of peripheral atherosclerosis are similar to those related to ischemic heart disease: older age, family history, smoking, diabetes mellitus, hypertension, obesity, and dyslipidemia. The risk of significant peripheral arterial disease and claudication is doubled in smokers compared with nonsmokers, and continued cigarette smoking increases the risk of progression from stable claudication to severe limb ischemia and amputation.

Signs and Symptoms

Intermittent claudication and rest pain are the principal symptoms of peripheral arterial disease. Intermittent claudication occurs when the metabolic requirements of exercising skeletal muscles exceed oxygen delivery. Rest pain occurs when the arterial blood supply does not meet even the minimal nutritional requirements of the affected extremity. Even minor trauma to an ischemic foot may produce a nonhealing skin lesion.

Decreased or absent arterial pulses are the most reliable physical findings associated with peripheral arterial disease. Bruits auscultated in the abdomen, pelvis, or inguinal area and decreased femoral, popliteal, posterior tibial, or dorsalis pedis pulses may indicate the anatomic site of arterial stenosis. Less commonly, reduced lower extremity pulses may be the presenting sign of undiagnosed aortic coarctation. Signs of chronic leg ischemia include subcutaneous atrophy, hair loss, coolness, pallor, cyanosis, and dependent redness. Patients may report relief with hanging the affected extremity over the edge of the bed, a move that increases hydrostatic pressure in the arterioles of the affected limb.

Diagnosis

Doppler ultrasonography and the resulting pulse volume waveform are used to identify arterial vessels with stenotic lesions. In the presence of severe ischemia, the arterial waveform may be entirely absent. The ABI is a quantitative means of assessing the presence and severity of peripheral arterial stenosis. Duplex ultrasonography can identify areas of plaque formation and calcification as well as blood flow abnormalities caused by arterial stenoses. Transcutaneous oximetry can be used to assess the severity of skin ischemia in patients with peripheral arterial disease. Results of noninvasive tests and clinical evaluation are usually sufficient for the diagnosis of peripheral arterial disease. MRI and contrast angiography are used to guide endovascular intervention or surgical bypass.

Treatment

Medical therapy for peripheral arterial disease includes exercise programs and treatment or modification of risk factors for atherosclerosis. Supervised exercise training programs can improve the walking capacity of patients with peripheral arterial disease even though no change in ABI can be demonstrated. Patients who stop smoking have a more favorable prognosis than those who continue to smoke. Aggressive lipid-lowering therapy slows the progression of peripheral atherosclerosis, and treatment of diabetes mellitus can slow microvascular disease progression.

Treatment of hypertension results in a reduction in stroke and cardiovascular morbidity. Although β-adrenergic antagonists are a mainstay for patients who have experienced MI, their use solely as an antihypertensive agent has fallen out of favor. In sum, patients with severe arterial insufficiency benefit from effective blood pressure control because cardiovascular and stroke risk are reduced, but the presence of peripheral arterial insufficiency does not in itself govern the choice of an antihypertensive agent.

Revascularization procedures are indicated in patients with disabling claudication, ischemic rest pain, or impending limb loss. The prognosis of the limb is determined by the extent of arterial disease, the severity of limb ischemia, and the feasibility and rapidity of restoring arterial circulation. In patients with chronic arterial occlusive disease and continuous progression of symptoms (i.e., development of new wounds, rest pain, or

gangrene) the prognosis is very poor unless revascularization can be accomplished. In patients who experience acute occlusive events resulting from arterial embolism in an extremity with little underlying arterial disease, the long-term prognosis of the limb is related to the rapidity and completeness of revascularization before the onset of irreversible ischemic tissue or nerve damage.

Revascularization can be achieved by endovascular interventions or surgical reconstruction. Percutaneous transluminal angioplasty of iliac arteries has a high initial success rate that is further improved by selective stent placement. Femoral and popliteal artery percutaneous transluminal angioplasty have lower success rates; however, stent placement has improved superficial femoral artery patency substantially.

Despite improvement in long-term outcome after percutaneous transluminal angioplasty and stenting of peripheral vessels, restenosis remains a significant problem, particularly in long lesions, small-diameter vessels, and recurrently stenotic lesions. Current therapies focus on the use of mechanical devices, stents, stent grafts, vascular irradiation, and drugs, although none of these approaches has yet become a definitive treatment.

The operative procedures used for vascular reconstruction depend on the location and severity of the peripheral arterial stenosis. Aortobifemoral bypass is a surgical procedure used to treat aortoiliac disease. Intraabdominal aortoiliac reconstructive surgery may not be feasible in patients with severe comorbid conditions. However, in these patients, axillobifemoral bypass can circumvent the abdominal aorta and achieve revascularization of both legs. Femorofemoral bypass can be performed in patients with unilateral iliac artery obstruction. Infrainguinal bypass procedures using saphenous vein grafts or synthetic grafts include femoropopliteal and tibioperoneal reconstruction. Amputation is frequently necessary for patients with advanced limb ischemia in whom revascularization is not possible or has failed. Lumbar sympathectomy is occasionally used to treat critical limb ischemia in cases of persistent vasospasm.

Management of Anesthesia

Management of anesthesia for surgical revascularization of the lower extremities incorporates principles similar to those described earlier for management of patients undergoing abdominal aortic aneurysm repair. For example, the principal risk during reconstructive peripheral vascular surgery is myocardial ischemia. The increased incidence of perioperative MI and cardiac death in patients with peripheral arterial disease is due to the high prevalence of CAD. Mortality following revascularization surgery is usually a result of MI in patients with preoperative evidence of ischemic heart disease.

Because patients with claudication are usually unable to perform an exercise stress test, pharmacologic stress testing with or without echocardiography or nuclear imaging is helpful to determine the presence and severity of ischemic heart disease preoperatively in patients with multiple cardiac risk factors. Depending on the severity of CAD and claudication, treatment of the ischemic heart disease by percutaneous coronary intervention or coronary artery bypass grafting may be considered before revascularization surgery is performed. In American College of Cardiology/American Heart Association (ACC/AHA) guidelines, unstable angina is considered an active cardiac condition requiring treatment or optimization before nonemergent surgery. However, in patients with anatomically significant but stable CAD, vascular surgery can proceed, and mortality and morbidity outcomes are similar to patients who undergo coronary artery revascularization before elective vascular surgery.

Perioperative heart rate control (usually with carefully titrated β blockers) in vascular surgery patients at high risk reduces the incidence of myocardial ischemia. The ACC/AHA guidelines on perioperative β-blocker therapy recommend β blockade for patients at intermediate and high risk who are undergoing vascular surgery. For patients with low cardiac risk who are undergoing vascular surgery, β blockers may still be considered. Both acute withdrawal of β blockers and initiation of high-dose β-blocker therapy on the day of surgery are associated with increased mortality. Perioperative initiation of statins is also reasonable in patients undergoing vascular surgery.

The choice of anesthetic technique must be individualized for each patient. Regional anesthesia and general anesthesia each offer specific advantages and disadvantages. Patient preference for general anesthesia, patient factors such as obesity or previous spine surgery, and use of antiplatelet or anticoagulant drugs may increase the risks associated with use of a regional technique. Regional anesthesia may also be poorly tolerated in patients with severe dementia but may reduce the risk of postoperative delirium compared with general anesthesia. Epidural or spinal anesthesia offers the advantages of increased graft blood flow, postoperative analgesia, less activation of the coagulation system, and fewer postoperative respiratory complications. Intraoperative heparinization is not in itself a contraindication to epidural anesthesia, but risk of bleeding may increase when the patient is also taking other anticoagulants or antiplatelet agents. If epidural catheter placement is attempted, it should occur at least 1 hour before intraoperative heparinization. In addition, before placement of the catheter is attempted, the surgical team should be consulted regarding the possible need to delay the procedure in the event of a bloody tap.

General anesthesia may be necessary when procedures are expected to require long operative hours or when vein harvesting from the upper extremities is needed. There is no strong evidence to suggest an advantage of one particular type of general anesthetic agent over another. The possible benefits of using inhalation anesthetics in patients with high cardiac risk resulting from the cardiac preconditioning effects of these agents are the subject of ongoing investigations.

During aortoiliac or aortofemoral surgery, infrarenal aortic cross clamping is associated with fewer hemodynamic derangements than higher aortic cross clamping. Likewise the hemodynamic changes associated with unclamping the abdominal aorta are less with infrarenal aortic cross clamping. Because of the comparatively benign effects of infrarenal clamping, many practitioners place a central venous pressure catheter in lieu of a pulmonary artery catheter in these patients, especially in the

absence of symptomatic left ventricular dysfunction. Monitoring of left ventricular function and intravascular volume may also be facilitated by the use of TEE.

Heparin is commonly administered before application of a vascular cross clamp to decrease the risk of thromboembolic complications. However, distal embolization may still occur to any downstream vascular bed, including to the bowel or kidneys. Administration of heparin does not obviate the importance of surgical care when manipulating and clamping an atherosclerotic artery to minimize the likelihood of distal embolization. Spinal cord damage associated with surgical revascularization of the legs is extremely unlikely, and special monitoring for this complication is not generally pursued.

Postoperative Management

Postoperative management includes provision of analgesia, treatment of fluid and electrolyte derangements, and maintenance of oxygenation, ventilation, heart rate, and blood pressure to reduce the incidence of myocardial ischemia or infarction. As with the choice of intraoperative anesthetics, there is no strong evidence to recommend a particular postoperative medication regimen so long as the goal of patient stability and comfort is achieved.

Subclavian Steal Syndrome

Occlusion of the subclavian or innominate artery proximal to the origin of the vertebral artery may result in reversal of flow through the ipsilateral vertebral artery into the distal subclavian artery (Fig. 12.9). This reversal of flow diverts blood from the brain to supply the arm (subclavian steal syndrome). Symptoms of central nervous system ischemia (syncope, vertigo, ataxia, hemiplegia) and/or arm ischemia are usually present. Extreme neck movements or exercise of the ipsilateral arm may accentuate these hemodynamic changes and cause neurologic symptoms. There is often an absent or diminished pulse in the ipsilateral arm, and systolic blood pressure is often found to be 20 mm Hg lower in that arm. A bruit may be heard over the subclavian artery. Stenosis of the left subclavian artery is responsible for this syndrome in most patients. Subclavian endarterectomy may be curative.

Coronary-Subclavian Steal Syndrome

A rare complication of using the left internal mammary artery for coronary revascularization is coronary-subclavian steal syndrome. This syndrome occurs when proximal stenosis in the left subclavian artery produces reversal of blood flow through the patent internal mammary artery graft (Fig. 12.10). This steal syndrome is characterized by angina pectoris and a 20 mm Hg or more decrease in systolic blood pressure in the ipsilateral arm. Angina pectoris associated with coronary-subclavian steal syndrome requires surgical bypass grafting.

Acute Arterial Occlusion

Acute arterial occlusion differs from the gradual development of arterial occlusion caused by atherosclerosis and is frequently the result of cardiogenic embolism. Systemic emboli may arise from a left atrial thrombus in the setting of atrial fibrillation or less commonly from an atrial myxoma. Left ventricular thrombi may develop after MI or in the setting of dilated cardiomyopathy. Other cardiac causes of systemic emboli are valvular heart disease, prosthetic heart valves, infective endocarditis, and paradoxical emboli from a patent foramen ovale. Noncardiac causes of acute arterial occlusion include atheroemboli from an upstream artery, plaque rupture, and hypercoagulability derangements. Aortic dissection and trauma can acutely occlude an artery by disrupting the integrity of the vessel lumen.

Signs and Symptoms

Acute arterial occlusion in an extremity presents with signs of limb ischemia: intense pain, paresthesias, and motor weakness distal to the site of arterial occlusion. Loss of a palpable peripheral pulse, cool skin, and sharply demarcated skin color changes (pallor or cyanosis) occur distal to the arterial occlusion. Large embolic fragments often lodge at an arterial bifurcation (e.g., aortic or femoral artery bifurcations).

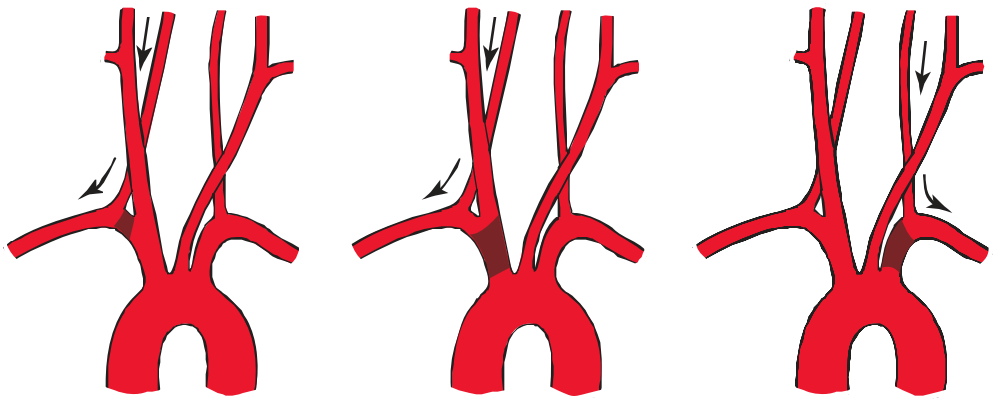

Fig. 12.9 Comparison of the frequency of occurrence of left, right, and bilateral subclavian steal syndrome. (Adapted from Heidrich H, Bayer O. Symptomatology of the subclavian steal syndrome. *Angiology*. 1969;20:406–413.)

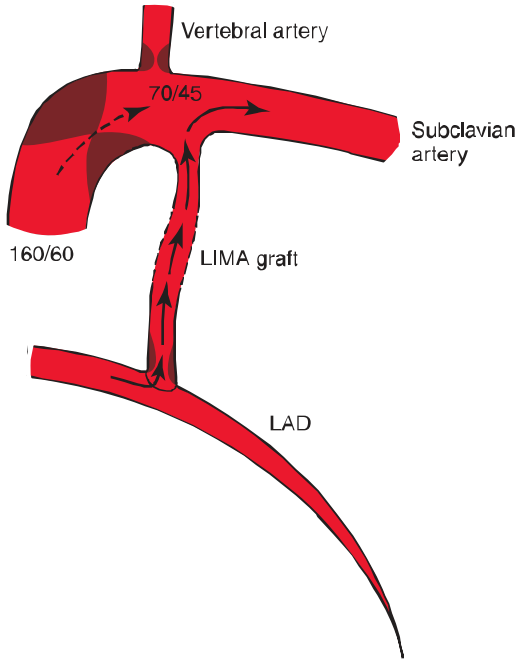

Fig. 12.10 Coronary-subclavian steal syndrome. Development of subtotal stenosis of the left subclavian artery may produce reversal of flow through a patent internal mammary graft *(LIMA)*, which thereby diverts flow destined for the left anterior descending *(LAD)* coronary artery. (Adapted from Martin JL, Rock P. Coronary-subclavian steal syndrome: anesthetic implications and management in the perioperative period. *Anesthesiology.* 1988;68:933–936.)

Diagnosis

Noninvasive tests can provide additional evidence of peripheral arterial occlusion and reveal the severity of the ischemia, but such testing should not delay definitive treatment. Arteriography may be used to define the site of acute arterial occlusion and the appropriateness of revascularization surgery.

Treatment

Surgical embolectomy is used to treat acute systemic embolism, typically thromboembolism, to a large peripheral artery. Embolectomy is rarely feasible for atheromatous embolism because the atheromatous material usually fragments into very small pieces. However, if the primary source of atheroembolism is identified and amenable to surgical exposure, it may be resectable. Once the diagnosis of acute arterial embolism is confirmed, anticoagulation with heparin is initiated to prevent propagation of the thrombus. Intraarterial thrombolysis with urokinase or recombinant tPA may restore vascular patency in acutely occluded arteries and synthetic bypass grafts. The clinical outcome is highly dependent on the rapidity of revascularization. Amputation may be necessary in some patients.

Management of Anesthesia

Management of anesthesia in patients undergoing surgical treatment of acute arterial occlusion resulting from a systemic embolism is similar to that in patients with chronic peripheral arterial disease.

Raynaud Phenomenon

Raynaud phenomenon is episodic vasospastic ischemia of the digits. It affects women more often than men and is characterized by digital blanching or cyanosis in association with cold exposure or sympathetic activation. Vasodilation with hyperemia is often seen after rewarming and reestablishment of blood flow. The disorder is categorized as either primary (also called Raynaud disease) (Table 12.4) or secondary when it is associated with other diseases.

Diagnosis

The primary diagnosis of Raynaud phenomenon is based on history and physical examination findings. When the clinical diagnosis is made, it may lead to workup for associated inflammatory diseases. Raynaud phenomenon sometimes appears as part of the constellation of symptoms seen with the scleroderma subtype known as CREST syndrome. CREST is an acronym for subcutaneous calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly (scleroderma limited to the fingers), and telangiectasia.

Treatment

Primary and secondary Raynaud phenomena are usually managed conservatively by protecting the hands and feet from exposure to cold. Pharmacologic intervention, including calcium channel blockade or α blockade may be helpful in some patients. In rare instances, surgical sympathectomy is considered for treatment of persistent severe digital ischemia.

TABLE 12.4 Secondary Causes of Raynaud Phenomenon

Connective Tissue Diseases
Scleroderma
Systemic lupus erythematosus
Rheumatoid arthritis
Dermatomyositis
Peripheral Arterial Occlusive Disease
Atherosclerosis
Thromboangiitis obliterans
Thromboembolism
Thoracic outlet syndrome
Neurologic Syndromes
Carpal tunnel syndrome
Reflex sympathetic dystrophy
Cerebrovascular accident
Intervertebral disk herniation
Trauma
Cold thermal injury (frostbite)
Percussive injury (vibrating tools)
Drugs
β-adrenergic antagonists
Tricyclic antidepressants
Antimetabolites
Ergot alkaloids
Amphetamines

Management of Anesthesia

There are no specific recommendations as to the choice of drugs to produce general anesthesia in patients with Raynaud phenomenon. Increasing the ambient temperature of the operating room and maintaining normothermia are basic considerations. Noninvasive blood pressure measurement techniques may be strongly considered to avoid any arterial compromise of potentially affected extremities.

Regional anesthesia is acceptable for peripheral operations in patients with Raynaud phenomenon, but to avoid undesirable vasoconstriction, it may be prudent not to include epinephrine in the local anesthetic solution.

PERIPHERAL VENOUS DISEASE

Common peripheral venous diseases encountered in patients undergoing surgery include superficial thrombophlebitis, deep vein thrombosis (DVT), and chronic venous insufficiency. The most important associated complication of DVT is pulmonary embolism, a leading cause of perioperative morbidity and mortality.

The major factors predisposing to venous thrombosis, classically referred to as Virchow triad, are routinely encountered in the perioperative period: (1) venous stasis (due to immobility), (2) hypercoagulability (due to inflammation and acute surgical stress), and (3) disruption of vascular endothelium (due to perioperative trauma). Table 12.5 expands on Virchow triad to include more recently appreciated risk factors such as the use of oral contraceptives.

Superficial Thrombophlebitis and Deep Vein Thrombosis

Thrombosis of deep or superficial peripheral veins is particularly common among surgical patients, occurring in approximately 50% of patients undergoing total hip replacement. Most of these thromboses are subclinical and resolve completely when mobility is restored. Although deep and superficial venous thromboses may coexist, isolated deep thrombosis may be distinguished from superficial venous thrombosis based on history, physical examination findings, and results of confirmatory ultrasonography.

Superficial venous thrombosis of a saphenous vein or its tributary often occurs in association with intravenous therapy, varicose veins, or systemic vasculitis and causes localized pain and superficial inflammation along the path of the involved vein. Superficial thrombophlebitis is rarely associated with pulmonary embolism. The intense inflammation that accompanies superficial thrombophlebitis rapidly leads to total venous occlusion. Typically the vein can be palpated as a cordlike structure surrounded by an area of erythema, warmth, and edema.

DVT is more often associated with generalized pain of the affected extremity, tenderness, and unilateral limb swelling, but diagnosis based on clinical signs alone is unreliable. Doppler ultrasonography with vein compression is highly sensitive for detecting proximal vein thrombosis (popliteal or femoral vein) but less sensitive for detecting calf vein thrombosis (Fig. 12.11). Venography and impedance plethysmography are also potential diagnostic modalities.

Most postoperative venous thrombi arise in the lower legs, often in the low-flow soleal sinuses and in large veins draining the gastrocnemius muscle. However, in approximately 20% of patients, thrombi originate in more proximal veins.

TABLE 12.5 Factors Predisposing to Thromboembolism

- Venous stasis
  - Recent surgery
  - Trauma
  - Lack of ambulation
  - Pregnancy
  - Low cardiac output (congestive heart failure, myocardial infarction)
  - Stroke
- Abnormality of venous wall
  - Varicose veins
  - Drug-induced irritation
- Hypercoagulable state
  - Surgery
  - Estrogen therapy (oral contraceptives)
  - Cancer
  - Deficiencies of endogenous anticoagulants (antithrombin III, protein C, protein S)
  - Stress response associated with surgery
  - Inflammatory bowel disease
- History of previous thromboembolism
- Morbid obesity
- Advanced age

Prevention of Venous Thromboembolism

Clinical risk factors. Assessment of clinical risk factors identifies patients who can benefit from prophylactic measures aimed at reducing the risk of DVT development (Table 12.6). Patients at low risk require only minimal prophylactic measures such as early postoperative ambulation and the use of compression stockings, which augment propulsion of blood from the ankles to the knees. The risk of DVT may be much higher in patients older than age 40 who are undergoing operations lasting longer than 1 hour, especially orthopedic surgery on the lower extremities, pelvic or abdominal surgery, and surgery that requires a prolonged convalescence period with bed rest or limited mobility. The presence of cancer also increases the risk of thrombotic complications.

Subcutaneous heparin in doses of 5000 units administered twice or three times daily reduces DVT risk, as does the use of intermittent external pneumatic compression devices (see Table 12.6).

Regional anesthesia. The incidence of postoperative DVT and pulmonary embolism in patients undergoing total knee or total hip replacement can be substantially decreased (20–40%) by using epidural or spinal anesthesia techniques instead of general anesthesia. Postoperative epidural analgesia does not augment this benefit but may allow earlier ambulation, which can reduce the risk of DVT.

Presumably the beneficial effects of regional anesthesia compared with general anesthesia are due to (1) vasodilation, which maximizes venous blood flow; and (2) the ability to provide excellent postoperative analgesia and early ambulation.

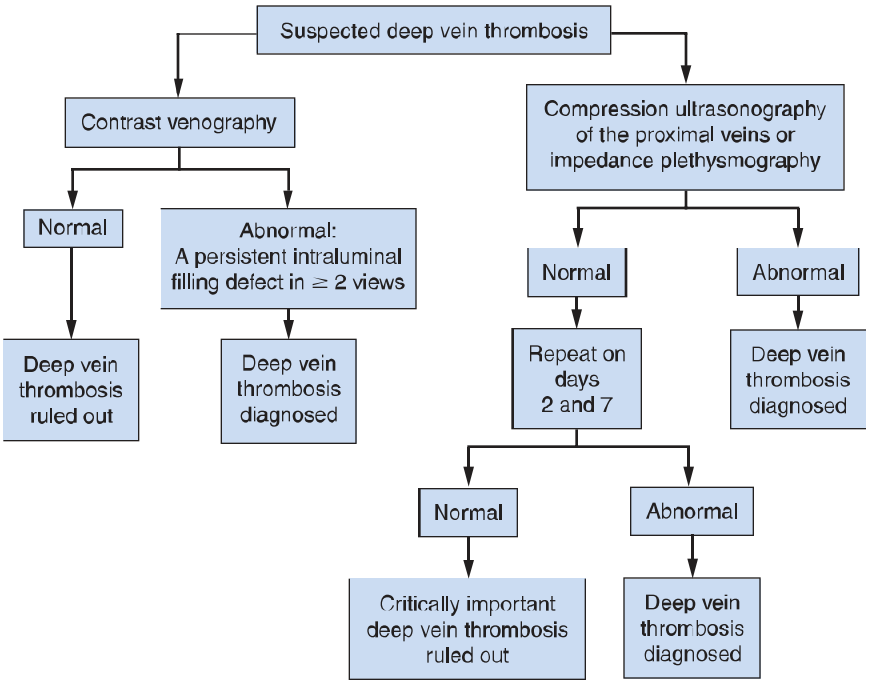

Fig. 12.11 Steps in the diagnosis of deep vein thrombosis. (Adapted from Ginsberg JS. Management of venous thromboembolism. *N Engl J Med.* 1996;335:1816-1828. Copyright 1996 Massachusetts Medical Society.)

TABLE 12.6 Risk and Predisposing Factors for Development of Deep Vein Thrombosis After Surgery or Trauma

Associated Conditions	Low Risk	Moderate Risk	High Risk
General surgery	Age <40 Operation <60 min	Age >40 Operation >60 min	Age >40 Operation >60 min Previous deep vein thrombosis Previous pulmonary embolism Extensive trauma Major fractures
Orthopedic surgery			Knee or hip replacement
Trauma			Extensive soft tissue injury Major fractures Multiple trauma sites
Medical conditions	Pregnancy	Postpartum period Myocardial infarction Congestive heart failure	Stroke
Incidence of deep vein thrombosis without prophylaxis	2%	10–40%	40–80%
Incidence of symptomatic pulmonary embolism	0.2%	1–8%	5–10%
Incidence of fatal pulmonary embolism	0.002%	0.1–0.4%	1–5%
Recommended steps to minimize deep vein thrombosis	Graduated compression stockings Early ambulation	External pneumatic compression Subcutaneous heparin Intravenous dextran	External pneumatic compression Subcutaneous heparin Intravenous dextran or vena cava filter Warfarin

Adapted from Weinmann EE, Salzman EW. Deep-vein thrombosis. *N Engl J Med.* 1994;331:1630-1642.

Treatment of Deep Vein Thrombosis

Anticoagulation is the first-line treatment for all patients with a diagnosis of DVT. Therapy is initiated with heparin (unfractionated or low-molecular-weight heparin [LMWH]) because this drug produces an immediate anticoagulant effect. Heparin has a narrow therapeutic window, and the response of individual patients can vary considerably. Advantages of LMWH over unfractionated heparin include a longer half-life, a more predictable dose response without the need for serial assessment of activated partial thromboplastin time, and a lower risk of

bleeding complications. Disadvantages include increased cost and lack of availability of a rapid reversal agent.

Therapy with warfarin, an oral vitamin K antagonist, is initiated during heparin treatment and adjusted to achieve a prothrombin time yielding an international normalized ratio (INR) between 2 and 3. Heparin is discontinued when warfarin has achieved its therapeutic effect. Oral anticoagulants may be continued for 3 to 6 months or longer. Inferior vena cava filters may be inserted into patients who experience recurrent pulmonary embolism despite adequate anticoagulant therapy or in whom anticoagulation is contraindicated.

Thrombophilia workup should be considered for patients with DVT. Laboratory abnormalities associated with initial and recurrent venous thrombosis or embolism include the presence of factor V Leiden and congenital deficiencies of antithrombin III, protein C, protein S, or plasminogen. Congenital resistance to activated protein C and increased levels of antiphospholipid antibodies are also associated with venous thromboembolism. A family history of unexplained venous thrombosis is often present.

Complications of anticoagulation. The most obvious complication of anticoagulant therapy is bleeding. Frequent monitoring of activated partial thromboplastin time in patients receiving intravenous heparin is necessary owing to the variability in dose response. Similarly, patients receiving warfarin must be monitored closely with frequent prothrombin times and INR. Life-threatening bleeding in patients receiving warfarin might require rapid correction with vitamin K, fresh frozen plasma infusions, and factor concentrates.

A frequently encountered complication of unfractionated heparin administration is heparin-induced thrombocytopenia (HIT). HIT is classically divided into two types. HIT type 1 is a benign thrombocytopenia seen soon after initiation of heparin therapy (within the first few days) that resolves spontaneously and does not preclude continued treatment with heparin. In HIT type 1, thrombocytopenia is mild, generally staying above 100,000 platelets/mm^3. In contrast, HIT type 2 is an immune-mediated phenomenon occurring in 1% to 3% of patients receiving unfractionated heparin. HIT type 2 is caused by antibodies to the heparin–platelet factor 4 complex and leads to severe thrombocytopenia and platelet activation that causes microvascular thrombosis. Identification of thrombosis in the setting of HIT type 2 necessitates treatment with a direct thrombin inhibitor such as argatroban or lepirudin to prevent further thrombosis. The diagnosis of HIT type 2 is based on the presence of heparin antibodies along with a positive result on a platelet serotonin-release assay. Such a diagnosis mandates avoidance of all future heparin exposure (Fig. 12.12).

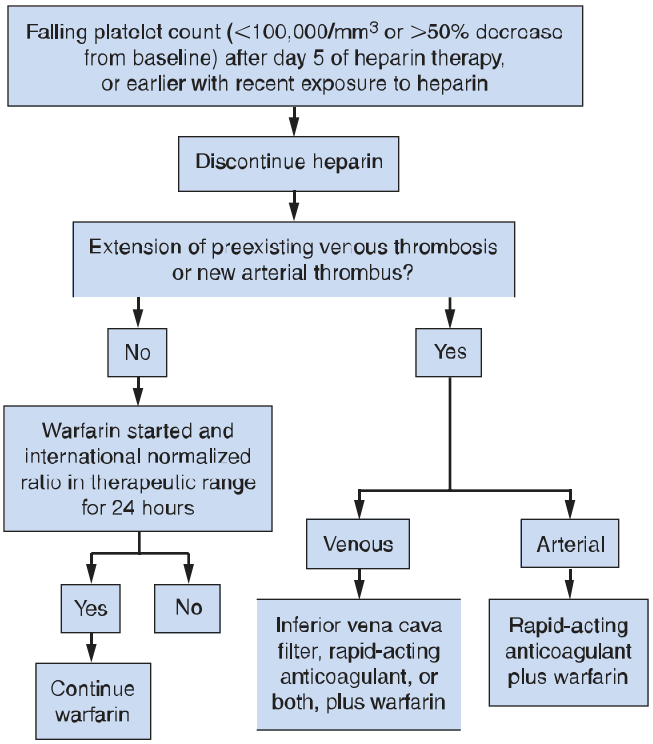

Fig. 12.12 Steps in the management of patients with venous thromboembolism and heparin-induced thrombocytopenia. (Adapted from Ginsberg JS. Management of venous thromboembolism. *N Engl J Med*. 1996;335:1816–1828. Copyright 1996 Massachusetts Medical Society.)

SYSTEMIC VASCULITIS

Inflammatory diseases of the vasculature form a diverse and numerous group of ailments with characteristic presentations that are often grouped by the size of the vessels at the primary site of clinically apparent abnormalities. Large-artery vasculitides include Takayasu arteritis and temporal (or giant cell) arteritis. In contrast, Kawasaki disease is a vasculitis affecting medium-sized arteries, most prominently the coronary arteries. Medium- and small-artery vasculitides include thromboangiitis obliterans, Wegener granulomatosis, and polyarteritis nodosa. In addition, vasculitis can be a feature of connective tissue diseases such as systemic lupus erythematosus and rheumatoid arthritis, which are discussed in other chapters.

Temporal (Giant Cell) Arteritis

Temporal arteritis is inflammation of the arteries of the head and neck, manifesting most often as headache, scalp tenderness, or jaw claudication. This diagnosis is suspected in any patient older than age 50 complaining of a unilateral headache. Superficial branches of the temporal arteries are often tender and enlarged. Arteritis of branches of the ophthalmic artery may lead to ischemic optic neuritis and unilateral blindness. Prompt initiation of treatment with corticosteroids is indicated in patients with visual symptoms to prevent blindness. Evidence of arteritis on a biopsy specimen of the temporal artery is present in approximately 90% of patients.

Thromboangiitis Obliterans (Buerger Disease)

Thromboangiitis obliterans is an inflammatory vasculitis leading to occlusion of small and medium-sized arteries and veins

in the extremities. The disease is most prevalent in men, and the onset is typically before age 45. The most important predisposing factor is tobacco use. The disorder has been identified as an autoimmune response triggered when nicotine is present. The traditional diagnosis of Buerger disease is based on five criteria: smoking history, onset before age 50, infrapopliteal arterial occlusive disease, upper limb involvement or phlebitis migrans, and the absence of risk factors for atherosclerosis other than smoking. The diagnosis of thromboangiitis obliterans is confirmed by biopsy of active vascular lesions.

Signs and Symptoms

Involvement of extremity arteries causes forearm, calf, or foot claudication. Severe ischemia of the hands and feet can cause rest pain, ulcerations, and skin necrosis. Raynaud phenomenon is commonly associated with thromboangiitis obliterans, and cold exacerbates the symptoms. Periods of vasospasm may alternate with periods of quiescence. Migratory superficial vein thrombosis develops in approximately 40% of patients.

Treatment

The most effective treatment for patients with thromboangiitis obliterans is smoking cessation. Surgical revascularization is not usually feasible because of the involvement of small distal blood vessels. There is no proven effective drug therapy, and the efficacy of platelet inhibitors, anticoagulants, and thrombolytic therapy is not established. Recently, gene therapy with vascular endothelial growth factor was found to be helpful in healing ischemic ulcerations and relieving rest pain. Cyclophosphamide therapy has been tried because of the autoimmune nature of the disease.

Management of Anesthesia

Management of anesthesia in the presence of thromboangiitis obliterans requires avoidance of events that might damage already ischemic extremities. Positioning and padding of pressure points must be meticulous. The operating room ambient temperature should be warm, and inspired gases should be warmed and humidified to maintain normal body temperature. When feasible, systemic blood pressure should be measured noninvasively rather than by intraarterial means. Coexisting pulmonary and cardiac disease are considerations.

Regional or general anesthetic techniques can be used in these patients. If regional anesthesia is selected, it may be prudent to omit epinephrine from the local anesthetic solution to avoid any possibility of accentuating vasospasm.

Polyarteritis Nodosa

Polyarteritis nodosa is an antineutrophyl cytoplasmic antibodies (ANCA)–negative vasculitis that sometimes occurs in association with hepatitis B, hepatitis C, or hairy cell leukemia. Males more frequently contract this disease than females. Small and medium-sized arteries are involved, with inflammatory changes resulting in glomerulonephritis, myocardial ischemia, peripheral neuropathy, and seizures. The lung vasculature is generally not affected. Hypertension is common and presumably reflects renal disease. Renal failure is the most common cause of death. Human immunodeficiency virus–associated vasculitis may present in a similar fashion.

The diagnosis of polyarteritis nodosa depends on histologic evidence of vasculitis on biopsy specimens and demonstration of characteristic aneurysms on arteriography. Treatment is empirical and usually includes corticosteroids and cyclophosphamide, removal of offending drugs, and treatment of underlying diseases such as cancer.

Management of anesthesia in patients with polyarteritis nodosa should take into consideration the likelihood of coexisting renal disease, cardiac disease, and systemic hypertension. Supplemental corticosteroids may be appropriate in patients who have been receiving these drugs as treatment for this disease.

Lower Extremity Chronic Venous Disease

Chronic venous disease includes symptoms associated with long-standing venous reflux and vein dilatation and affects approximately 50% of the population. Presentation varies from mild to severe, beginning with telangiectasias and varicose veins, to the more severe group of chronic venous insufficiency that includes clinical signs of edema, skin changes, and ultimately ulcerations. Risk factors include advanced age, family history, pregnancy, ligamentous laxity, and previous venous thrombosis as well as lower extremity injuries, prolonged standing, obesity, smoking, sedentary lifestyle, and high estrogen states.

Diagnosis includes symptoms of leg pain, fatigue, and heaviness and is confirmed by ultrasound studies that point toward venous reflux, which is defined by retrograde blood flow of greater than 0.5-second duration.

Treatment is conservative initially and includes leg elevation, exercise, weight reduction, compression therapy, skin barrier therapy, emollients, steroids in certain cases, and wound management for ulcerations. Conservative medical management may include diuretics, aspirin, systemic antibiotics, micronized purified flavonoid fraction, pentoxifylline, stanozolol, escin (horse chestnut seed extract), hydroxyethylrutoside, sulodexide, prostacyclin analogues, and zinc sulfate.

If medical management fails and/or symptoms progress, ablation therapies can be performed. Indications include vein hemorrhage, superficial thrombophlebitis, and venous reflux associated with symptoms. Contraindications include pregnancy, vein thrombosis (superficial or deep), moderate to severe peripheral artery disease, joint disease that limits mobility, and congenital venous anomalies. Methods of venous ablation include thermal ablation with laser and light therapy, radiofrequency ablation, endovenous laser ablation, and sclerotherapy with chemical sclerosing agents. Surgical methods include saphenous vein inversion and removal, high saphenous ligation, ambulatory phlebectomy, transilluminated powered phlebectomy, conservative venous ligation, and perforator ligation.

KEY POINTS

- Cardiac complications are the leading cause of perioperative morbidity and mortality in patients undergoing noncardiac surgery. Compared with the general surgical population, the incidence of these complications is higher in patients undergoing vascular surgery. Vascular surgery patients have a higher incidence of coronary artery disease and are at particularly high risk of perioperative myocardial infarction (MI). However, the risk of perioperative cardiac complications differs based on the type of vascular surgery performed. For example, peripheral vascular procedures carry a higher rate of cardiovascular complications than central vascular procedures such as aortic aneurysm repair. The trend toward endovascular management of aortic and peripheral vascular disease may change cardiovascular risk substantially.
- Atherosclerosis is a systemic disease. Patients with peripheral arterial disease have a three to five times greater risk of cardiovascular ischemic events such as MI, ischemic stroke, and death than those without this disease. Critical limb ischemia is associated with very high intermediate-term morbidity and mortality resulting from cardiovascular events.
- Aortic cross clamping and unclamping are associated with significant hemodynamic disturbances because of the decrease in blood flow distal to the aortic clamp and the increase in blood flow proximal to the level of aortic occlusion. The hemodynamic response to aortic cross clamping differs depending on the level of clamping: thoracic, supraceliac, or infrarenal.
- Perfusion pressures distal to the aortic cross clamp are decreased and directly dependent on the pressure above the level of aortic clamping to aid in blood flow through collateral vessels or a shunt, not on cardiac output or intravascular volume.
- Aortic cross clamping is associated with formation and release of hormonal factors (activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system) and other mediators (prostaglandins, oxygen free radicals, complement cascade). Overall, injury to the spinal cord, lungs, kidneys, and abdominal viscera is principally due to ischemia and subsequent reperfusion injury caused by the aortic cross clamp (local effects) and/or release of mediators from ischemic and reperfused tissues (distant effects).
- The principal causes of unclamping hypotension are (1) central hypovolemia caused by pooling of blood in reperfused tissues, (2) hypoxia-mediated vasodilation causing an increase in vascular capacitance in the tissues below the level of aortic clamping, and (3) accumulation of vasoactive and myocardial-depressant metabolites in these tissues.
- Data from transcranial Doppler and carotid duplex ultrasonography studies suggest that carotid artery stenosis with a residual luminal diameter of 1.5 mm (70–75% stenosis) represents the point at which the stenosis becomes hemodynamically significant. Therefore, if collateral cerebral blood flow is not adequate, transient ischemic attacks and ischemic infarction can occur.
- Both hypertension and hypotension may be observed frequently during the period immediately after carotid endarterectomy.
- Acute arterial occlusion is typically caused by cardiogenic embolism. Systemic emboli may arise from a mural thrombus in the left ventricle that develops because of MI or dilated cardiomyopathy. Other cardiac causes of systemic emboli are valvular heart disease, prosthetic heart valves, infective endocarditis, left atrial myxoma, atrial fibrillation, and atheroemboli from the aorta and iliac or femoral arteries.
- Thromboangiitis obliterans is an inflammatory vasculitis leading to occlusion of small and medium-sized arteries and veins in the extremities.
- Patients at low risk for deep vein thrombosis (DVT) require only minimal prophylactic measures such as early postoperative ambulation and use of compression stockings. The risk of DVT may be much higher in patients older than age 40 who are undergoing operations lasting longer than 1 hour, especially orthopedic surgery on the lower extremities, pelvic or abdominal surgery, and surgery that requires a prolonged convalescence with bed rest or limited mobility. The presence of cancer also increases the risk of thrombotic complications. Subcutaneous heparin (minidose heparin) and intermittent external pneumatic compression of the legs help prevent DVT in patients at moderate risk following abdominal and orthopedic surgery.
- Endovascular repair of aortic lesions is a relatively new technique for which data on long-term outcomes and randomized trials are lacking, but the significant improvement in perioperative mortality together with development of new grafts and devices has started a new era in vascular surgery. Carotid and peripheral arterial endovascular procedures have emerged as alternative, less invasive methods of arterial repair.

RESOURCES

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13

Diseases Affecting the Brain

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OUTLINE

CEREBRAL PHYSIOLOGY

Cerebral Blood Flow, Blood Volume, and Metabolism

Cerebral blood flow (CBF) is modulated by cerebral metabolic rate, cerebral perfusion pressure (CPP, the difference between the mean arterial pressure [MAP] and intracranial pressure [ICP]), and arterial blood carbon dioxide ($Paco_2$) and oxygen (Pao_2) tensions. Various drugs and intracranial pathologies can also impact CBF. During normal physiologic conditions, CBF is autoregulated over a range of CPPs. With intact autoregulation, normal CBF in an awake person is approximately 50 mL/100 g brain tissue per minute. In the past, CBF was thought to be autoregulated over a range of CPPs of 50 to 150 mm Hg in chronically normotensive patients. However, more recent data suggest that the lower limit of autoregulation may be greater than 50 mm Hg in normotensive individuals. Also, the autoregulatory range may be dynamic, changing in response to physiologic factors (e.g., sleep-wake cycles) and likely varies among individuals. Given that a normal adult brain weighs approximately 1500 g and normal cardiac output is 5 L/min, CBF is therefore 750 mL/min or 15% of cardiac output during the awake state.

Normal cerebral metabolic rate, generally measured as rate of oxygen consumption ($CMRO_2$), is 3.0 to 3.8 mL O_2/100 g brain tissue per minute. During awake resting conditions, total body oxygen consumption is approximately 250 mL O_2/min. Therefore total brain oxygen consumption is 18% to 23% of total body oxygen consumption. $CMRO_2$ can be decreased by temperature reductions and various anesthetic drugs and increased by temperature increases and seizures.

Anesthetic and intensive care management of neurologically impaired patients relies heavily on manipulation of intracranial volume and pressure. These in turn are influenced by cerebral blood volume (CBV) and CBF. CBF and CBV do not always change in parallel. For example, vasodilatory anesthetics and hypercapnia may produce parallel increases in CBF and CBV. Conversely, moderate systemic hypotension still within the brain's autoregulatory capacity can produce minimal change in CBF but, as a result of compensatory vessel dilation, an increase in CBV. Similarly, partial occlusion of an intracranial artery, such as occurs in embolic stroke, may reduce regional CBF. However, vessel dilation distal to the occlusion, which is an attempt to restore circulation, can produce an increase in CBV.

Arterial Carbon Dioxide Partial Pressure

Variations in $Paco_2$ produce corresponding changes in CBF (Fig. 13.1). As a guideline, CBF increases by 1 to 2 mL/100 g/min (or ~15 mL/min for a 1500-g brain) for every 1 mm Hg increase in $Paco_2$. A similar decrease occurs during hypocapnia when $Paco_2$ is acutely decreased. The impact of $Paco_2$ on CBF is mediated by variations in the pH of the cerebrospinal fluid (CSF). Decreased CSF pH causes cerebral vasodilation, and increased CSF pH results in vasoconstriction. $Paco_2$ can also modulate CBV. The extent of CBV reduction is dependent on the anesthetic being used. In general, vasoconstricting anesthetics tend to attenuate the effects of $Paco_2$ on CBV.

The ability of hypocapnia to acutely decrease CBF, CBV, and ICP is fundamental to the practice of clinical neuroanesthesia. Significant acute hypocapnia can increase risk for cerebral ischemia due to excessive vasoconstriction. The ability of hypocapnia to decrease CBV, and thus ICP, is attenuated by the return of CSF pH to normal after approximately 6 hours of hypocapnia. This reduces the effectiveness of induced hypocapnia as a means of long-term control of intracranial hypertension.

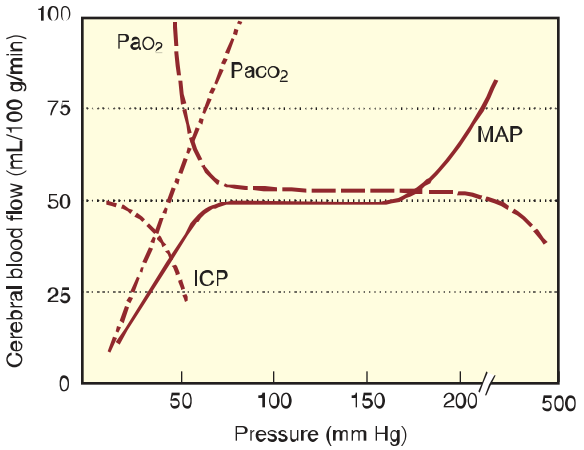

Fig. 13.1 Impact of intracranial pressure *(ICP)*, Pao_2, $Paco_2$, and mean arterial pressure *(MAP)* on cerebral blood flow.

Arterial Oxygen Partial Pressure

Decreased Pao_2 does not significantly affect CBF until a threshold value of approximately 50 mm Hg is reached (see Fig. 13.1). Below this threshold, there is abrupt cerebral vasodilation, and CBF increases. Hyperoxia has minimal, if any, effect on CBF.

Cerebral Perfusion Pressure and Cerebral Autoregulation

The ability of the brain to maintain CBF at constant levels despite changes in CPP is known as autoregulation (see Fig. 13.1). Autoregulation is an active vascular response characterized by (1) arterial constriction when CPP is increased and (2) arterial dilation in response to decreases in CPP. When CPP is below the lower limit of autoregulation, cerebral blood vessels are maximally dilated, and CBF decreases. CBF becomes directly related to CPP. As CPP is further decreased, cerebral ischemia may ensue, causing nausea, dizziness, and altered consciousness. When CPP is increased above the upper limit of autoregulation, cerebral arterioles are maximally constricted, and CBF varies proportionally with CPP. If CPP increases further, fluid may be forced across blood vessel walls into the brain parenchyma, producing cerebral edema. The risk of cerebral hemorrhage also increases.

In the setting of chronic hypertension, the autoregulation curve is displaced to the right so that pressure dependence of CBF occurs at a higher CPP at both the lower and upper limits of autoregulation. In those with chronic hypertension, risk for cerebral ischemia can occur at systemic blood pressures that would be tolerated by normotensive individuals. Gradual treatment of hypertension can restore the autoregulation curve to normal. Acute hypertension can produce signs of central nervous system dysfunction at MAP values that are well tolerated in chronically hypertensive patients. Similarly, an acute hypertensive response associated with direct laryngoscopy or surgery may exceed the upper limit of autoregulation in chronically normotensive patients. Autoregulation of CBF may be lost or impaired during a variety of conditions, including the presence of intracranial tumors or head trauma and the administration of volatile anesthetics. Increased impairment of autoregulation leads to greater dependence of CBF on systemic blood pressure such that the autoregulation curve is no longer flat.

Cerebral Venous Blood Pressure

Increases in intracranial venous blood pressure can impede venous drainage from the brain and may predispose the patient to cerebral edema and cerebral ischemia, the latter due to increases in ICP, which in turn reduces CPP. Impaired venous drainage can increase brain bulk and complicate intracranial surgery. Examples of situations that can cause impaired venous drainage include superior vena cava syndrome, cerebral venous thrombosis, or jugular vein compression, as can occur with improper neck positioning during surgery. With coughing against a partially closed glottic opening, increases in intrathoracic pressure result in

transient increases in cerebral venous pressure. However, if a coughing or bucking patient is trachcally intubated, the glottis is stented open by the endotracheal tube, and the effects of a cough or buck on cerebral venous pressure will be decreased compared to those encountered in nonintubated patients.

Anesthetic Drugs

During normal physiologic conditions, changes in $CMRO_2$ usually lead to parallel changes in CBF, a phenomenon known as CBF-$CMRO_2$ coupling. The volatile anesthetics, isoflurane, sevoflurane, and desflurane, particularly when administered in concentrations greater than 0.6 to 1.0 minimum alveolar concentration (MAC), are potent direct cerebral vasodilators that produce dose-dependent increases in CBF despite concomitant decreases in cerebral metabolic oxygen requirements. Below 1 MAC, volatile anesthetics alter CBF minimally, in part because any direct effects of the anesthetics are counterbalanced by CBF-$CMRO_2$ coupling. When volatile anesthetic–induced $CMRO_2$ depression is maximized, concomitant with maximal depression of cerebral electrical activity, larger dosages of volatile anesthetic will dilate cerebral blood vessels. This vascular dilation can lead to increases in CBF, CBV, and possibly ICP. With halothane, which at clinically relevant dosages does not induce the extent of $CMRO_2$ depression that is seen with other volatile anesthetics (isoflurane, sevoflurane, desflurane), direct vasodilatory effects predominate, which results in greater increases in CBV at equipotent doses compared with other commonly used volatile anesthetics. The effect of volatile anesthetics on CBF can be attenuated by hypocapnia or cerebral vasoconstrictive drugs, such as propofol.

Nitrous oxide also causes an increase in CBF, but, in contrast to volatile anesthetics, nitrous oxide does not appear to interfere with autoregulation. The initiation of nitrous oxide administration after closure of the dura or use of nitrous oxide in a patient with intracranial air, such as those who underwent recent craniotomy, should be with caution as nitrous oxide can diffuse into the gas space. This leads to an increase in the size and pressure of the air pocket. Clinically, tension pneumocephalus usually presents as delayed emergence from general anesthesia after craniotomy.

Like the volatile anesthetics, ketamine is considered to be a cerebral vasodilator. Propofol, barbiturates, and etomidate are potent cerebral vasoconstrictors capable of decreasing CBF, CBV, and ICP. Opioids are also cerebral vasoconstrictors, assuming that opioid-induced ventilatory depression is controlled and no increase in $Paco_2$ is allowed. Drugs that produce cerebral vasoconstriction predictably decrease CBV and ICP.

Administration of nondepolarizing neuromuscular blocking drugs does not meaningfully alter ICP. However, muscle relaxation may help prevent acute increases in ICP resulting from movement or coughing during direct laryngoscopy. The use of succinylcholine in the setting of increased ICP may temporarily raise ICP. The mechanism for this effect is most likely due to increases in muscle afferent activity, a process somewhat independent of visible muscle fasciculations. This can lead to cerebral arousal (which can be seen on electroencephalography [EEG]) and corresponding increases in CBF and CBV. These cerebral effects of succinylcholine can be attenuated by prior induction of deep anesthesia with a cerebral vasoconstricting anesthetic or a defasciculating dose of a nondepolarizing neuromuscular blocking drug.

INCREASED INTRACRANIAL PRESSURE

The intracranial and spinal vault contains neural tissue (brain and spinal cord), blood, and CSF, and is enclosed by the dura mater and bone. During normal conditions, brain tissue, intracranial CSF, and intracranial blood have a combined volume of approximately 1200 to 1500 mL, and normal ICP is usually 5 to 15 mm Hg (or 7–20 cm H_2O). Any increase in one component of intracranial volume must be offset by a decrease in the volume of another intracranial component to prevent an increase in ICP. During normal physiologic conditions, changes in one component are well compensated for by changes in other components, but eventually a point can be reached at which even a small change in intracranial contents results in a large change in ICP (Fig. 13.2), as described by the Monro-Kellie hypothesis. Since ICP is one of the determinants of CPP, homeostatic mechanisms work to increase MAP to help support CPP despite increases in ICP, but eventually compensatory mechanisms can fail, and cerebral ischemia will result.

Factors leading to alterations in CSF flow or its absorption into the vasculature can often lead to increased ICP. CSF is produced by two mechanisms: (1) ultrafiltration and secretion by the cells of the choroid plexus and (2) the passage of water, electrolytes, and other substances across the blood-brain barrier. CSF is therefore a direct extension of the extracellular fluid compartment of the central nervous system. CSF is produced at a constant rate of 500 to 600 mL/day in adults and is contained within the ventricular system of the brain, the central canal of the spinal cord, and the subarachnoid space, as well as the

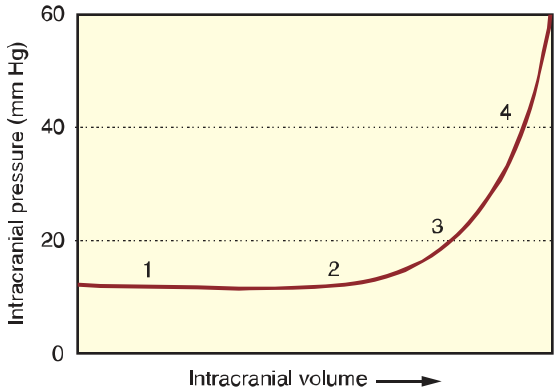

Fig. 13.2 Intracranial elastance curve depicting the impact of increasing intracranial volume on intracranial pressure (ICP). As intracranial volume increases from point 1 to point 2, ICP does not increase because of compensatory mechanisms. Patients on the rising portion of the curve (point 3) can no longer compensate for increases in intracranial volume; the ICP begins to increase and is likely to be associated with clinical symptoms. Additional increases in intracranial volume at this point (point 3), as produced by anesthetic drug–induced increases in cerebral blood volume, can precipitate abrupt increases in ICP (point 4).

extracellular compartment of the central nervous system. CSF is absorbed from microscopic arachnoid villi and macroscopic arachnoid granulations within the dura mater and bordering venous sinusoids and sinuses, and at the blood-brain barrier.

It is important to note that the intracranial vault is considered to be compartmentalized. Specifically, there are various meningeal barriers within the intracranial vault that functionally separate the contents: the falx cerebri (a reflection of dura mater that separates the two cerebral hemispheres) and the tentorium cerebelli (a reflection of dura mater that lies rostral to the cerebellum and marks the border between the supratentorial and infratentorial spaces). Increases in the contents of one region of brain may cause regional increases in ICP, and in extreme instances, the contents of that compartment can move (herniate) into a different compartment. Various types of herniation syndromes are categorized based on the region of brain affected (Fig. 13.3). Herniation of cerebral hemispheric contents under the falx cerebri is referred to as subfalcine herniation. Typically, this condition leads to compression of branches of the anterior cerebral artery and is evident on radiographic imaging as midline shift. Herniation of the supratentorial contents past the tentorium cerebelli is referred to as transtentorial herniation, in which evidence of brainstem compression occurs in a rostral to caudal manner, resulting in altered consciousness, defects in gaze and afferent ocular reflexes, and, finally, hemodynamic and respiratory compromise followed by death. The uncus (i.e., the medial portion of the temporal lobe) may herniate over the tentorium cerebelli, which results in a subtype of transtentorial herniation referred to as uncal herniation. A specific sign is ipsilateral oculomotor nerve dysfunction because the oculomotor nerve is compressed against the brainstem; this results in pupillary dilatation, ptosis, and lateral deviation of the affected eye, which occurs before evidence of brainstem compression and death. Herniation of the cerebellar tonsils can occur in the setting of elevated infratentorial pressure, which leads to extension of these cerebellar structures through the foramen magnum. Typical signs are those indicating medullary dysfunction, including cardiorespiratory instability and subsequently death.

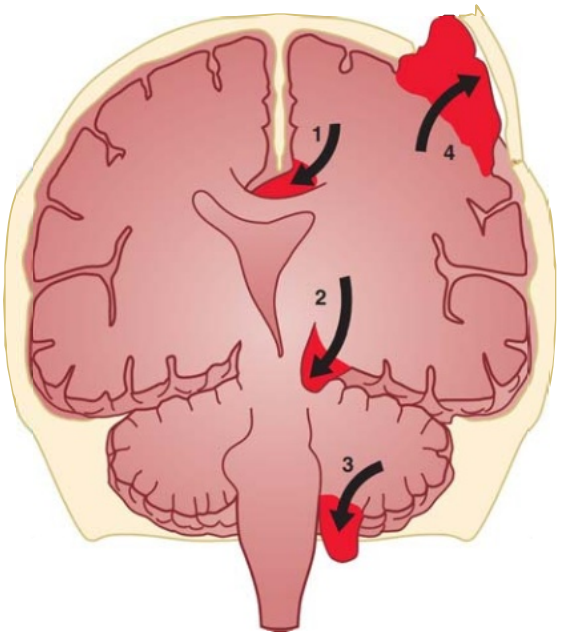

Fig. 13.3 Herniation syndromes. An increase in the contents of the supratentorial space caused by masses, edema, or hematoma can lead to *(1)* herniation of the cingulate gyrus under the falx (i.e., subfalcine herniation); *(2)* herniation of contents over the tentorium cerebelli (i.e., transtentorial herniation); *(3)* herniation of the cerebellar tonsils out through the foramen magnum; and *(4)* herniation of brain contents out of a traumatic defect in the cranial cavity. (Adapted from Fishman RA. Brain edema. *N Engl J Med.* 1975;293:706–711.)

Nonspecific signs and symptoms of increased ICP include headache, nausea, vomiting, and papilledema. As ICP further increases and cerebral perfusion becomes limited, decreased levels of consciousness and possibly coma can be observed.

Increased ICP is often diagnosed clinically based on the symptoms described earlier, by radiographic means, and by direct measurement of ICP. Typically, computed tomography (CT) or magnetic resonance imaging (MRI) will help identify the cause of an increase in ICP. For example, a large mass or hematoma may be evident. If aqueductal stenosis is present, the third, but not fourth, ventricle is enlarged.

Several methods are currently available to measure and monitor ICP. The choice of technique depends on the clinical situation. The gold standard technique is the ventriculostomy that allows not only for ICP measurement but also the removal of CSF for analysis or as a treatment of intracranial hypertension. A catheter can also be placed in the CSF in the lumbar region of the spine to monitor ICP and to remove CSF. However, because of the compartmentalization of the intracranial contents, lumbar CSF pressure may not accurately reflect ICP in all circumstances. In certain clinical settings, such as a brain tumor, there is also a risk of herniation of the cerebellar tonsils when CSF is drained using the lumbar subarachnoid approach. ICP can also be measured via transducers placed in the epidural or subdural spaces as well as in brain parenchyma, but these latter techniques do not allow for CSF removal. Other techniques, such a measurement of optic nerve sheath diameter via ultrasonography, may provide a noninvasive way to assess ICP.

A normal ICP waveform is pulsatile and varies with the cardiac impulse and spontaneous breathing. An ICP remaining below 15 mm Hg is normal. In patients with increased intracranial elastance, not only may ICP be greater than 15 mm Hg, but abnormal waveforms may also appear. There are three types of Lundberg waves that may appear on an ICP waveform tracing. Lundberg A waves (or "plateau waves") are abrupt increases in ICP from 20 to 100 mm Hg that can last for up to 20 minutes. Lundberg A waves occur in the setting of increased ICP with impaired oxygen and substrate delivery that results in abrupt vasodilation and an increase in ICP. During these dramatic increases in ICP, patients may become symptomatic and manifest evidence of inadequate cerebral perfusion. Spontaneous hyperventilation or changes in mental status may occur. Lundberg A waves are related to poor outcome. Lundberg B waves are sharp, brief spikes in ICP to 20 to 50 mm Hg occurring approximately every 0.5 to 2 minutes. They also indicate increased intracranial elastance but not to the degree where one may

observe Lundberg A waves. Lundberg C waves are rhythmic, very short-duration spikes in ICP up to 20 mm Hg of unknown etiology. Lundberg C waves are considered benign.

Methods to Decrease Intracranial Pressure

Methods to decrease ICP include elevation of the head; hyperventilation; CSF drainage; administration of hyperosmotic drugs, diuretics, corticosteroids, cerebral vasoconstricting anesthetics (such as propofol), and surgical decompression. It is not possible to reliably identify the level of ICP that will interfere with regional CBF or alter cerebral function and well-being in individual patients unless other monitors are employed. These monitors include, but are not limited to, cerebral near-infrared spectroscopy, cerebral microdialysis, and brain tissue oxygen partial pressure monitoring. Improvements in neurologic status, such as improved level of consciousness that occurs with reduction in ICP, can serve as a crude monitor of cerebral well-being. In the absence of these additional monitors or a reliable neurologic exam, a frequent recommendation is to treat any sustained increase in ICP that exceeds 20 mm Hg. Treatment may be indicated even when the ICP is less than 20 mm Hg if the appearance of occasional plateau waves suggests the presence of increased intracranial elastance.

Elevating the patient's head above heart level encourages venous outflow from the brain and can lower ICP. Extreme flexion or rotation of the head can obstruct the jugular veins and restrict venous outflow from the brain. The head-down position can increase ICP.

Hyperventilation, and hence lowering of the $Paco_2$, is an effective method for rapidly reducing ICP. In adults a frequent recommendation is to maintain the $Paco_2$ near 30 to 35 mm Hg. Lowering the $Paco_2$ more than this may not meaningfully decrease ICP further but may result in adverse changes in systemic physiology. The effects of hyperventilation will diminish after 6 hours. When prolonged hyperventilation is discontinued, rebound increases in ICP are a potential problem, especially if normocapnia is rapidly restored.

Intravenous infusion of drugs and fluids, such as mannitol and hypertonic saline, are effective at decreasing ICP. These osmotic diuretics produce transient increases in the osmolarity of plasma, which acts to draw water across the blood-brain barrier, thus decreasing the water content of the brain and decrease ICP. An adverse effect from osmotic diuretics is diuresis that can lead to systemic dehydration and subsequent impaired cerebral and other end-organ perfusion, if not rectified. In regions of brain where the integrity of the blood-brain barrier is compromised, osmotic diuretics can enter the brain parenchyma, causing water to follow, and paradoxically increase brain water volume and ICP. The brain eventually adapts to sustained increases in plasma osmolarity, so long-term use of hyperosmotic drugs results in reduced effectiveness.

Mannitol is ideally administered in doses of 0.25 to 0.5 g/kg IV. Larger initial doses have little incremental effect on ICP and may predispose the patient to rebound increases in ICP. Hence it is better to give an initial dose of 0.25 to 0.5 g/kg IV and, if the desired effect is not achieved, either administer another dose or switch to another type of therapy. Also, no further mannitol should be administered if serum osmolarity is greater than 320 mOsm/L. Decreases in ICP occur within 30 minutes with maximum effect observed in 1 to 2 hours and a duration of 6 hours. Mannitol can initially increase intravascular fluid volume and should be used with caution, if at all, in patients who are not tolerant of increases in cardiac preload, such as those with congestive heart failure. Mannitol also has direct vasodilating properties and can produce brief hypotension if administered quickly. Hypertonic saline is an alternate option to decrease ICP and can be administered in concentrations of 2% to 23%. Hypertonic saline at a concentration of 3% or more should be administered via a central venous catheter as extravasation can lead to local tissue irritation. For adult patients, administration of 1 to 2 mL/kg of 3% sodium chloride over 5 minutes can be considered. Additional drug can be administered to obtain a target serum sodium concentration of 145 to 155 mEq/L and a serum osmolarity of less than 320 mOsm/L if the initial dose fails to reduce ICP. Serum sodium concentrations greater than 160 mEq/L can lead to renal injury, pulmonary edema, cardiac dysfunction, and seizures. As such, serum sodium should be checked frequently until target serum sodium and osmolarity are obtained and then at least every 6 hours for the duration of the infusion.

Loop diuretics, such as furosemide, have been used to decrease ICP, although their efficacy is significantly less than that of mannitol or hypertonic saline. Since loop diuretics exert their effect on brain water volume by inducing systemic hypovolemia, their use to treat intracranial hypertension is falling out of favor.

Corticosteroids, such as dexamethasone or methylprednisolone, are effective in lowering ICP caused by the development of localized vasogenic cerebral edema from loss of blood-brain barrier integrity. This is due in part to a steroid-induced upregulation of the expression of proteins responsible for the integrity of the tight junctions between endothelial cells constituting a major component of the blood-brain barrier. Patients with brain tumors often exhibit improved neurologic status and disappearance of headache within 12 to 36 hours after initiation of corticosteroid therapy. Corticosteroids are also effective in treating increased ICP in patients with pseudotumor cerebri (benign intracranial hypertension). On the other hand, corticosteroids are *not* effective in reducing ICP due to nonvasogenic edema–related causes. Corticosteroids can increase blood glucose concentration, which may adversely affect outcome if ongoing cerebral ischemia is present. Corticosteroids are associated with poor outcome when used to treat intracranial hypertension following traumatic brain injury.

Propofol is effective in treating increased ICP by inducing a decrease in both $CMRO_2$ and CBF. Patients receiving prolonged propofol infusions, particularly pediatric patients, should be monitored for drug-associated high-anion-gap metabolic acidosis (aka propofol infusion syndrome), which can also herald multiorgan dysfunction or injury and can be fatal.

Specific Causes of Increased Intracranial Pressure

Increased ICP is typically a sign of an underlying intracranial pathologic process. Therefore one should seek the cause of

increased ICP in addition to instituting treatment. Causes of increased ICP are many. Tumors can lead to increased ICP either (1) directly because of their size, (2) indirectly by causing edema in normal surrounding brain tissue, or (3) by causing obstruction of CSF flow, as is commonly seen with tumors involving the third ventricle. Intracranial hematomas can cause increased ICP in a manner similar to mass lesions. Blood in the CSF, as is seen in subarachnoid hemorrhage, may lead to obstruction of CSF reabsorption at the arachnoid villi and granulations and may further exacerbate increased ICP. Infection, such as meningitis or encephalitis, can lead to edema or obstruction of CSF reabsorption. Some causes of intracranial hypertension not discussed elsewhere in this chapter are described in the following sections.

Aqueductal Stenosis

Stenosis of major CSF flow channels may impede CSF flow and can lead to increased ICP. Aqueductal stenosis, one of the more common causes of obstructive hydrocephalus, results from congenital narrowing of the cerebral aqueduct that connects the third and fourth ventricles. Obstructive hydrocephalus can present during infancy when the narrowing is severe. Lesser obstruction results in slowly progressive hydrocephalus, which may not be evident until adulthood. Diagnosis is made by brain imaging, and treatment includes ventricular shunting of endoscopic fenestration of the floor of the third ventricle allowing CSF to flow into the basal cisterna avoiding the need to flow through the cerebral aqueduct.

Benign Intracranial Hypertension

Benign intracranial hypertension (pseudotumor cerebri) is a syndrome characterized by ICP higher than 20 mm Hg, normal CSF composition, normal sensorium, and absence of local intracranial lesions. This disorder typically occurs in obese women and is observed more commonly in patients with various systemic diseases, including polycystic ovary syndrome, systemic lupus erythematosus, Addison disease, hypoparathyroidism, and hypervitaminosis A. Imaging indicates a normal or even small cerebral ventricular system. Headaches and bilateral visual disturbances typically occur, and symptoms may be exaggerated during pregnancy. No identifiable cause of increased ICP is found in most patients, and the pathogenesis is still unknown. The prognosis is usually excellent. Treatment includes acetazolamide to decrease CSF formation, removal of CSF from the lumbar intrathecal space, ventricular shunting of CSF, or optic nerve fenestration. Anesthesia management for patients without shunts involves avoiding exacerbation of intracranial hypertension and ensuring an adequate CPP. Hypoxia and hypercarbia must be rigorously avoided. Spinal anesthesia may be used in select parturients with mildly increased ICP so long as the patient has no significant neurologic deficits or alterations in consciousness. In patients with elevated ICP, epidural analgesia should be avoided in most cases as the volume of drug required may exacerbate elevated ICP. In the presence of a lumboperitoneal shunt there is a theoretical possibility that local anesthetic solution injected into the subarachnoid space could escape into the peritoneal cavity, decreasing anesthesia density. In parturients with a functioning ventriculoperitonal shunt, spinal and epidural analgesia and anesthesia can be used safely as long as the shunt is working correctly. Occasionally, the intraperitoneal drainage catheter can become compressed by the gravis uterus resulting in inadequate shunting and elevated ICP causing signs and symptoms such as headaches, visual changes, papilledema, or alterations in consciousness.

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus usually presents as the triad of dementia, gait changes, and urinary incontinence that develops over a period of weeks to months. The mechanism is thought to be related to compensated but impaired CSF absorption from a previous insult, such as subarachnoid hemorrhage, meningitis, or head trauma. In most cases, however, the cause is never identified. Lumbar puncture usually reveals normal or low CSF pressure, yet CT or MRI will often demonstrate large ventricles. Treatment typically involves drainage of CSF via ventriculoperitoneal shunting.

SPONTANEOUS INTRACRANIAL HYPOTENSION

Patients with spontaneous intracranial hypotension (SIH) often present with an abrupt-onset orthostatic headache when assuming the upright position. Symptoms frequently increase during the second half of the day and may be associated with tinnitus, muffled hearing, or other cranial nerve deficits. The headache is relieved by assuming a horizontal position. SIH is caused by leaking of CSF from the spine though meningeal diverticula, dural tears, or CSF-venous fistulas. MRI of the brain can be normal, but findings suggestive of SIH include meningeal enhancement, engorgement of venous sinuses, or herniation of the cerebellar tonsil though the foramen magnum. A CSF opening pressure of less than 6 cm H_2O may or may not be present in patients with SIH as symptoms are thought to be related to low CSF volume rather than low CSF pressure. CT myelography is the gold standard to identify spinal CSF leaks. Dynamic imaging studies using CT or fluoroscopy can also be used with or without digital subtraction, which can be helpful in localizing leaks. Treatment of SIH can include supportive measures, epidural blood patch, and surgery. Surgical procedures to repair the site of leak can be performed. Of note, patients may experience rebound intracranial hypertension following surgical repair and may require therapeutic lumbar puncture.

INTRACRANIAL TUMORS

Intracranial tumors may be classified as primary (those arising from the brain and its coverings) or metastatic. Primary brain tumors, also called gliomas, can originate from virtually any cell type within the central nervous system. The classification of gliomas depends on histologic cell type, but these tumors are frequently subclassified based on specific oncogenic mutations that can influence choice of treatment and prognosis. Supratentorial tumors are more common in adults and often

present with headache, seizures, or new neurologic deficits, whereas infratentorial tumors are more common in children and often present with obstructive hydrocephalus and ataxia.

Treatment may consist of surgical resection or debulking, chemotherapy, or radiation. Gamma knife irradiation differs from traditional radiation therapy in that multiple radiation sources are used, and because the tumor is addressed from multiple angles, radiation to the tumor can be maximized while the radiation dose to any single area of surrounding brain tissue can be diminished. Such treatment can also be accomplished with the use of x-ray and particle-based modalities such as proton beam. Emerging therapies include immunotherapy and oncolytic virotherapy, the latter employing viruses specifically programmed to kill neoplastic cells.

Specific Brain Tumor Classes

Astrocytoma

Astrocytes are the most prevalent glial cells in the central nervous system and give rise to many types of infratentorial and supratentorial tumors. Well-differentiated (low-grade) gliomas are the least aggressive class of astrocyte-derived tumors. They often are found in young adults and generally present as new-onset seizures. Imaging generally shows minimal enhancement with contrast. Surgical or radiation treatment of low-grade gliomas usually results in symptom-free long-term survival.

Pilocytic astrocytomas usually affect children and young adults. They often arise in the cerebellum (cerebellar astrocytoma), cerebral hemispheres, hypothalamus, or optic pathways (optic glioma). The tumor usually appears as a contrast-enhancing, well-demarcated lesion with minimal to no surrounding edema. Because of its benign pathologic characteristics, prognosis following surgical resection is generally very good. However, the location of the lesion, such as within the brainstem, may preclude resection.

Anaplastic astrocytomas are poorly differentiated, usually appear as a contrast-enhancing lesion on imaging because of disruption of the blood-brain barrier, and generally evolve into glioblastoma multiforme. Treatment involves resection, radiation, or chemotherapy. Prognosis is intermediate between that for low-grade gliomas and glioblastoma multiforme.

Glioblastoma multiforme accounts for 30% of all primary brain tumors in adults. Imaging usually reveals a ring-enhancing lesion reflecting central necrosis and surrounding edema. Because of microscopic infiltration of normal brain by tumor cells, resection alone is usually inadequate. Instead, treatment generally consists of surgical debulking combined with chemotherapy and radiation and is aimed at palliation, not cure. Despite treatment, life expectancy may be measured in weeks.

Oligodendroglioma

Oligodendrogliomas arise from myelin-producing cells within the central nervous system and account for only 6% of primary intracranial tumors. Classically, seizures predate the appearance of tumor on imaging, often by many years. Calcifications within the tumor are common and are visualized on CT imaging. The tumor usually consists of a mixture of both oligodendrocytic and astrocytic cells. Treatment and prognosis depend on the pathologic features. Initial treatment involves resection, since early in the course the tumor typically consists of primarily oligodendrocytic cells, which are radioresistant.

Ependymoma

Arising from cells lining the ventricles and central canal of the spinal cord, ependymomas commonly present in childhood and young adulthood. Their most common location is the floor of the fourth ventricle. Symptoms include obstructive hydrocephalus, headache, nausea, vomiting, and ataxia. Treatment consists of resection and radiation. Tumor infiltration into surrounding tissues may preclude complete resection. Prognosis depends on the completeness of resection.

Primitive Neuroectodermal Tumor

Primitive neuroectodermal tumor represents a diverse class of tumors, including retinoblastoma, medulloblastoma, pineoblastoma, and neuroblastoma, all believed to arise from primitive neuroectodermal cells. Medulloblastoma is the most common pediatric primary malignant brain tumor and may disseminate throughout the central nervous system via the CSF. The presentation of medulloblastoma is similar to that of ependymoma. Treatment usually involves a combination of resection, radiation, and possibly intrathecal instillation of chemotherapeutic drugs. Prognosis is very good in children if treatment leads to disappearance of both tumor on MRI and tumor cells within the CSF. Prognosis is less optimistic if there is evidence of tumor dissemination within the central nervous system.

Meningioma

Meningiomas are usually extraaxial (arising outside of the brain proper), slow-growing, well-circumscribed benign tumors arising from arachnoid cap cells, not the dura mater. Because of their slow growth, they can be very large at the time of diagnosis. They can occur anywhere arachnoid cap cells exist, but are most common near the sagittal sinus, falx cerebri, and cerebral convexity. Tumors are usually apparent on plain radiographs and CT scans as a result of the presence of calcifications. On MRI and conventional angiography, these tumors are often seen to receive their blood supply from the external carotid artery. Surgical resection is the mainstay of treatment. Prognosis is usually excellent. However, some tumors may be recurrent and require additional resection. Malignant meningiomas are rare.

Pituitary Tumor

Pituitary adenomas usually arise from cells of the anterior pituitary gland. They may occur along with tumors of the parathyroid glands and pancreatic islet cells as part of multiple endocrine neoplasia type I. These tumors are usually divided into functional (i.e., hormone-secreting) and nonfunctional types. The former usually present as an endocrinologic disturbance related to the hormone secreted by the tumor. Functional tumors are usually smaller (<1 cm in diameter) at the time of diagnosis; hence they are often called microadenomas.

Macroadenomas are usually nonfunctional, present with symptoms related to their mass (i.e., headache or visual changes resulting from compression of the optic chiasm), and are larger at the time of diagnosis, usually greater than 1 cm in diameter. Panhypopituitarism may be caused by either tumor type because of compression of normally functioning pituitary gland tissue. Pituitary tumors may also present as pituitary apoplexy, which is characterized by the abrupt onset of headache, visual changes, ophthalmoplegia, and altered mental status secondary to hemorrhage, necrosis, or infarction within the tumor. These tumors can also invade the cavernous sinus or internal carotid artery or compress various cranial nerves, causing an array of symptoms. Treatment depends on tumor type. Prolactinomas are often initially treated medically with bromocriptine. Surgical resection via the transsphenoidal approach or open craniotomy can be curative for most pituitary tumors.

Corticosteroids, such as dexamethasone for nausea and vomiting prophylaxis, should not be administered during pituitary tumor resection. Dexamethasone is a potent suppressor of the hypothalamic-pituitary-adrenal axis. Often, serum cortisol is assessed on the day following surgery to screen for postoperative hypopituitarism, and dexamethasone use may result in a false diagnosis of hypopituitarism.

Acoustic Neuroma

The term *acoustic neuroma* is a misnomer as the tumor is usually a benign schwannoma involving the vestibular (not auditory) component of cranial nerve VIII within the internal auditory canal. However, bilateral tumors may occur as part of neurofibromatosis type 2. Common presenting symptoms include hearing loss, tinnitus, and disequilibrium. Larger tumors, which grow out of the internal auditory canal and into the cerebellopontine angle, may cause symptoms related to compression of a cranial nerve, especially the facial nerve, or compression of the brainstem. Treatment usually consists of surgical resection with or without radiation therapy. Surgery generally involves intraoperative cranial nerve monitoring with electromyography or brainstem auditory evoked potentials as resection carries a high risk for cranial nerve injury. Prognosis is usually very good; however, recurrence of tumor is not uncommon.

Central Nervous System Lymphoma

Central nervous system lymphoma is a rare tumor that can arise as a primary brain tumor or via metastatic spread from a systemic lymphoma. Primary central nervous system lymphoma can occur anywhere within the brain but is most common in supratentorial locations. Immunocompromised patients are at increased risk for central nervous system lymphoma as are those with autoimmune diseases. Diagnosis is made by imaging as well as biopsy. During biopsy, it may be reasonable to wait to administer corticosteroids, such as dexamethasone, until after pathologic specimens have been obtained since these tumors may be very sensitive to steroids. Indeed, steroid-associated tumor lysis before a biopsy is performed may result in failure to obtain an adequate sample to make the diagnosis. The mainstay of treatment is chemotherapy (including intraventricularly delivered drugs) and whole-brain radiation. Prognosis is poor despite treatment.

Metastatic Tumor

Metastatic brain tumors originate most often from primary sites in the lung or breast. Malignant melanoma, renal cell cancer, and carcinoma of the colon are also likely to spread to the brain. Metastatic brain tumor is the likely diagnosis when more than one intracranial lesion is present. Because of abnormal angiogenesis in metastatic lesions, these tumors tend to bleed more during resection than other central nervous system tumors.

Management of Anesthesia

Management of anesthesia during tumor resection procedures can be challenging since patients may be of any age and a variety of operative positioning issues may arise. Furthermore, some procedures may be conducted with electrophysiologic monitoring, which may have implications for anesthetic drug choices and the use of muscle relaxants. Some procedures may even be performed in awake patients to facilitate resection of a mass located near an eloquent region of brain, such as the motor cortex. Major goals during anesthesia include (1) maintaining adequate cerebral perfusion and oxygenation of normal brain, (2) optimizing operative conditions to facilitate resection, (3) ensuring a rapid emergence from anesthesia at the conclusion of the procedure to facilitate neurologic assessment, and (4) accommodating intraoperative electrophysiologic monitoring if needed.

Preoperative Management

Preoperative evaluation of a patient with an intracranial tumor is directed toward identifying the presence of increased ICP, documenting preoperative neurologic deficits, and optimizing other systemic diseases. Patients with an intracranial pathologic process may be extremely sensitive to the central nervous system depressant effects of opioids and sedatives. Drug-induced hypoventilation can lead to accumulation of arterial carbon dioxide and further increase ICP. Likewise, drug-induced sedation can mask alterations in the level of consciousness that accompany intracranial hypertension. Preoperative sedation can also unmask subtle neurologic deficits that may not usually be apparent. This is thought to result from an increased sensitivity of injured neurons to the depressant effects of various anesthetic and sedative drugs. Considering all the potential adverse effects of preoperative medication, it is prudent to use premedication very sparingly and with continuous respiratory and neurologic monitoring.

Induction of Anesthesia

Anesthesia induction is typically achieved with propofol as it produces a rapid, reliable onset of unconsciousness without increasing ICP. A nondepolarizing muscle relaxant can be used to facilitate tracheal intubation. Administration of succinylcholine may be associated with a modest transient increase in ICP and may be considered if otherwise indicated. Succinylcholine should be avoided in patients with preexisting significant motor

deficits due to concern for hyperkalemia. Mechanical hyperventilation is initiated with the goal of decreasing $Paco_2$ to approximately 35 mm Hg. Adequate depth of anesthesia and profound skeletal muscle paralysis should be achieved before laryngoscopy to avoid the noxious stimulation or patient movement that can abruptly increase CBF, CBV, and ICP. Additional doses of intravenous anesthetic drugs, lidocaine, esmolol, or potent short-acting opioids may help blunt the response to laryngoscopy or other forms of intraoperative stimulation, such as placement of pinions or skin incision.

Abrupt, sustained increases in systemic blood pressure, particularly in areas of impaired cerebral autoregulation, may be accompanied by undesirable increases in CBF, CBV, and ICP and precipitate cerebral edema. Sustained hypotension must also be avoided to prevent brain ischemia. Positive end-expiratory pressure has a highly variable effect on ICP. Hence it should be used with caution, and attention must be paid to changes in ICP, MAP, and CPP as a result of this intervention. The efficacy of brain volume management can be assessed after craniotomy by direct visualization and communication with the surgeon.

Maintenance of Anesthesia

Maintenance of anesthesia in patients undergoing surgical resection of supratentorial brain tumors is often achieved by combining drugs of various classes, including nitrous oxide, volatile anesthetics, opioids, dexmedetomidine, and propofol. Both nitrous oxide and potent volatile anesthetics have the potential to increase CBV and ICP as a result of direct cerebral vasodilation. However, low concentrations of volatile anesthetics (0.6–1.0 MAC) likely have minimal effect on cerebral volume. In patients with significantly elevated ICP, a cerebral vasoconstricting anesthetic, such as one that employs propofol as the hypnotic instead of inhaled drugs, can be used. Although modest cerebrovascular differences can be demonstrated with different combinations of drugs, there is no evidence that any particular combination is significantly different from another or superior in terms of effects on ICP and short-term patient outcome.

The use of nitrous oxide is controversial if there is any potential for venous air embolism, such as during procedures performed in the sitting position. Despite theoretical concerns, however, the actual incidence of venous air embolism in sitting patients is not influenced by nitrous oxide use. Once a venous air embolism has been detected, nitrous oxide use must be discontinued because of the concern that the embolus volume will expand and exacerbate the physiologic consequences of the embolus. Nitrous oxide should also be avoided if there is concern for preexisting air within the central nervous system, as may occur after prior craniotomy, spine surgery involving durotomy, basilar skull fracture, or percutaneous instrumentation (e.g., insertion of a ventricular shunt, pneumoencephalography), as nitrous oxide has the potential to expand these gas spaces leading in increased ICP or exacerbating preexisting intracranial hypertension.

Spontaneous movement by patients undergoing surgical resection of brain tumors must be prevented. Such movement could result in an increase in intracranial volume and ICP, increased surgical bleeding (making surgical exposure difficult), or direct injury to the head and brain from pinions or surgical instrumentation. Therefore, in addition to adequate depth of anesthesia, skeletal muscle paralysis is typically maintained during intracranial surgery.

Fluid Therapy

Relatively isoosmolar solutions (e.g., 0.9% sodium chloride, lactated Ringer solution) do not adversely affect brain water or edema formation if they are used in modest amounts provided the blood-brain barrier is intact. In contrast, free water in hypoosmolar solutions, such as 0.45% sodium chloride, is rapidly distributed throughout body water, including brain water, and may adversely affect ICP. Regardless of the crystalloid solution selected, any solution administered in large amounts can increase CBV and ICP in patients with brain tumors. Therefore the rate of fluid infusion should be titrated to maintain euvolemia. Intravascular fluid volume depletion caused by blood loss during surgery should be corrected with packed red blood cells or colloid solutions supplemented with balanced salt solutions. Glucose-containing solutions should be avoided or used with caution, since hyperglycemia in the setting of central nervous system ischemia will exacerbate neuronal injury and worsen outcome.

Monitoring

The insertion of an intraarterial catheter is useful for continuous monitoring of blood pressure and blood sampling as needed. Capnography can facilitate ventilation and $Paco_2$ management as well as detect venous air embolism (see "Sitting Position and Venous Air Embolism" later). Continuous ICP monitoring, although not routine, can be of value, especially prior to dural opening. Temperature is monitored to prevent hyperthermia or uncontrolled hypothermia. A urinary bladder catheter has utility in managing perioperative fluid balance. It is necessary if drug-induced diuresis is planned; if the patient has diabetes insipidus, syndrome or inappropriate secretion of antidiuretic hormone, or other aberration of salt or water physiology; or if a lengthy surgical procedure is anticipated and bladder distention is a concern.

Intravenous access with large-bore catheters should be obtained, given the likelihood of bleeding and the need for transfusion or rapid administration of fluids. Central venous catheterization can be useful for both intravenous access and monitoring of fluid status. Additionally, it also has utility as a means to aspirate intracardiac air following venous air embolism, should this occur during surgery performed with the patient in the sitting position. The impact of central access for air aspiration is controversial as, even in the setting of a large air embolism, the volume of air that can be aspirated from the catheter may not be enough to improve clinical outcome. Transesophageal echocardiography can also be useful for procedures in the sitting position to identify intravenous air and help assess cardiac function. Pulmonary artery catheterization may be considered in patients with significant cardiac disease.

A peripheral nerve stimulator is helpful for monitoring the persistence of drug-induced skeletal muscle paralysis. One must

be aware that when paresis or paralysis of an extremity is associated with the brain tumor, the paretic extremity will show resistance (decreased sensitivity) to nondepolarizing muscle relaxants compared with a normal extremity leading to potential overdosing of muscle relaxant drugs. Electrocardiogram (ECG) changes can reflect increased ICP or surgical retraction or manipulation of the brainstem or cranial nerves. Indeed, the cardiovascular centers, respiratory control areas, and nuclei of the lower cranial nerves lie in close proximity in the brainstem. Manipulation of the brainstem may produce systemic hypertension and bradycardia or hypotension and tachycardia.

Postoperative Management

In most circumstances the goal following surgery for brain tumor is to facilitate a rapid emergence from anesthesia that will allow the patient to participate in a gross neurologic examination to allow for recognition of any adverse neurologic events related to the surgery. In some circumstances, such as when there is expectation for significant lower cranial nerve injury that might impair the ability of the patient to protect the airway, the decision might be made to not proceed with emergence and extubation immediately following surgery. Systemic hypertension during emergence or following surgery is associated with increased risk for surgical site intracranial hemorrhage. Systolic blood pressure should be maintained less than 160 mm Hg. Hypothermia may be a cause of slow postoperative awakening. Other causes of delayed emergence from anesthesia include residual neuromuscular block, residual effects of drugs with sedative effects (i.e., opioids, benzodiazepines, volatile anesthetics), electrolyte distrubances, or a primary central nervous system event, such as ischemia, hematoma, or tension pneumocephalus.

Following general anesthesia, a preexisting neurologic deficit may be exacerbated by the sedative effects of anesthetic drugs, which makes a subtle preoperative deficit appear more severe. This differential awakening is thought to be due to increased sensitivity of insulted or injured neurons to the depressant effects of anesthetic drugs. Often these deficits will disappear and neurologic function will return to its baseline state with time. Any persistent new deficit that does not quickly resolve must be further investigated.

Sitting Position and Venous Air Embolism

Craniotomy to remove a supratentorial tumor is usually performed with the patient in the supine position with the head elevated 10 to 15 degrees to facilitate cerebral venous drainage. Infratentorial tumors have more unusual patient positioning requirements and may be performed with the patient in the lateral, prone, or sitting position.

The sitting position deserves special attention since it has a variety of implications for management of anesthesia. The sitting position may be used during surgery in the posterior fossa as well as for cervical spine surgery, denervation of cervical nerve roots in patients with torticollis, and for implantation of deep brain stimulator leads. Advantages of the sitting position include excellent surgical exposure and enhanced cerebral venous and CSF drainage, which minimizes blood loss and reduces brain bulk. Disadvantages include decreases in systemic blood pressure and cardiac output due to decreased preload, macroglossia if a transesophageal echocardiography is used, brachial plexus injury if the arms are not supported, and venous air embolism. For these reasons, the lateral or prone position is often selected as an alternative. However, as long as no contraindication to the sitting position exists, the outcome of patients undergoing surgery in the sitting position is similar to that of patients placed in other positions. Sitting position may have specific advantages in certain patient populations, including obese patients (as mechanical ventilation will be easier than in prone position) as well as in pregnant patients.

If the sitting position is used, one should account for the effect of hydrostatic pressure gradients on CPP. Specifically, CPP should reflect correction for the hydrostatic pressure difference between the heart and the brain. This is generally accomplished by measuring blood pressure via an intraarterial catheter and referencing the pressure transducer to the vertical height of the external auditory meatus, which approximates the position of the circle of Willis. Lack of correction for hydrostatic pressure may put the patient at undue risk of cerebral hypoperfusion since the measured systemic blood pressure, but not necessarily the true pressure at the level of the brain, will be greater if the transducer is referenced at the level of the heart.

Venous air embolism is a potential hazard whenever the operative site is above the level of the heart, so that pressure in the exposed veins is subatmospheric. Although this complication is most often associated with neurosurgical procedures, venous air embolism may also occur during operations involving the neck, thorax, abdomen, and pelvis and during open-heart surgery, repair of liver and vena cava lacerations, obstetric and gynecologic procedures, and total hip replacement. Patients undergoing intracranial surgery are at increased risk not only because the operative site is above the level of the heart but also because veins in the skull or intracranial venous sinuses may not collapse when cut, owing to their attachment to bone or dura. Indeed, the cut edge of cranial bone, including that associated with burr holes, is a common site for the entry of air into veins.

Venously entrained air enters the right-sided cardiac chambers and then the pulmonary artery, where it can impair right-side cardiac output and alveolar perfusion causing systemic hypotension and an increase in dead space ventilation. With significant increases in dead space ventilation, end-expired carbon dioxide tension may decrease. Intrapulmonary air can also induce pulmonary edema formation and bronchoconstriction.

The entry of air from the systemic venous system into the systemic arterial system is called paradoxical air embolism. This can occur via several mechanisms, including through an intracardiac shunt (i.e., patient foramen ovale or other atrial septal defects, ventricular septal defects), or in the setting of large venous air embolism, overwhelming the ability of alveoli to clear air thus leading to transit of air across the pulmonary capillaries. A known intracardiac connection that could result in a right-to-left shunt is a relative contraindication to use of the sitting position. Echocardiography is frequently used in cases at significant risk for venous air embolism to screen for intracardiac shunt, although the false negative rate for detection of intracardiac shunt is not trivial, and the clinician should always

have concern for risk of paradoxical air embolism in patients who sustain a venous air embolism.

Paradoxical air embolism causes injury due to air entering the brain, coronary circulation, and kidneys leading to stroke, myocardial injury, and renal injury, respectively. Early detection of venous air embolism is important for successful treatment. A Doppler ultrasonographic transducer placed over the heart is a sensitive detector for intracardiac air and venous air embolism. However, this transducer cannot provide information regarding the volume of air that has entered the venous circulation as large and small volume emboli will produce similar Doppler signals. Transesophageal echocardiography is useful for assessing both the presence and quantity of intracardiac air. A sudden decrease in end-expired carbon dioxide tension may reflect increased alveolar dead space and/or diminished cardiac output resulting from air embolism. An increase in right atrial and pulmonary artery pressure can reflect acute cor pulmonale. Sudden attempts by an unparalyzed patient to initiate spontaneous breaths (gasp reflex) may also indicate venous air embolism. Hypotension, tachycardia, cardiac arrhythmias, and cyanosis are late signs of venous air embolism. Detection of the characteristic mill wheel murmur, as heard through an esophageal stethoscope, is also a late sign of catastrophic venous air embolism.

Once a venous air embolism is detected, the surgeon should flood the operative site with fluid, apply occlusive material to all bone edges, and attempt to identify any other sources of air entry, such as perforation of a venous sinus. Administration of nitrous oxide should be promptly discontinued to avoid increasing the size of any venous air bubbles. Pure oxygen should be substituted for nitrous oxide. Direct jugular venous compression may increase venous pressure at the surgical site entraining air. Positive end-expiratory pressure to accomplish this same effect has not been shown to be of value as it further impairs venous return to the right side of the heart leading to an exacerbation of systemic hypotension. In cases at risk for a large venous air embolism, such as a posterior fossa craniotomy, the clinician may elect to place a right atrial catheter. The catheter can be placed preferably in the subclavian or antecubital vein. If available, aspiration of air should be attempted through the right atrial catheter. The ideal location for the tip of the right atrial catheter is controversial, but evidence suggests that the junction of the superior vena cava with the right atrium is preferable. Multiorifice right atrial catheters permit aspiration of larger amounts of air than do single-orifice catheters. The use of right atrial catheters for sitting neurosurgery cases is decreasing as the amount of air that can be aspirated in the setting of a very large venous air embolism is typically not enough to modulate outcome.

Extreme hypotension from massive air embolism may require support of the blood pressure using sympathomimetic drugs with inotropic and vasoconstrictive properties. Bronchospasm is treated with β_2-adrenergic agonists delivered by aerosol. Placing the patient in the supine position in cases of severe air embolism can be useful as it will lead to an increase in venous pressure, decreasing further air entrainment, and will allow for effective cardiopulmonary resuscitation. If the patient is to be placed in the supine position, the Mayfield head holder should be disengaged from the arch frame so as to not injure the cervical spine during movement. Although the traditional admonition is to treat venous air embolism by placing the patient in the left lateral decubitus position, this is rarely possible or safe during intracranial surgery. It is likely that attempting to attain this patient position would lose valuable time that would be better spent supporting the circulation.

After successful treatment of small or modest venous air embolism, the surgical procedure can be resumed. However, the decision to reinstitute administration of nitrous oxide must be individualized. If nitrous oxide is not used, maintenance of an adequate depth of anesthesia requires administration of larger doses of volatile or intravenous anesthetics.

Hyperbaric therapy may be useful in the treatment of both severe venous air embolism and paradoxic air embolism. Transfer of patients to a hyperbaric chamber in an attempt to decrease the size of air bubbles and improve blood flow is likely to be helpful only if the transfer can be accomplished within 8 hours.

DISORDERS RELATED TO VEGETATIVE BRAIN FUNCTION

Coma

Coma is a state of profound unconsciousness produced by drugs, disease, or injury affecting the central nervous system. It is usually caused by dysfunction of regions of the brain that are responsible for maintaining consciousness, such as the pontine reticular activating system, midbrain, or cerebral hemispheres. The causes of coma are many and can be divided into two groups: structural lesions (i.e., tumor, stroke, abscess, intracranial bleeding) and diffuse disorders (i.e., hypothermia, hypoglycemia, hepatic or uremic encephalopathy, postictal state following seizures, encephalitis, drug effects). The most common means used to assess the overall severity of coma is the Glasgow Coma Scale (Table 13.1).

TABLE 13.1 Glasgow Coma Score

Response	Score
Eye Opening	
Spontaneous	4
To speech	3
To pain	2
No eye opening	1
Best Motor Response	
Obeys	6
Localizes	5
Withdraws (flexion)	4
Abnormal flexion	3
Extension	2
None	1
Best Verbal Response	
Oriented	5
Confused conversation	4
Inappropriate words	3
Incomprehensible sounds	2
None	1

TABLE 13.2 Abnormal Breathing Patterns Associated With Brain Injury

Abnormality	Pattern	Site of Lesion/ Condition
Ataxic (Biot breathing)	Unpredictable sequence of breaths varying in rate and tidal volume	Medulla
Apneustic breathing	Gasps and prolonged pauses at full inspiration	Pons
Cheyne-Stokes breathing	Cyclic crescendo-decrescendo tidal volume pattern interrupted by apnea	Cerebral hemispheres, congestive heart failure
Central neurogenic hyperventilation	Marked hyperventilation	Cerebral thrombosis or embolism
Posthyperventilation apnea	Awake apnea following moderate decreases in $Paco_2$	Frontal lobes

The initial management of any comatose patient involves establishing a patent airway and ensuring the adequacy of oxygenation, ventilation, and circulation. One should then attempt to determine the cause of coma. This attempt should begin with obtaining a medical history from family members or caretakers, if possible, and conducting a physical examination followed by diagnostic studies. Blood pressure and heart rate assessments are important because they might suggest a cause, such as hypothermia. Respiratory patterns can also aid in diagnosis. Irregular breathing patterns may reflect an abnormality at a specific site in the central nervous system (Table 13.2). The basic neurologic examination can be the key to diagnosis and should, at a minimum, include examination of the pupils and pupillary responses to light, function of the extraocular muscles via reflexes, and gross motor responses in the extremities (Table 13.3).

In cases in which the cause of coma is unknown, useful discriminatory laboratory tests include measurement of serum electrolytes and blood glucose concentrations to assess for disorders of sodium and glucose, as well as the anion gap. Liver and renal function tests help to evaluate for hepatic or uremic encephalopathy. Drug and toxicology screens may help to identify exogenous intoxicants. A complete blood count and results of coagulation studies may suggest the risk of intracranial bleeding from thrombocytopenia or coagulopathy. CT or MRI may reveal a structural cause such as tumor or stroke. A lumbar puncture can be performed if meningitis or subarachnoid hemorrhage is suspected. Outcomes for patients in comatose states depend on many factors but are usually related to the cause and extent of injury to brain tissue.

Management of Anesthesia

Comatose patients may be brought to the operating suite either for treatment of the cause of the coma (e.g., burr hole drainage of an intracranial hematoma) or for treatment of injuries related to the comatose state (e.g., bone fractures caused by a motor vehicle accident in an intoxicated patient). It is important for the anesthesia provider to be aware of the likely cause of the coma since anesthetic management will vary depending on the cause as well as the type of surgery planned. Primary overall goals should be to safely establish an airway, provide adequate cerebral perfusion and oxygenation, and optimize operating conditions. Intraarterial catheterization is useful for blood pressure optimization as well as management of hyperventilation, if needed. Careful attention should be paid to avoiding increases in ICP during stimulating events in those with increased intracranial elastance. Anesthetic drugs that increase ICP, such as ketamine, should be used with caution in those with increased intracranial elastance, but volatile drugs such as isoflurane and sevoflurane used at low doses ($\leq$ 1 MAC) in combination with intravenous cerebral vasoconstrictive anesthetics are acceptable. Administration of nondepolarizing muscle relaxants helps to facilitate tracheal intubation and patient positioning; however, succinylcholine should be used with caution in those with increased ICP since it may transiently lead to further increases in ICP. Succinylcholine can also potentially cause hyperkalemia in patients with preexisting motor deficits and should be avoided in those with motor deficits. Nitrous oxide should be avoided if the patient has known or suspected pneumocephalus (e.g., after recent intracranial surgery, basilar skull fracture).

Brain Death and Organ Donation

Brain death is defined as the permanent and irreversible cessation of total brain function. The original Harvard criteria used to define brain death were established in 1968, and despite currently accepted and published guidelines there remains variability in the diagnosis of brain death in clinical practice. The currently published guidelines include the following:

TABLE 13.3 Neurologic Findings Associated With Progressive Brainstem Compression During Transtentorial Herniation

Region of Compression	Pupillary Examination	Response to Oculocephalic or Cold Caloric Testing	Gross Motor Findings
Diencephalon	Small pupils (2 mm) reactive to light	Normal	Purposeful, semipurposeful, or decorticate (flexor) posturing
Midbrain	Midsize pupils (5 mm) unreactive to light	May be impaired	Decerebrate (extensor) posturing
Pons or medulla oblongata	Midsize pupils (5 mm) unreactive to light	Absent	No response

Prerequisites for brain death testing:

- Coma of an established and irreversible cause with clinical and neuroimaging evidence that is consistent with history
- Absence of sedative or paralytic drugs, as well as severe acid-base, electrolyte, or endocrine abnormality
- Normal or near-normal body temperature (core temperature ≥ 36°C)
- Systolic blood pressure above 100 mm Hg
- No spontaneous ventilation
- All listed tests and assessments of reflexes should be performed after all possible reversible causes of coma have been ruled out:
  a. Lack of spontaneous movement, with the recognition that spinal reflexes may remain intact
  b. Lack of all cranial nerve reflexes and function, including absence of pupil reactivity to bright light; corneal, oculocephalic, and oculovestibular reflexes; cough and gag reflexes; facial movements or motor response to noxious stimuli
  c. Positive result on an apnea test indicating lack of function of the respiratory control nuclei in the brainstem (The test is performed in hemodynamically stable and euvolemic patients by initially ensuring a $Paco_2$ of 40 ± 5 mm Hg and adequate oxygenation with a positive end-expiratory pressure at 5 cm H_2O. The patient is then ventilated with 100% oxygen for 10 minutes for preoxygenation. Then, while vital signs are monitored and the trachea is insufflated with 100% oxygen, mechanical ventilation is discontinued for 10 minutes. There should be no signs of spontaneous respiration, and an arterial blood gas obtained at 8–10 minutes following the cessation of mechanical ventilation must show a $Paco_2$ ≥ 60 mm Hg of a 20 mm Hg rise from normal baseline value. Given that hypercarbia [$Paco_2$ ≥ 60 mm Hg] is a potent stimulus for ventilation, if no respiratory activity is noted, the result of the apnea test is deemed positive.)

During circumstances where the apnea test cannot be reliable performed, such as in patients who have significant preexisting lung disease, additional tests must be completed. Other confirmatory test results include isoelectricity demonstrated by EEG and absence of CBF as demonstrated by various techniques, including transcranial Doppler ultrasonography, cerebral angiography, and magnetic resonance angiography. Of note, EEG isoelectricity may be difficult to document if the patient is within an "electrically noisy" environment (e.g., intensive care unit or operating room) because it will be difficult to discriminate between extraneous electrical noise and brain electrical activity.

Following the establishment of the diagnosis of brain death and discussions with the immediate family, legal guardian, or next of kin, the decision is made either to withdraw artificial means of support or to proceed to organ retrieval if that was the wish of the patient or is the desire of the family or legal guardian.

Management of Anesthesia

The major goal when patients diagnosed with brain death undergo surgery for multiorgan retrieval is to attempt to optimize oxygenation and perfusion of the organs to be retrieved. It is important to be aware of the various physiologic sequelae of brain death and direct physiologic and pharmacologic management with the needs of the organ recipient, not the donor, in mind. Because of loss of central hemodynamic regulatory mechanisms (i.e., the presence of neurogenic shock) brain-dead patients are often hypotensive. Hypovolemia caused by diabetes insipidus, third space losses, or drugs can contribute to hypotension. Aggressive fluid resuscitation should be considered, with efforts made to avoid hypervolemia, which could lead to pulmonary edema, cardiac distention, or hepatic congestion. When treating hypotension, ionotropic drugs are preferred, and vasoconstrictive drugs should be avoided. Dopamine and dobutamine should be first-line drugs for the treatment of hypotension in euvolemic patients, with low-dose epinephrine as a second-line drug. For those in whom the heart is to be retrieved, catecholamine doses should be minimized because of the theoretical risk of catecholamine-induced cardiomyopathy. ECG abnormalities such as ST-segment and T-wave changes, as well as arrhythmias, can occur. Possible causes include electrolyte abnormalities, loss of vagal nerve function, and cardiac contusion (if death was trauma related). Arrhythmias should be treated pharmacologically or by electrical pacing.

Hypoxemia can occur as a result of diminished cardiac output or multiple pulmonary factors such as aspiration, edema, contusion, or atelectasis. Inspired oxygen concentration and ventilatory parameters should be adjusted in an attempt to maintain normoxia and normocapnia. Excessive positive end-expiratory pressure should be avoided because of its effect on cardiac output as well as the risk of barotrauma in the setting of possible trauma-related lung injury. Oxygen delivery to tissues should be optimized by treating coagulopathy and anemia with blood products.

Diabetes insipidus frequently occurs in brain-dead patients and, if not treated, can lead to hypovolemia, hyperosmolality, and electrolyte abnormalities that could contribute to hypotension and cardiac arrhythmias. Treatment should initially include volume replacement with hypotonic solutions titrated to volume status and electrolyte concentrations. In severe cases, patients may need inotropic support and either vasopressin (0.04–0.1 units/hr IV) or desmopressin (0.3 μg/kg IV) to treat the diabetes insipidus. Because of its vasoconstrictive properties, vasopressin use should be minimized to avoid end-organ ischemia. A vasodilator such as nitroprusside may be administered with the vasopressin to avoid vasopressin-induced hypertension and vasoconstriction in end organs.

Because of loss of temperature-regulatory mechanisms, brain-dead patients tend to become poikilothermic and may require aggressive measures to avoid hypothermia. Although mild hypothermia possibly provides some degree of organ protection, it can also result in cardiac arrhythmias, coagulopathy, and reduced oxygen delivery to tissue, thus causing harm to the organs to be retrieved. A good rule of thumb for the management of patients for organ donation is the rule of 100s (systolic blood pressure ≥ 100 mm Hg, urine output ≥ 100 mL/hr, Pao_2 ≤ 100 mm Hg, and hemoglobin level ≥ 100 g/L).

CEREBROVASCULAR DISEASE

Stroke is characterized by sudden neurologic deficits resulting from ischemia (88% of cases) or hemorrhage (12% of cases). Globally, stroke is the leading cause of death and disability. In developed countries, stroke-related mortality has decreased over the past several decades, probably because of better control of coexisting diseases such as hypertension and diabetes, smoking cessation, and greater awareness of stroke risk factors and the clinical cues of stroke onset (allowing faster initiation of treatment).

Other stroke-related disorders of the cerebrovascular system include atherosclerotic disease of the carotid artery, cerebral aneurysm, arteriovenous malformation, and moyamoya disease.

Cerebrovascular Anatomy

Blood supply to the brain is via two pairs of vessels: the internal carotid arteries and the vertebral arteries (Fig. 13.4). These vessels join on the inferior surface of the brain to form the circle of Willis, which, during ideal circumstances, provides collateral circulation to multiple areas of the brain. Unfortunately, all the elements of an intact circle of Willis are present and functional in only about one-third of people as some segments may be hypoplastic or absent. Each internal carotid artery gives rise to an anterior cerebral artery and continues on to become a middle cerebral artery. These vessels arising from the carotid arteries comprise the anterior circulation and ultimately supply the frontal, parietal, and lateral temporal lobes; the basal ganglia; and most of the internal capsule. The vertebral arteries each give rise to a posterior-inferior cerebellar artery before converging at the level of the pons to form the basilar artery. The basilar artery generally gives rise to two anterior-inferior and two superior cerebellar arteries before dividing to become the paired posterior cerebral arteries. Vessels that receive their predominant blood supply from this vertebral-basilar system comprise the posterior circulation and typically supply the brainstem, occipital lobes, cerebellum, medial portions of the temporal lobes, and most of the thalamus. The anterior and posterior circulations communicate via the posterior communicating artery, and the left and right anterior cerebral arteries communicate via the anterior communicating artery. Occlusion of specific arteries distal to the circle of Willis results in predictable clinical neurologic deficits (Table 13.4).

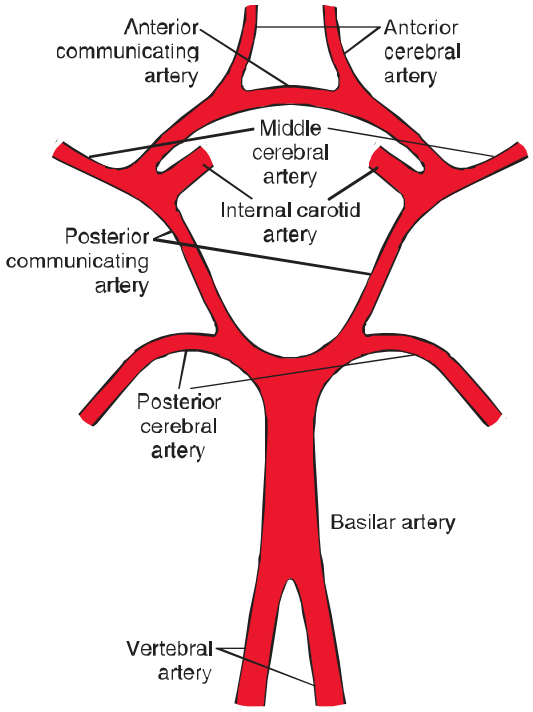

Fig. 13.4 Cerebral circulation and circle of Willis. The cerebral blood supply is from the vertebral arteries (arising from the subclavian arteries) and the internal carotid arteries (arising from the common carotid arteries).

Acute Ischemic Stroke

Patients who experience the sudden onset of neurologic dysfunction or describe neurologic signs and symptoms evolving over minutes to hours are most likely experiencing a stroke. An ischemic stroke is the result of an occlusion of a vessel that supplies a region of brain resulting in cellular ischemia and subsequent cellular death. A transient ischemic attack is a sudden vascular-related focal neurologic deficit that resolves within 24 hours without intervention. Approximately one-third of patients who suffer a transient ischemic attack will subsequently suffer a stroke. Stroke represents a medical emergency, and the prognosis depends on the time elapsed from the onset of symptoms to thrombolytic intervention if thrombosis is the cause of the symptoms. Patients who receive early treatment to restore cerebral perfusion have better outcomes.

Systemic hypertension is the most significant risk factor for acute ischemic stroke, and long-term treatment of systolic or diastolic hypertension dramatically reduces the risk of a first stroke. Cigarette smoking, hyperlipidemia, diabetes mellitus, excessive alcohol consumption, and increased serum homocysteine

TABLE 13.4 Clinical Manifestation of Regional Stroke Syndromes

Occluded Artery	Clinical Features
Anterior cerebral artery	Contralateral leg weakness
Middle cerebral artery	Contralateral hemiparesis and hemisensory deficit (face and arm more than leg) Aphasia (dominant hemisphere) Contralateral visual field defect
Posterior cerebral artery	Contralateral visual field defect Contralateral hemiparesis
Penetrating arteries	Contralateral hemiparesis Contralateral hemisensory deficits
Basilar artery	Oculomotor deficits and/or ataxia with crossed sensory and motor deficits
Vertebral artery	Lower cranial nerve deficits and/or ataxia with crossed sensory deficits

Adapted from Morgenstern LB, Kasner SE. Cerebrovascular disorders. *Sci Am Med.* 2000:1–15.

concentrations are also associated with increased risk of acute ischemic stroke.

In patients with suspected stroke, the brain should be imaged using noncontrast CT, which reliably distinguishes acute intracerebral hemorrhage from ischemia. This distinction is important because treatment of hemorrhagic stroke is substantially different from treatment of ischemic stroke. CT is relatively insensitive to ischemic changes during the first few hours after a stroke but is very sensitive for detection of intracranial bleeding.

Conventional angiography is useful for demonstrating arterial occlusion. The vasculature can also be visualized noninvasively using CT or magnetic resonance angiography. Alternatively, transcranial Doppler ultrasonography can provide indirect evidence of major vascular occlusion and offers the advantage of real-time bedside monitoring in patients undergoing thrombolytic therapy.

The etiologies of acute ischemic stroke are categorized according to the TOAST classification into five groups:

1. Large artery atherosclerosis (e.g., carotid stenosis)
2. Small vessel occlusion (e.g., lacunar stroke)
3. Cardioaortic embolic (e.g., emboli from atrial fibrillation)
4. Other etiology (e.g., stroke due to hypercoagulable states or vasculopathies)
5. Undetermined etiology

Management of Acute Ischemic Stroke

Aspirin by mouth is often recommended as initial therapy in patients with an acute ischemic stroke and for the prevention of recurrent stroke. Intravenous or directed intraarterial recombinant tissue plasminogen activator is used in patients who meet specific eligibility requirements and in whom treatment can be initiated within a limited time window of the onset of acute symptoms due to concern for hemorrhagic transformation. Use of first-generation technologies, such as the MERCI device that consisted of a corkscrew inserted in the occlusive mass to allow for mass removal and the Penumbra device that allowed for aspiration of the occlusive mass, began around 2005. However, data from three large trials published in 2013 showed no benefit of these devices over thrombolytic therapy, an effect that was attributed to two factors: (1) prolonged time for these devices to restore flow in the vessel delaying reperfusion and (2) risk for distal embolization of the fragments of occlusive mass associated with the use of these first-generation devices. Second-generation thrombectomy devices, such as the Solitaire Stent Retriever, allow for rapid restoration of flow by initially stenting the vessel open prior to mass removal. Use of second-generation thrombectomy devices have been shown in multiple large investigations to lead to better outcomes than intravenous or intraarterial thrombolytic therapy. Use of second-generation devices also did not lead to increased risk for complications if used to treat larger vessel occlusion within 24 hours of the time the patient was last known to be well.

Management of Anesthesia for Ischemic Stroke Revascularization

Preanesthetic evaluation should be concise and focused so as not to delay reperfusion. This evaluation should focus on assessment of at least neurologic status, ability to safely lay flat, and cardiovascular function. Assessment of neurologic status could help determine whether sedation could be used or if the patient needs to have the airway secured due to significantly depressed level of consciousness or inability to protect the airway. If the patient is unable to lie flat and remain relatively motionless due to factors such as severe claustrophobia, excessive anxiety, full stomach with significant gastroesophageal reflux, or pulmonary disorders that make spontaneous respiration difficult in the supine position, then sedation may be difficult. Patients with ischemic stroke frequently have cardiovascular risk factors, including hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, and structural cardiac problems, such as valvular disease, that could impact vasoactive drug choices and hemodynamic goals during the procedure.

Stroke revascularization is conducted within the interventional radiology suite allowing for angiographic assessment of vascular anatomy and site of occlusion as well as radiographic guidance of administration of intraarterial thrombolytics or performance of mechanical thrombectomy. Clinicians should take care to minimize exposure of themselves to radiation. This includes not only wearing lead aprons but also utilizing lead shields, which can help minimize exposure of the eyes since chronic x-ray exposure is associated with increased risk for cataracts. One should also be prepared to manage complications specific to the interventional radiology suite such as acute contrast reactions.

Patient monitors should include American Society of Anesthesiologists standard monitors. Continuous invasive blood pressure monitoring is critical to manage blood pressure and to obtain blood samples for laboratory tests. This continuous monitoring can be accomplished via the arterial access port used by the radiologist to perform the procedure. Additional arterial access can be helpful prior to induction of general anesthesia to help avoid induction-associated hypotension, but the procedure should not be delayed in order to obtain arterial access.

Either monitored anesthesia care, with or without sedation, or general anesthesia can be used to facilitate endovascular management of acute ischemic stroke. Monitored anesthesia care with or without sedation will require a cooperative patient who is able to lie flat and motionless. One major advantage of monitored anesthesia care is that it allows for continual neurologic assessment of the patient. General anesthesia may be required if the patient cannot lay flat, cannot protect the airway, or is unable to remain motionless. In patients with significant neurologic impairment, endotracheal intubation may be required with minimal use of sedative/hypnotic drugs. In patients who would be candidates for either technique, earlier retrospective data suggested that overall outcome was worse in patients who received general anesthesia. However, these data were biased in that patients with greater neurologic impairment were more likely to receive general anesthesia. Multiple prospective trials that randomized patients who would be candidates for either technique to receive either general anesthesia or monitored anesthesia care did not demonstrate

increased risk or poorer outcome in those who received general anesthesia. Additionally, general anesthesia was not associated with delay in revascularization. Therefore the choice of anesthetic technique should be made on an individualized basis, and general anesthesia should not be dogmatically avoided. There is currently no data to support that any drug or group of drugs used to provide sedation or general anesthesia is superior to any other set of drugs. In patients who receive general anesthesia, a rapid sequence induction should be performed if the patient meets full stomach criteria. In those who receive monitored anesthesia care, drugs and equipment required to convert to general anesthesia with a secured airway should be immediately available.

Independent of anesthetic technique, oxygen should be titrated to maintain Pao_2 above 60 mm Hg and Sao_2 above 92%. Prior to restoration of blood flow to the ischemic region of brain, systolic blood pressure should be maintained between 140 and 180 mm Hg and diastolic blood pressure below 105 mm Hg. Following revascularization, blood pressure should be decreased to 120 to 140 mm Hg to minimize risk for hemorrhagic transformation of the ischemic region of brain. In patients who receive monitored anesthesia care, the neurologic exam can be used to further titrate blood pressure. Fluids should consist of isotonic solutions that are titrated to maintain euvolemia. Hyperglycemia is common in patients with acute stroke, even in those without diabetes mellitus. Serum blood glucose should be monitored. It is reasonable to maintain blood glucose concentrations between 140 and 180 mg/dL. Serum glucose concentrations below 60 mg/dL should be rapidly treated with intravenous dextrose solution. A goal core temperature of 35°C to 37°C should be maintained. Hyperthermia is associated with adverse outcomes and current data do not suggest a benefit from induced hypothermia in patients with acute ischemic stroke. Heparin is frequently administered to maintain an activated clotting time (ACT) of 250 to 300 seconds, and heparin is generally not reversed with protamine at the end of the procedure to minimize risk of thrombotic complications. Following the procedure, the patient should be monitored in an intensive care unit.

One of the most feared complications during endovascular treatment of acute ischemic stroke is intracranial hemorrhage that could be due to iatrogenic arterial perforation or hemorrhagic transformation. Intracranial hemorrhage can present as new neurologic deficits, acute decreased level of consciousness, hemodynamic instability, or evidence of contrast extravasation on radiographic imaging. Immediate management includes notifying a neurosurgeon and decreasing systolic blood pressure to just below 140 mm Hg, as increased blood pressure can exacerbate bleeding, but excessively low blood pressure can result in impaired cerebral perfusion if ICP is elevated. In consultation with the proceduralist, the decision should be made as to whether or not to reverse heparin with protamine and whether or not to reverse any other anticoagulants or antiplatelet drugs. Tissue plasminogen activator can be reversed by administering two units each of platelets, fresh frozen plasma, and cryoprecipitate with administration of further blood products guided by laboratory data.

Perioperative and Periprocedural Stroke

Most perioperative strokes are ischemic, and patients undergoing cardiac, neurologic, and major vascular surgery are at greatest risk for stroke. Invasive radiologic procedures performed on the heart and major arteries also carry a risk for periprocedural stroke. The higher incidence of stroke in these patient populations is related to (1) a higher incidence of baseline stroke risk factors (e.g., hypertension, atherosclerosis, diabetes mellitus), (2) risks of perioperative emboli (e.g., open cardiac procedures, invasive radiologic procedures to the cerebrovasculature), and (3) acute alterations in systemic physiology, including systemic or regional hypotension resulting in impairment of blood flow.

Patients having noncardiovascular and nonneurologic surgery and procedures are still at risk for perioperative stroke. Overall, the risk for perioperative symptomatic stroke in adults having noncardiovascular and nonneurologic procedures is about 0.1%, with patients having amputations, abdominal exploration, and small bowel resection at greatest risk.

Risk factors for symptomatic perioperative stroke include increasing age, myocardial infarction within 6 months, renal dysfunction, history of stroke or transient ischemic attack, hypertension, chronic obstructive pulmonary disease, smoking, and preoperative or intraoperative metoprolol use. β blockers, especially metoprolol, should be instituted with caution in the perioperative period and titrated with care to avoid hypotension.

Patients who suffer a perioperative stroke have an eightfold increased risk for death within 30 days of surgery compared to those who did not suffer a stroke. Elective surgery should be delayed following a stroke for up to 9 months to allow for return of cerebral autoregulation, risk factor reduction, and treatment of underlying stroke etiology, if one can be identified.

If perioperative stroke occurs, it should be recognized early. That can be difficult in the perioperative period because patients may have residual effects from general anesthetics or sedatives. One should have an index of suspicion for stroke in the postoperative period if a patient's mental status does not improve as expected, a relationship between opioid administration and fluctuations in consciousness can be ruled out, or there is evidence of a focal neurologic deficit. If one has a high suspicion for stroke, a gross neurologic examination should be conducted and documented to establish a baseline and note focal deficits. Downstream, the patient should undergo a noncontrast CT of the head to rule out other causes such as intracranial hemorrhage. If suspicions for stroke are confirmed, a neurologist or equally qualified expert should be consulted to determine if the patient is a candidate for thrombolytics despite recent surgery. Meanwhile, oxygen delivery to the brain should be optimized by avoiding hypoxia and hypotension.

Perioperative covert stroke is a new focal region of cerebral ischemic injury following surgery and anesthesia that is without clinical manifestations and is only evident on brain MRI. Covert stroke occurs in about 7% of patients older than 65 years having elective, noncardiac surgery. Risk factors for covert stroke appear to only be increasing age. Sex, prior history of stroke or transient ischemic attack, history of vascular disease, type of surgery, and anesthetic technique do not appear to influence risk

for covert stroke. Patients who have a covert stroke are also at increased risk for perioperative delirium as well as overt stroke and cognitive decline 1 year following surgery.

Acute Hemorrhagic Stroke

Acute hemorrhagic stroke results from the extravasation of blood in the cranial vault that in turn impairs perfusion of normal brain. Hemorrhagic stroke is four times more likely to cause death than is ischemic stroke. Acute hemorrhagic stroke cannot be reliably distinguished from ischemic stroke based on clinical criteria alone. A noncontrast CT evaluation is needed to detect the presence of bleeding. The estimated volume of extravasated blood and the level of consciousness are the two most reliable predictors of outcome.

Subtypes of hemorrhagic strokes are defined based on the location of blood. Blood located within the brain proper is called an intraparenchymal hemorrhage. Blood located in the epidural, subdural, or subarachnoid spaces are referred to as epidural hematoma, subdural hematoma, and subarachnoid hemorrhage, respectively. Also, blood located in the ventricular system is an intraventricular hemorrhage, and it is usually not an isolated event but instead occurs in the setting of other types of hemorrhagic stroke.

Intraparenchymal Hemorrhage

Intraparenchymal hemorrhage, also known as intracerebral hemorrhage, refers to a collection of blood in the brain parenchyma. A primary intraparenchymal hemorrhage can occur in the absence of a gross anatomic source (e.g., arteriovenous malformation) for the hemorrhage. It occurs at a higher rate in blacks and those with poorly controlled hypertension. Secondary causes of intraparenchymal hemorrhage are rupture of an arteriovenous malformation, trauma, or bleeding from a brain tumor. Patients with intracerebral hemorrhage often deteriorate clinically as a result of hematoma expansion or cerebral edema that worsens during the first 24 to 48 hours following the acute bleed. Late hematoma evacuation is ineffective at decreasing mortality. The efficacy of earlier surgical evacuation of a hematoma to decrease ischemic injury and edema to the surrounding tissue remains unclear. More recently, the stereotactic intracerebral hemorrhage underwater blood aspiration (SCUBA) technique has been described as a treatment for intraparenchymal hemorrhage. The SCUBA technique involves stereotactic implantation of a small catheter into the hematoma allowing for aspiration of blood and a decrease in hematoma size. Intravenous administration of recombinant activated factor VII has also been tried and has minimal effect on hematoma expansion rate, no significant effect on overall outcome, and may increase risk for arterial thrombosis.

Intraventricular hemorrhage is a particularly ominous form of intracranial hemorrhage because the blood will occlude CSF drainage. Prompt ventricular drainage should be performed to treat any signs of hydrocephalus. Sedation, with or without drug-induced skeletal muscle paralysis, is often helpful in managing patients who require prolonged tracheal intubation to protect the airway and manage ventilation and oxygenation.

The goal of blood pressure management involves balancing the need to maintain cerebral perfusion while decreasing risk for rebleeding or hematoma expansion. The American Heart Association and American Stroke Association recommend the following:

- In patients with an initial systolic blood pressure between 150 and 220 mm Hg, systolic blood pressure should be decreased to a goal of 140 mm Hg. Further decreases in blood pressure do not improve neurologic outcome and may predispose to renal injury.
- In patients with an initial systolic blood pressure above 220 mm Hg, systolic blood pressure should aggressively be decreased to 140 to 160 mm Hg.

The choice of antihypertensive drug used to decrease blood pressure should depend on extent of desired blood pressure reduction, titratability, patient comorbidities, and clinician experience.

Epidural Hematoma

Epidural hematoma most commonly occurs in the setting of trauma. The arteries that supply the dura mater are located between the dura mater and the periostium of the cranial bones, and epidural hematoma is generally due to traumatic rupture of a meningeal artery. Generally, patients have a lucid interval following trauma but, as blood accumulates in the epidural space, hematoma volume can compress the brain and decrease perfusion. This results in progressive alterations in consciousness corresponding with ICP increases and CPP decreases. The prognosis following early hematoma evacuation is excellent.

Subdural Hematoma

Subdural hematoma occurs when blood accumulates between the dura mater and arachnoid layer. Most commonly, subdural hematoma occurs in the setting of trauma. This can occur following either major or minor trauma, with the latter often occurring in older patients with cerebral atrophy (i.e., a condition than lends itself to stretching and rupture of bridging veins that run in the subdural space). Patients who take chronic anticoagulants and antiplatelet drugs are at greatest risk. As with epidural hematomas, early evacuation is associated with better outcome.

Signs and symptoms of a subdural hematoma characteristically evolve gradually over several days because the hematoma is due to slow venous bleeding. Headache is a universal complaint. Drowsiness and obtundation are characteristic findings, but the magnitude of these changes may fluctuate from hour to hour. Lateralizing neurologic signs eventually occur, manifesting as hemiparesis, hemianopsia, or language disturbances. Elderly patients may have unexplained signs of progressive cognitive decline or dementia.

Conservative medical management of subdural hematomas may be acceptable for patients whose condition stabilizes, but surgical evacuation of the clot is desirable in most patients. Most subdural hematomas can be drained via burr holes; the procedure can be performed during general anesthesia, local anesthesia, or monitored anesthesia care. If the subdural

hematoma is particularly large, is chronic, or consists of clotted blood, removal may require craniotomy. Because a subdural hematoma is usually caused by venous bleeding, normocapnia is desirable following evacuation of the hematoma to allow for a larger brain volume, which may help to tamponade any sites of venous bleeding. Following hematoma evacuation, it may be best to avoid significant head elevation if the patient is able to tolerate a more horizontal position. The horizontal position allows for a large brain volume due to increased venous blood volume that can tamponade further bleeding.

Subarachnoid Hemorrhage and Intracranial Aneurysms

Spontaneous subarachnoid hemorrhage most commonly results from rupture of an intracranial aneurysm. Various pathologic conditions such as hypertension, coarctation of the aorta, polycystic kidney disease, fibromuscular dysplasia, and the occurrence of cerebral aneurysms in first-degree relatives are associated with the presence of cerebral aneurysms. Larger aneurysms are more likely to rupture. Other risk factors for rupture include hypertension, cigarette smoking, cocaine abuse, female sex, and use of oral contraceptives.

Patients may also present clinically with unruptured aneurysms. A common presentation of an unruptured aneurysm is the development of a new focal neurologic deficit. The cause of this new deficit may be either a mass effect from an expanding aneurysm that compresses normal neurologic structures or small emboli to the distal cerebral circulation from a thrombus contained within the aneurysm. Headache caused by mass effect can occur. New-onset seizures can indicate an unruptured aneurysm and are thought to result from the formation of a glial scar (gliosis) in brain parenchyma adjacent to the aneurysm. Unruptured aneurysms may also be identified incidentally on cerebral imaging performed for unrelated reasons. Aneurysm diameter is not static. Thus, although smaller aneurysms may be followed with serial imaging, larger aneurysms are often considered for treatment because of their increased risk for spontaneous rupture.

Signs and symptoms of subarachnoid hemorrhage include severe headache, photophobia, nuchal rigidity, focal neurologic deficits, and decreased level of consciousness. The diagnosis is confirmed by CT demonstration of subarachnoid blood as MRI is not as sensitive as CT for detecting acute hemorrhage. MRI may be useful for demonstrating subacute or chronic subarachnoid hemorrhage or infarction after CT findings have returned to normal. In patients where there is a strong suspicion for subarachnoid hemorrhage even with a negative head CT, lumbar puncture with CSF analysis (especially evaluating red blood cell count in successive collection tubes and xanthochromia) should be performed. Prompt establishment of the diagnosis followed by treatment of the aneurysm can decrease morbidity and mortality. Two of the most common methods used to grade the severity of subarachnoid hemorrhage are the Hunt and Hess classification and the World Federation of Neurologic Surgeons grading system (Table 13.5). These grading systems are useful because their stratification of severity helps prognosticate outcome and the efficacy of various therapies.

A significant increase in serum catecholamine concentration is associated with acute subarachnoid hemorrhage, with greater concentration increases being associated with worsened severity of subarachnoid hemorrhage. This increase in serum catecholamines can impact the cardiovascular system. Manifestations include changes in the ECG, such as ST-segment depression, T-wave inversion, and various arrhythmias. A mild increase in serum cardiac enzymes can also occur. On echocardiography, decreased myocardial contractility, regional wall motion abnormalities that do not follow a distribution of a coronary artery, and Takotsubo cardiomyopathy can be observed. Of note, apical cardiac function may be preserved, a phenomenon attributed to the paucity of sympathetic innervation at the cardiac apex.

TABLE 13.5 Two Common Grading Systems for Subarachnoid Hemorrhage Severity

The Hunt and Hess Classification and the World Federation of Neurological Surgeons Grading System

HUNT AND HESS CLASSIFICATION

Score	Neurologic Finding	Mortality
0	Unruptured aneurysm	0%–2%
1	Ruptured aneurysm with minimal headache and no neurologic deficits	2%–5%
2	Moderate to severe headache, no deficit other than cranial nerve palsy	5%–10%
3	Drowsiness, confusion, or mild focal motor deficit	5%–10%
4	Stupor, significant hemiparesis, early decerebration	25%–30%
5	Deep coma, decerebrate rigidity	40%–50%

WORLD FEDERATION OF NEUROLOGIC SURGEONS GRADING SYSTEM

Score	Glasgow Coma Scale Score	Presence of Major Focal Deficit
0		Intact, unruptured aneurysm
1	15	No
2	13 or 14	No
3	13 or 14	Yes
4	7–12	Yes or no
5	3–6	Yes or no

Treatment of subarachnoid hemorrhage involves localizing the aneurysm with conventional or magnetic resonance angiography and operatively excluding the aneurysmal sac from the intracranial circulation while preserving its parent artery, if possible. Depending on the location and characteristics of the aneurysm, and the volume and placement of associated bleeding, this can be accomplished by craniotomy and surgery or via invasive radiologically guided techniques (e.g., aneurysm coiling). Outcome is optimal when surgical treatment is performed within the first 72 hours after bleeding. Operative surgical treatments include placement of a clip across the neck of the aneurysm with aneurysm wrapping or trapping reserved for very large aneurysms or those that lack a definitive neck. In aneurysm trapping, a clip is placed on the artery both proximal and distal to the aneurysm after the artery distal to the aneurysm has been bypassed, usually by means of the superficial temporal artery. Endovascular techniques involve placing soft metallic coils in the dome of an aneurysm or placement of a stent in the parent artery so that the walls of the stent do not allow blood flow into the aneurysm.

Surgery is often delayed in patients with severe symptoms, such as coma. In these patients, other options, including interventional radiographic procedures, may be used. Anticonvulsants are administered should seizure activity occur. Systemic blood pressure is controlled, in recognition that hypertension increases the risk of rebleeding. Hydrocephalus is common after subarachnoid hemorrhage and is treated with ventricular drainage. Any change in mental status must be promptly evaluated by CT to look for signs of rebleeding or hydrocephalus.

Following subarachnoid hemorrhage with or without surgical or endovascular treatment of the aneurysm, an important goal is prevention of vasospasm (intracranial arterial narrowing) and its consequences. Development of vasospasm can be triggered by many mechanisms, the most important of which is the contact of free hemoglobin with the abluminal surface of cerebral arteries. Not surprisingly, the incidence and severity of vasospasm correlate with the amount of subarachnoid blood seen on CT. Vasospasm typically occurs 3 to 15 days after subarachnoid hemorrhage. For this reason, daily transcranial Doppler ultrasonographic examinations may be performed to detect and follow the efficacy of treatment of cerebral vasospasm. Nimodipine, a calcium channel blocker, has been shown to decrease risk of developing vasospasm and may improve outcome in those who develop vasospasm when initiated on the first day of the bleed and continued for 21 days after subarachnoid hemorrhage. If vasospasm is identified, triple H therapy (*h*ypertension, *h*ypervolemia, passive *h*emodilution) was traditionally initiated. However, currently only hypertension is generally employed with the goal of maintaining euvolemia, as complications such as pulmonary edema and other adverse complications related to hypervolemia and hemodilution, if they occur, can negatively impact outcome. In addition to hypertension, cerebral vasospasm can be treated angiographically with either balloon dilatation or via directed instillation of vasodilators, such as papaverine, nicardipine, milrinone, or verapamil, into the spastic vessels.

Management of anesthesia. The goals of anesthesia during intracranial aneurysm clipping surgery are to limit the risk of aneurysm rupture, prevent cerebral ischemia, and facilitate surgical exposure.

The goal during the induction of anesthesia is to prevent any increase in the transmural pressure of the aneurysmal sac, which could increase the risk of aneurysm rupture. Therefore significant increases in systemic blood pressure must be avoided. In those patients with cerebral aneurysms without increased ICP and in those with unruptured aneurysms, it is reasonable to avoid excessive decreases in ICP before dural opening so as not to diminish the tamponading force on the external surface of the aneurysm. Profound hyperventilation then should be avoided. Patients who have increased ICP before surgery present a challenge because they may not tolerate a decrease in MAP to protect against aneurysm rupture without developing cerebral ischemia. Patients with vasospasm also present a quandary because systemic hypertension may improve flow through vasospastic vessels but may increase the risk of aneurysm rebleeding. Aneurysm clipping during the period in which the patient is at high risk of vasospasm is associated with increased mortality. Therefore, in patients with vasospasm who require anesthetic care, CPP should be kept elevated to maintain blood flow through vasospastic arteries.

Monitoring of the blood pressure via an intraarterial catheter is desirable to ensure the adequacy of blood pressure control during direct laryngoscopy and at other times of noxious stimulation. Prophylaxis against significant hypertension during direct laryngoscopy may be accomplished by administration of esmolol, lidocaine, propofol, clevidipine, or short-acting opioids. Loss of consciousness is achieved with intravenous administration of propofol, or etomidate. Nondepolarizing neuromuscular blocking drugs are most often selected to facilitate tracheal intubation.

Placement of a CVP catheter may be useful because of large intraoperative fluid shifts associated with osmotic diuretics, intraoperative aneurysm rupture, and the need for fluid resuscitation. However, for a patient with an unruptured aneurysm or one with a lower-grade subarachnoid hemorrhage having surgery with a skilled surgeon, a CVP catheter may not be necessary. A pulmonary artery catheter or transesophageal echocardiography may be considered when patients have known cardiac disease. Electrophysiologic monitoring (EEG, somatosensory or motor-evoked potentials) may be helpful to identify intraoperative cerebral ischemia.

The goals of anesthesia maintenance include providing a depth of anesthesia appropriate to the level of surgical stimulation, facilitating surgical exposure through optimal brain relaxation, maintaining CPP, reducing transmural pressure in the aneurysm during dissection and clip placement, and prompt awakening of the patient at the end of the procedure to permit immediate neurologic assessment. Drugs, fluid, and blood must be immediately available to manage resuscitation should the aneurysm rupture intraoperatively. The risk of intraoperative rupture is approximately 7%, and rupture most commonly occurs during the late stages of surgical dissection and during clip placement. Anesthetic management of rupture consists of aggressive volume resuscitation to maintain normovolemia combined with controlled hypotension to temporarily limit

hemorrhage and permit the neurosurgeon to gain control of the aneurysm. Hypotension will reduce the turgor on the aneurysm sack to facilitate clipping. Options to induce hypotension include esmolol, nitroprusside, and clevidipine. Additionally, bolus doses of adenosine can be administered to cause sinus arrest allowing for significant, but temporary, hypotension and circulatory arrest.

Anesthesia is typically maintained with volatile anesthetics (isoflurane, desflurane, sevoflurane) with or without the addition of nitrous oxide and may be supplemented with intermittent (fentanyl) or continuous (remifentanil) infusion of opioids. Alternatively, a total intravenous anesthetic technique (e.g., propofol and short-acting opioid) can be used. Cerebral vasoconstricting anesthetics, such as propofol, help reduce brain volume and may provide some degree of neuronal protection against ischemia. Muscle paralysis is critical to prevent movement during aneurysm clipping. Also, electrophysiologic monitoring, such as somatosensory or motor evoked potential monitoring, may be employed and will require changes in anesthetic plan to facilitate monitoring.

Patients may have hydrocephalus as a result of hematoma volume, brain edema, or obstruction of arachnoid granulations by blood thus impairing the reabsorption of CSF. Therefore optimization of brain relaxation is an important part of anesthetic maintenance, and combinations of lumbar CSF drainage, mild hyperventilation, administration of osmotic diuretics, and proper positioning to facilitate cerebral venous drainage can help to optimize surgical exposure. The timing and extent of these interventions is critical to achieving overall management goals. Normovolemia is the goal for fluid administration and is best achieved by intravenous administration of balanced salt solutions. Intravenous solutions containing glucose are not recommended because of fear of exacerbating neuronal injury. Current best evidence suggests no benefit to intraoperative hypothermia in patients undergoing aneurysm clipping. However, hyperthermia must be avoided because it increases $CMRO_2$ and CBV.

Long ago, drug-induced controlled hypotension was used to decrease transmural pressure in the aneurysm and thereby decrease the risk of aneurysm rupture during surgery. Controlled hypotension is rarely used now because of concerns about the impairment of autoregulation that follows subarachnoid hemorrhage, unpredictable cerebrovascular responses to drug-induced hypotension, and the risk of global ischemia. Instead, regional controlled hypotension produced by placing a vascular clamp on the parent artery supplying the aneurysm provides protection against aneurysm rupture without incurring the risk of global cerebral ischemia. Ideally, temporary occlusion of the parent artery does not exceed 10 minutes. If longer periods of occlusion are needed, the administration of metabolism-suppressing anesthetics, such as propofol, might provide protection against regional cerebral ischemia and infarction. Propofol dosing is optimally titrated to achieve burst suppression in the electroencephalogram. However, the utility and efficacy of this intervention remains controversial. During temporary clamping of the feeding vessel, systemic blood pressure should be maintained toward the higher end of the patient's normal blood pressure range to encourage collateral circulation.

At the conclusion of the surgical procedure, prompt emergence from anesthesia is desirable to facilitate immediate neurologic evaluation of the patient. Once the aneurysm is isolated from the circulation there is no longer concern for rupture, and avoidance of hypertension become less crucial. In general, maintenance of systolic blood pressures below 160 mm Hg is a reasonable goal and can be accomplished by administration of antihypertensives, such as labetalol or esmolol. Tracheal extubation immediately after surgery is acceptable and encouraged in patients who are awake with adequate spontaneous ventilation and protective upper airway reflexes. Patients who were obtunded preoperatively are likely to require continued intubation and mechanical ventilation during the postoperative period. Patients who experience intraoperative rupture of an intracranial aneurysm may recover slowly and benefit from postoperative airway and ventilatory support.

Neurologic status is assessed at frequent intervals in the postanesthesia care unit or intensive care unit. Patients may manifest delayed emergence from anesthesia or focal neurologic deficits after intracranial aneurysm surgery, and it may be difficult to distinguish between drug-induced causes and surgical causes. The appearance of a new focal deficit should raise suspicion of a surgical cause since—in all instances other than differential awakening—anesthetic drugs would be expected to cause primarily global effects. Inequality of pupils that was not present preoperatively is also likely to reflect a surgical event. CT or angiography may be necessary if the patient does not awaken promptly. Successful surgical therapy may be followed by delayed neurologic deficits (hours to days later) resulting from cerebral vasospasm. This in turn requires aggressive therapy, including hypertension or invasive radiographic interventions.

The anesthetic goals for patients undergoing angiographically guided cerebral aneurysm coil placement are similar to those for patients undergoing aneurysm clip placement. Typically, coil placement or stenting procedures are performed using sedation or general anesthesia. The principal advantage of sedation is that intraprocedural neurologic assessment can be performed. However, patient movement during the procedure poses the risk of aneurysm rupture or coil dislodgment resulting in coil embolization. For this reason, general anesthesia is preferred during coil placement. Anesthetic goals include ICP control, maintenance of adequate cerebral perfusion without excessive hypertension, and facilitation of a rapid postprocedural assessment of neurologic function.

Arteriovenous Malformation

Arteriovenous malformations (AVMs) are abnormal collections of blood vessels in which multiple direct arterial-to-venous connections exist without intervening capillaries. There is also no neural tissue within the nidus. AVMs typically represent high-flow, low-resistance shunts, with vascular intramural pressure being less than systemic arterial pressure. Thus rupture does not appear to be clinically associated with acute or chronic hypertension. These malformations are believed to be congenital.

Signs and symptoms of AVMs include headache, new focal neurologic deficits due to edema or compression of normal brain, acute hemorrhage, or seizure. The exact cause of AVM-associated seizures is unknown but has been attributed to either steal (e.g., shunting of blood away from normal brain tissue toward the low-resistance AVM) or gliosis due to hemosiderin deposits from previous hemorrhage. Most AVMs are supratentorial. An aneurysm can be found on the feeding artery in 4% to 10% of AVMs. AVMs presenting in the neonatal or childhood period usually involve the vein of Galen, and presenting symptoms include hydrocephalus or macrocephaly and prominence of forehead veins, as well as evidence of a high-output cardiac state or heart failure. Diagnosis is made by either MRI or angiography.

Before the advent of focused, high-dose radiation and selective cerebral angiography-based treatment regimens, primary surgical treatment of AVMs was associated with a high morbidity and mortality. Currently, treatment may involve a combination of radiation, such as with gamma knife, angiographically guided embolization, and/or surgical resection. With smaller AVMs, patients may respond completely to radiation or embolization therapy. With larger AVMs, however, these two techniques are typically used as adjunctive therapy before surgery to decrease the size of the AVM nidus and reduce both the complexity and risks of surgery. Prognosis and perioperative outcome can be estimated using the Spetzler-Martin AVM grading system, which classifies the AVM based on three features (Table 13.6).

Other types of intracranial AVMs include venous angiomas, cavernous angiomas, capillary telangiectasias, and arteriovenous fistulas.

TABLE 13.6 Spetzler-Martin Arteriovenous Malformation (AVM) Grading System

Graded Feature	Points Assigned
Nidus Size	
Small (<3 cm)	1
Medium (3–6 cm)	2
Large (>6 cm)	3
Eloquence of Adjacent Brain[a]	
Noneloquent	0
Eloquent	1
Pattern of Venous Drainage	
Superficial only	0
Deep only or deep and superficial	1

SURGICAL OUTCOME BASED ON SPETZLER-MARTIN AVM GRADE

Total Number of Points	Percent of Patients With No Postoperative Neurologic Deficit
1	100
2	95
3	81
4	73
5	69

Adapted from Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg.* 1986;65:476–483.
[a]Eloquent brain includes the sensory, motor, language, and visual areas as well as the hypothalamus, thalamus, internal capsule, brainstem cerebellar peduncles, and deep nuclei.

Venous Angioma

Venous angiomas or malformations consist of tufts of veins. Often they are occult lesions found during cerebral angiography or MRI performed to evaluate other disease states. Rarely will a venous angioma present as either hemorrhage or new-onset seizures. These are low-flow, low-pressure lesions and usually contain intervening brain parenchyma within the nidus; they are therefore treated only if bleeding or intractable seizures occur.

Cavernous Angioma

Cavernous angiomas, also known as cavernous hemangiomas or cavernomas, are typically benign lesions consisting of vascular channels without large feeding arteries or large veins. Brain parenchyma is not found within the nidus of the lesion. These low-flow, well-circumscribed lesions often present as new-onset seizures but occasionally manifest as hemorrhage. They may be seen on CT or MRI scans and typically appear as a flow void on cerebral angiograms. Treatment involves surgical resection of symptomatic lesions.

Capillary Telangiectasia

Capillary telangiectasias are low-flow, enlarged capillaries and are probably one of the least understood vascular lesions in the central nervous system. They are angiographically silent and difficult to diagnose antemortem. The risk of hemorrhage is low except for lesions occurring in the brainstem. They are often found incidentally at autopsy and are often associated with other disorders, including Osler-Weber-Rendu syndrome and Sturge-Weber syndrome.

Arteriovenous Fistula

Arteriovenous fistulas are direct communications between arteries and veins without an intervening nidus of smaller blood vessels. They commonly occur between meningeal vessels within the dura mater or between the carotid artery and venous sinuses within the cavernous sinus. Some arteriovenous fistulas are thought to occur spontaneously. Many others are associated with a previous traumatic injury or, in the case of carotid-cavernous fistulas, with previous rupture of an intracavernous carotid artery aneurysm. Dural arteriovenous fistulas commonly present with pulsatile tinnitus or headache. An occipital bruit can be appreciated in 24% of these cases since the occipital artery is a common arterial feeder of an arteriovenous fistula. Treatment options include angiographically guided embolization or surgical ligation. Surgical treatment is associated with a risk of rapid and significant blood loss.

Patients with carotid-cavernous arteriovenous fistulas often have orbital or retroorbital pain, arterialization of the conjunctiva, or visual changes. Diagnosis is made by magnetic resonance

or conventional angiography. Embolization is usually an effective treatment option.

Management of Anesthesia

Surgical resection of low-flow vascular malformations, such as cavernous angiomas, is generally associated with fewer intraoperative and postoperative complications than resection of high-flow vascular lesions such as AVMs and arteriovenous fistulas. AVMs often involve multiple feeding and draining vessels, unlike arteriovenous fistulas, which involve a single feeding and a single draining vessel. As such, surgical resection of AVMs can pose greater clinical challenges during resection and postoperative care.

Preoperatively, a patient with an intracranial vascular malformation should be evaluated for evidence of cerebral ischemia or increased ICP. The nature of the malformation—including size, location, mechanism of venous drainage; presence of associated aneurysms; and any prior treatment—should be elicited since these factors may help in anticipating perioperative complications. Medications, including antiepileptic drugs if the patient has a concurrent seizure disorder, should be continued through the perioperative period.

In addition to standard monitoring, an intraarterial catheter may be placed before induction of anesthesia. Blood pressure control throughout anesthesia, surgery, and the postoperative period is critical since hypotension may result in ischemia in hypoperfused areas, and hypertension may increase the risk of rupture of an associated aneurysm, exacerbate intraoperative bleeding, or worsen intracranial hypertension. For embolization or surgical resection of a vascular malformation in an eloquent region of brain, monitored anesthesia care is an attractive option. In cases requiring general anesthesia, a hemodynamically stable induction is desirable, although AVMs—unlike cerebral aneurysms—are unlikely to bleed even with moderate increases in blood pressure. Propofol and etomidate are effective and safe induction drugs. Muscle relaxation should be accomplished with a nondepolarizing neuromuscular blocking drug since succinylcholine may induce further increases in ICP as well as cause hyperkalemia if motor deficits are present. Techniques to blunt the hemodynamic responses to stimulating events such as laryngoscopy, pinion placement, and incision should be used as needed. These techniques may include lidocaine, esmolol, clevidipine, or nitroprusside or deepening of the anesthetic state with either higher concentrations of volatile anesthetics, small doses of intravenous anesthetics, or short-acting opioids.

Given the risk of severe and rapid intraoperative hemorrhage during resection, especially with AVMs and arteriovenous fistulas, adequate intravenous access is essential. Further, central venous access may be useful in some cases to monitor volume status or to allow rapid administration of large volumes of fluids or blood products. Monitoring via a pulmonary artery catheter or transesophageal echocardiography can be useful in patients with cardiac disease.

In cases of large or high-flow vascular malformations, frequent communication with the surgeon is of paramount importance because surgical and anesthetic goals for safe resection may change during the operation. This is due in part to changing surgical requirements during various stages of resection of a large, complex lesion. Hemodynamic stability, optimal surgical conditions, and rapid emergence from anesthesia at the end of surgery are appropriate goals when selecting anesthetic maintenance medications. Both intravenous and volatile anesthetic–based techniques are appropriate.

Hypotonic and glucose-containing solutions should be avoided since the former can exacerbate cerebral edema and the latter can worsen outcome following neurologic ischemia. Mild hyperventilation ($Paco_2$ of 30–35 mm Hg) will help facilitate surgical exposure. Lumbar CSF drainage may also help to decrease intracranial volume and improve exposure. Cerebral edema of surrounding brain tissue can be a significant problem during and following AVM resection. As edema often develops despite normal systemic blood pressure, the etiology is referred to as normal perfusion pressure breakthrough. The exact mechanism leading to normal perfusion pressure breakthrough is not exactly clear but has been attributed to two possible causes. First, because AVMs represent high-flow, low-resistance vascular lesions, as arterial feeders are ligated during resection or embolization, blood flow is then directed toward the surrounding brain tissue. These surrounding blood vessels may have experienced a chronic reduction in vascular resistance to compete with the AVM, so development of cerebral edema is quite possible. Alternatively, stasis of blood and the development of microthrombi in the recently ligated feeder arterioles and draining veins can perturb local microcirculation leading to cerebral edema. Treatment of cerebral edema may include moderate hyperventilation as a temporizing measure, administration of mannitol, and blood pressure reduction. In extreme cases, high-dose propofol anesthesia or temporary craniectomy with postoperative ventilatory support may be useful.

Most patients respond quite well to surgical resection, and emergence from anesthesia should be smooth and rapid. Drugs such as Ξ-adrenergic antagonists as well as lidocaine, clevidipine, or nitroprusside can be used to control short-term hypertension during emergence. Prompt neurologic assessment should follow emergence.

Moyamoya Disease

Progressive stenosis of intracranial vessels with the secondary development of an anastomotic capillary network is the hallmark of moyamoya disease. *Moyamoya* is the Japanese term for "puff of smoke" and refers to the angiographic finding of a cluster of small abnormal blood vessels. There seems to be a familial tendency toward the development of this disease, but it may be seen following head trauma or in association with other disorders such as neurofibromatosis, tuberous sclerosis, and fibromuscular dysplasia. Affected arteries have a thickened intima and a thin media. Since similar pathologic findings may be found in other organs, central nervous system abnormalities may be manifestations of a systemic disease. Intracranial aneurysms occur with increased frequency in those with moyamoya disease. Symptoms of ischemia, such as transient ischemic attacks and cerebral infarcts, are common initial findings in children, whereas hemorrhagic complications are usually

the presenting symptoms in adults. The diagnosis is typically made by conventional or magnetic resonance angiography, which demonstrates a cluster of small abnormal blood vessels. Conventional MRI and CT imaging will show a tissue void or hemorrhage.

Medical treatment is aimed at decreasing ischemic symptoms and usually consists of a combination of vasodilators and anticoagulants. Surgical options can be divided into two categories: direct and indirect revascularization. Direct revascularization procedures involve direct anastomosis of an extracranial artery, such as the superficial temporal artery or middle meningeal artery, with an intracranial artery, such as the middle cerebral artery. A major advantage of extracranial-to-intracranial bypass procedures is that blood flow is restored immediately following the procedure. However, fewer patients with moyamoya disease are candidates for direct approaches because they do not have an adequately large intracranial vessel to allow for anastomosis. Indirect revascularization procedures involve placement of an extracranial vessel onto the pia mater to allow for the growth of a new vascular network, derived from the extracranial vessel, to perfuse the ischemic brain. Advantages of indirect techniques include less procedural complications and a greater number of patients that are candidates. Unfortunately, indirect procedures are often less successful than direct procedures at restoring cerebral perfusion, and the beneficial effects take weeks to months to occur as success depends on the growth of a new vascular network.

Management of Anesthesia

Preoperative assessment of the patient with moyamoya disease should involve documentation of preexisting neurologic deficits, a history of hemorrhage, or the concurrent presence of an intracranial aneurysm. Anticoagulant or antiplatelet drug therapy should be discontinued, if possible, to avoid bleeding complications intraoperatively.

The goals of induction and maintenance of anesthesia include (1) ensuring hemodynamic stability because hypotension could lead to ischemia in the distribution of the abnormal vessels and hypertension may cause hemorrhagic complications; (2) avoiding factors that lead to cerebral or peripheral vasoconstriction, such as hypocapnia or phenylephrine, which can compromise blood flow in the feeding or recipient vessels; and (3) facilitating a rapid emergence from anesthesia so that neurologic function can be assessed. In addition to standard monitoring, intraarterial catheterization is essential to rapidly assess changes in blood pressure. If possible, this should be done before induction of anesthesia to help ensure a hemodynamically stable induction sequence. Central venous catheterization is not essential but can be useful to guide fluid management and can provide access for administering vasoactive drugs or blood products. Any intravenous induction drug can be used safely. Inhalational induction with sevoflurane is an option for children. Succinylcholine should be used with caution in patients with preexisting neurologic deficits because of the potential risk of hyperkalemia. Hemodynamic responses to stimulating events should be blunted. A volatile anesthetic–based technique may have the theoretical advantage of enhancing cerebral vasodilation. Excessive hyperventilation should be avoided because of its cerebral vasoconstrictive effect. Hypovolemia should be treated with colloid or crystalloid solutions. Dopamine and ephedrine are reasonable options for the pharmacologic treatment of hypotension because they will avoid the adverse effects on the cerebral vasculature that can result from the use of a pure vasoconstrictor. Anemia should be avoided to prevent ischemia in already compromised brain regions. Postoperative complications include stroke, seizure, and hemorrhage. Any of these may present as delayed awakening or a new neurologic deficit.

TRAUMATIC BRAIN INJURY

Traumatic brain injury is a heterogeneous disease and a leading cause of death and disability in the Unites States, particularly among younger individuals. Traumatic brain injury can be categorized as either penetrating or nonpenetrating, depending on whether the dura mater is breached. The severity of traumatic brain injury can be categorized by multiple metrics, but the most widely used is the Glasgow Coma Score (see Table 13.1). Traumatic brain injury can be stratified into mild, moderate, or severe for Glasgow Coma Scores of 13 to 15, 9 to 12, and less than 9, respectively. The nature of brain injury associated with traumatic brain injury is categorized into primary and secondary injuries. Primary injuries occur at the time of trauma and are due to the effect of external forces on intracranial contents. These include but are not limited to penetrating injuries, shearing of white matter tracts, and cerebral contusions. Secondary injuries are those that occur following the injury and include neuroinflammation, cerebral edema, increased ICP, systemic hypotension, hypoxia, anemia, and electrolyte abnormalities. Systemic conditions that can contribute to sources of secondary injury are neurogenic shock following cervical spinal cord injury; thoracic, abdominal, and orthopedic injuries that lead to hypovolemia causing hypotension and anemia; and pulmonary contusions, aspiration, or pulmonary edema causing impaired gas exchange and systemic hypoxia. In the management of patients with traumatic brain injury, the primary focus should be on the minimization or prevention of secondary injuries.

Prehospital or initial hospital management should begin with establishing adequate intravenous access. Intubation should be considered in patients with severe traumatic brain injury (i.e., Glasgow Coma Score 9); those with significant facial, airway, or chest trauma; or those in significant respiratory distress. Oxygenation and ventilation should be adjusted to maintain SaO_2 above 90%, Pao_2 above 60 mm Hg, and normocapnia, except in those where mild hyperventilation ($Paco_2$ 30–40 mm Hg) can be used for a brief time to control high ICP while other means to treat intracranial hypertension are employed. A noncontrast CT scan of the head and, at minimum, the cervical spine should be performed as soon as possible in any patient who sustained a traumatic head injury and has a Glasgow Coma Score of 14 or less. This CT scan can be used to identify intracranial hematoma, skull fracture, or cervical spinal cord injury.

Management of Anesthesia

Patients with traumatic brain injury may require anesthesia for either neurologic or nonneurologic causes. Neurologic causes include intracranial hematoma evacuation or stabilization of a spinal cord injury. Nonneurologic causes include treatment of intrathoracic or intraabdominal injuries or stabilization or treatment of bone fractures. Patients may also require anesthesia to facilitate radiologic procedures. Patients with traumatic brain injuries should be stabilized prior to proceeding with nonemergent or nonurgent surgical procedures. The primary goal of an anesthetic in patients with traumatic brain injury is to minimize risk for secondary injury.

Preanesthetic assessment should be comprehensive but should not unnecessarily delay emergent or very urgent access to surgery or diagnostic procedures. Preanesthetic assessment should optimally include a review of comorbidities, assessment of the degree and nature of all injuries, review of imaging and laboratory results, and gross neurologic examination.

The degree of intravenous access needed should be based on the nature of the procedure requiring anesthesia, preprocedural volume status and hemodynamics, and estimated procedural blood loss. Central access can be helpful if vasopressors are expected to be administered, but placement should minimally, if at all, delay progress for emergent procedures. Care should be taken to avoid placement of the patient with elevated intracranial pressure in Trendelenburg position, such as may be used when placing a central line in the internal jugular vein. In addition to American Society of Anesthesiologists standard monitors, arterial access can be very useful to manage blood and cerebral perfusion pressure and to obtain blood samples for labs. Placement of an arterial catheter should also not delay access for emergent procedures, if appropriate. Placement of objects in the nose, such as nasogastric tubes or nasal thermometers, should be avoided due to potential for unrecognized basal skull fracture and risk for these objects entering the cranial vault.

Patients with traumatic brain injury frequently have intracranial pressure monitors in place with the most common being the ventriculostomy. Ventriculostomy catheters should be clamped during transport. While open, the transducer should be zeroed at the level of the external auditory meatus. Care must be taken to avoid having the transducer remain significantly lower than the external auditory meatus due to concern for overdrainage of CSF and brain herniation. Unlike transducer systems for arterial lines and central venous lines, a pressure bag should never be connected to the transducer system of a ventriculostomy.

Considerations during induction of anesthesia include concerns for trauma-related cervical spine injury, aspiration risk, hypovolemia due to bleeding from other sources (i.e., long bone fracture, hepatic or splenic injury), and concern for increased intracranial pressure. Concomitant cervical spine injury occurs in up to 11% of patients with traumatic brain injury. Unless the cervical spine has been formally cleared, cervical spine injury should be assumed, even with normal findings on neck imaging. Premedication should be used with caution, if at all, in patients with evidence of increased intracranial pressure because drug-induced hypoventilation can exacerbate intracranial hypertension. In those with presumed gastric contents, a rapid sequence induction and intubation should be performed. Induction drug choice should depend on the patient's neurologic and hemodynamic status and can include propofol, etomidate, or even ketamine in select cases. The primary goal should be to facilitate induction of anesthesia and intubation of the trachea while avoiding extremes in blood pressure. Induction drug dosing should also be planned such as to avoid significant hypotension.

Succinylcholine can be considered to facilitate airway management in patients with traumatic brain injury. In those with elevated intracranial pressure, succinylcholine can briefly exacerbate intracranial hypertension, but this effect can be minimized with a defasciculating dose of a nondepolarizing muscle relaxant given prior to succinylcholine. Succinylcholine can be used in patients with new-onset neuromuscular weakness from either intracranial or spinal cord injury with minimal concern for causing hyperkalemia if used within 24 hours of initial injury. Succinylcholine should not be used in the setting of new motor deficits if greater than 24 hours have passed since injury due to concern for hyperkalemia. Alternatively, a nondepolarizing muscle relaxant, such as rocuronium, should be considered.

No specific airway management technique has been shown to be superior at avoiding cervical cord injury in patients with or at risk for cervical spine instability. The choice of airway technique should depend on multiple factors, including patient cooperativeness, potential ease of mask ventilation, airway bleeding, and clinician expertise. In all circumstances, neck motion during mask ventilation, laryngoscopy, and during the remainder of the periprocedural period should be minimized. Direct or video laryngoscopy can be considered in a patient in whom the ability to mask ventilate is not deemed to be difficult. Manual inline stabilization must be applied throughout airway management, and soft cervical collar should not be considered a good substitute for manual inline stabilization. Cricoid pressure should be used with caution, especially in patients with or at risk for midcervical spine fractures as the external pressure may be transmitted to the spine and exacerbate the fracture. Awake fiberoptic intubation can be considered for a cooperative patient without airway bleeding. However, uncontrolled coughing and movement can occur during airway topicalization or intubation and can potentially injure an unstable cervical spine.

Drugs used to maintain general anesthesia will depend on the surgical procedure and patient comorbidities. Both injectable and inhaled anesthetics can usually be used alone or in combination. Nitrous oxide should be avoided due to concern for air in closed spaces such as the cranial vault, thoracic, or abdominal cavity. Hemodynamic goals include maintaining systolic blood pressure above 100 mm Hg for patients 50 to 69 years old and above 110 mm Hg for patients 15 to 49 years old or over 70 years old. Cerebral autoregulation may be impaired following traumatic brain injury and may take weeks to months to renormalize. Cerebral perfusion pressure (i.e., MAP – ICP) should be maintained between 60 and 70 mm Hg if intracranial pressure monitoring is available. Treatment of low cerebral perfusion pressure should focus on both increasing

systemic blood pressure and decreasing intracranial pressure, as appropriate. Treatment of intracranial hypertension in patients with traumatic brain injury should include optimization of cerebral venous drainage by avoiding neck flexion or Trendelenburg position. Other treatments can include short-term mild hyperventilation, osmotic diuretics, removal of CSF from a ventriculostomy, and cerebral vasoconstricting anesthetic drugs such as propofol. However, prolonged high-dose propofol infusions should be avoided due to concerns for propofol infusion syndrome. For refractory intracranial hypertension, decompressive craniectomy and therapeutic hypothermia can be considered.

Other physiologic goals should include maintaining an arterial oxygen tension above 60 mm Hg and a peripheral oxygen saturation above 90%. Ventilation should be guided by arterial blood gas data and not solely by end-expired carbon dioxide tension as pulmonary disease or injury could impair the relationship between arterial and end-expired carbon dioxide tension. Hypercarbia should be avoided because it will exacerbate intracranial hypertension. Hyperventilation should be used cautiously, sparingly, and for a short duration if needed to acutely treat intracranial hypertension while other treatments are implemented. Otherwise, the goal arterial carbon dioxide tension should be between 35 and 45 mm Hg. Fever should be aggressively treated as it will increase cerebral oxygen requirements and exacerbate injury. Hypothermia has not been shown to be of benefit and may lead to negative outcomes unless it is being considered to treat malignant intracranial hypertension refractory to other therapies. Both hyperglycemia and hypoglycemia can have an adverse impact on the injured brain, thus serum glucose concentration should be maintained between 80 and 180 mg/dL. Glucocorticoids, independent of their effect on serum glucose concentration, have been found to be harmful to patients with moderate or severe traumatic brain injury and should be avoided.

Following brain injury, the brain is at increased risk for seizures. Seizures can increase cerebral metabolic rate and can be a source of secondary brain injury, especially when oxygen delivery is limited. Administration of antiepileptic drugs, such as phenytoin, fosphenytoin, or levetiracetam, should be considered in consultation with the neurosurgeon or neurologist.

Isotonic nonglucose containing crystalloids should be used to maintain euvolemia. Hypotonic solutions can exacerbate cerebral edema. The role of colloid solutions in patients with traumatic brain injury is controversial. In the Saline Versus Albumin Trial, patients with traumatic brain injury who received albumin, especially those with severe traumatic brain injury, had significantly higher mortality than those who received only crystalloid solutions. Until evidence supports their safety, starch-based colloid solutions should also be avoided due to concern for coagulopathy. Significant anemia can potentially impair cerebral oxygen delivery. However, there is currently no data to support the use of a liberal transfusion end point such as a goal of maintaining a serum hemoglobin concentration above 10 g/dL. In those with traumatic brain injury, hemoglobin concentration above 10 g/dL was associated with increased risk of thromboembolic events. As such, in the absence of active bleeding with no evidence of impairment of end-organ oxygen delivery, maintaining a serum hemoglobin concentration of 7 to 8 g/dL is reasonable.

About one-third of patients with severe traumatic brain injury develop coagulopathy. Tranexamic acid has been shown to improve outcome in patients with mild to moderate traumatic brain injury when administered within 3 hours of injury. Tranexamic acid can be infused as 1 g over 10 min followed by 1 g over 8 hours. Coagulation parameters should be monitored during surgery, and abnormalities should be treated. Clinicians should have a high index of suspicion for the development of disseminated intravascular coagulation in patients with severe traumatic brain injury due to release of thromboplastin from the brain and activation of the coagulation cascade. Postoperatively, stable patients who suffered a mild traumatic brain injury can be monitored on the medical floor. Otherwise, intensive care unit monitoring should be considered postprocedurally, especially in those with severe traumatic brain injury or if the patient was in the intensive care unit prior to the procedure.

CONGENITAL ANOMALIES OF THE BRAIN

Congenital anomalies of the central nervous system result from defects in the development or structure of the nervous system. Often a hereditary pattern is responsible. Pathologic processes may be diffuse or may involve only those structures and neurons that are anatomically and functionally related.

Chiari Malformation

Chiari malformation refers to a group of disorders consisting of congenital displacement of the cerebellum. A Chiari I malformation consists of downward displacement of the cerebellar tonsils over the cervical spinal cord, whereas a Chiari II malformation is downward displacement of the cerebellar vermis and is often associated with a meningomyelocele. Chiari III malformations are extremely rare and represent displacement of the cerebellum into an occipital encephalocele. Chiari IV malformations consist of cerebellar hypoplasia and do not involve displacement of posterior fossa contents.

Signs and symptoms of Chiari I malformation can appear at any age. The most common complaint is occipital headache, often extending into the shoulders and arms, with corresponding cutaneous dysesthesias. Pain is aggravated by coughing or moving the head. Visual disturbances, intermittent vertigo, and ataxia are prominent symptoms. Signs of syringomyelia are present in approximately 50% of patients with this disorder. Chiari II malformations usually present in infancy with obstructive hydrocephalus plus lower brainstem and cranial nerve dysfunction.

Treatment of Chiari malformation consists of surgical decompression by freeing adhesions and enlarging the foramen magnum. Management of anesthesia must consider the possibility of increases in ICP as well as significant intraoperative blood loss, especially in the case of Chiari II malformations.

Tuberous Sclerosis

Tuberous sclerosis (Bourneville disease) is an autosomal dominant disease where benign hamartomas, angiofibromas, and other malformations may occur in any organ of the body. Brain

lesions include cortical tubers and giant cell astrocytomas. Cardiac rhabdomyoma, although rare, is the most common benign cardiac tumor associated with tuberous sclerosis. Both echocardiography and MRI are useful for detecting cardiac tumors. Wolff-Parkinson-White syndrome can be associated with tuberous sclerosis. Coexisting angiomyolipomas and cysts of the kidney may result in renal failure. Oral lesions such as nodular tumors, fibromas, or papillomas may be present on the tongue, palate, pharynx, and larynx. The clinical spectrum for patients with tuberous sclerosis depends on the organ systems involved and ranges from no symptoms to life-threatening complications.

Anesthesia management must consider the likely presence of mental retardation and a seizure disorder requiring antiepileptic drugs. Upper airway abnormalities must be identified preoperatively. Cardiac involvement may be associated with intraoperative cardiac arrhythmias. Impaired renal function may have implications when selecting drugs that depend on renal clearance mechanisms. Although experience is limited, these patients seem to respond normally to inhaled and intravenous drugs, including opioids.

Von Hippel–Lindau Disease

Von Hippel–Lindau disease is a familial disease transmitted by an autosomal dominant gene with variable penetrance. It is characterized by retinal angiomas, hemangioblastomas, and central nervous system and visceral tumors. Central nervous system lesions occur most commonly in the cerebellum, brainstem, and spinal cord. Although these tumors are benign, they can cause symptoms resulting from pressure on surrounding structures or bleeding. The incidence of pheochromocytoma, renal cysts, and renal cell carcinoma is increased in some patients with this syndrome.

Management of anesthesia in patients with von Hippel–Lindau disease must consider the possibility of pheochromocytoma. Preoperative treatment with antihypertensive drugs and vascular volume reexpansion is indicated if a pheochromocytoma is identified. Exaggerated hypertension, especially during direct laryngoscopy or sudden changes in the intensity of surgical stimulation, may require intervention with esmolol, labetalol, sodium nitroprusside, anesthetics, or a combination of these drugs. The possibility of spinal cord hemangioblastomas may limit the use of spinal anesthesia, although epidural anesthesia has been described for cesarean section.

Neurofibromatosis

Neurofibromatosis is due to an autosomal dominant mutation. Both sexes are equally affected. Expressivity is variable, but penetrance of the trait is virtually 100%. The disorder is characterized by tumors that grow in the nervous system. There are three types of neurofibromatosis (type 1, type 2, and schwannomatosis), and each has distinctly different genetic mutations.

Type 1 neurofibromatosis occurs in 1 of 3000 to 4000 persons. The diagnosis of type 1 neurofibromatosis is based on the National Institutes of Health criteria. Patients must have at least two of the following:

- At least six café au lait spots
- Two or more neurofibromas or one plexiform neuroma
- Freckling in the axilla or inguinal areas
- At least two Lisch nodules (hammartomas of the iris)
- Optic glioma
- Osseous lesions such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis
- First-degree relative with type 1 neurofibromatosis

Although both neurofibromas (observed in type 1 neurofibromatosis) and schwannomas (observed in type 2 neurofibromatosis and schwannomatosis) consist predominantly of Schwann cells, there are differences in their characteristics. Neurofibromas consist of Schwann cells intermixed with other components such as fibroblasts, neurons, and collagen strands whereas schwannomas consist almost entirely of Schwann cells. Also, neurofibromas tend to encase the parent nerve (often requiring either debulking or en bloc resection of the nerve and tumor) whereas schwannomas tend to displace the parent nerve allowing for possible resection with sparing of the parent nerve.

In addition to abnormalities in the diagnostic criteria, patients with type 1 neurofibromatosis may have macrocephaly, short stature, obstructive hydrocephalus, epilepsy, hypertension, congenital heart defects, and both learning and behavioral disorders. There is an increased incidence of cancer in patients with neurofibromatosis. Commonly associated cancers include neurofibrosarcoma, malignant schwannoma, Wilms tumor, rhabdomyosarcoma, and leukemia. There is an association between type 1 neurofibromatosis and multiple endocrine neoplasia type 2b that consists of mucocutaneous tumors, medullary thyroid cancer, and pheochromocytoma. Generally, neurofibromas are removed if they become symptomatic, painful, cancerous, or for cosmetic reasons.

Type 2 neurofibromatosis is much rarer that the type 1 variant. It is diagnosed by the presence of at least one of the following: (1) bilateral vestibular schwannomas, (2) a family history of type 2 disease or unilateral vestibular schwannoma before age 30 years, or (3) any two of glioma, meningioma, peripheral nerve schwannoma, or juvenile cataracts. Patients may undergo surgery for resection of tumors associated with this condition or removal of cataracts.

Schwannomatosis is the rarest variant of neurofibromatosis. It consists of diffuse schwannomas but the absence of a schwannoma of the vestibular nerve.

Management of anesthesia in patients with neurofibromatosis includes consideration of the many clinical presentations of this disease. The possible presence of a pheochromocytoma should be considered during the preoperative evaluation. Signs of increased ICP may reflect expanding intracranial tumors. Expanding laryngeal neurofibromas may jeopardize airway patency. Patients with neurofibromatosis and scoliosis are likely to have cervical spine defects that could influence positioning for direct laryngoscopy and the subsequent surgical procedure. In the past, patients with neurofibromatosis were described as being sensitive to muscle relaxant, although that is likely not substantiated by data. Neuraxial anesthesia should be avoided in patients with tumors involving the proximal peripheral nerves (i.e., those near the spine) or tumors within the spinal canal. In the absence of these tumors, epidural analgesia is an effective method for producing analgesia during labor and delivery.

DEGENERATIVE DISEASES OF THE BRAIN

Degenerative diseases of the central nervous system usually involve neuronal malfunction or loss within specific anatomic regions representing a diverse group of disease states.

Alzheimer Disease

Alzheimer disease is a chronic neurodegenerative disorder. It is the most common cause of dementia in patients older than 65 years of age and the fourth most common cause of disease-related death in patients older than age 65. Diffuse amyloid beta-rich plaques and neurofibrillary tangles that consist of hyperphosphorylated tau protein are the hallmark pathologic findings. There are also changes in synapses and in the activity of several major neurotransmitters, especially acetylcholine. Patients with Alzheimer disease have reduced activity of choline acetyl transferase, an enzyme responsible for acetylcholine synthesis.

Two types of Alzheimer disease have been described: early onset and late onset. Early-onset Alzheimer disease presents before age 65 and appears to be due to mutations in genes responsible for amyloid beta synthesis, aggregation, or clearance. These mutations have an autosomal dominant mode of transmission with very high penetrance. Late-onset Alzheimer disease usually develops after age 65, and genetic factors appear to play a relatively minor role in the risk of developing this disorder. Risk factors include hypertension, hyperlipidemia, cerebrovascular disease, type 2 diabetes mellitus, and prior traumatic brain injury. In both forms of the disease, patients typically develop progressive cognitive impairment that can consist of problems with memory as well as apraxia, aphasia, and agnosia. Definitive diagnosis is usually made on postmortem examination. The antemortem diagnosis of Alzheimer disease is one of exclusion. There is currently no cure for Alzheimer disease, and treatment focuses on control of symptoms. Pharmacologic options include cholinesterase inhibitors such as tacrine, donepezil, rivastigmine, and galantamine. Memantine, an N-methyl-d-aspartate receptor antagonist, has also been shown to improve cognitive function although the mechanism for this effect is not well understood. Drug therapy should be combined with nonpharmacologic therapy, including caregiver education and family support. Even with treatment, the prognosis for patients with Alzheimer disease is poor.

Patients with Alzheimer disease may come for a variety of surgical interventions that are common in the elderly population. Patients are often confused and sometimes uncooperative, which makes monitored anesthesia care or regional anesthesia challenging. There is no one single anesthetic technique or drug that is ideal in this group of patients. Shorter-acting sedative-hypnotic drugs and opioids are preferred since they allow a more rapid return to baseline mental status. One should be aware of potential drug interactions, especially prolongation of the effect of succinylcholine and relative resistance to nondepolarizing muscle relaxants resulting from the use of cholinesterase inhibitors. Patients with baseline cognitive impairment may be at increased risk for postoperative delirium. Anesthetic technique appears to have minimal effect on risk for postoperative delirium with a few notable exceptions. Specifically, a deeper anesthetic state, inadequate analgesia, and use of benzodiazepines appear to increase risk for delirium, whereas perioperative use of dexmedetomidine may reduce risk for delirium. Nonetheless, patients with Alzheimer disease and other forms of dementia, and their families, should be counseled preoperatively about increased risk for postoperative delirium and cognitive dysfunction.

Parkinson Disease

Parkinson disease is a neurodegenerative disorder of unknown cause. Increasing age is the single most important risk factor in the development of this disease. There is a characteristic loss of dopaminergic fibers normally present in the basal ganglia, and as a result regional dopamine concentrations are depleted. Dopamine is presumed to inhibit the rate of firing of the neurons that control the extrapyramidal motor system. Depletion of dopamine results in diminished inhibition of these neurons and unopposed stimulation by acetylcholine.

The classic triad of major signs of Parkinson disease consists of skeletal muscle tremor, rigidity, and akinesia. Skeletal muscle rigidity first appears in the proximal muscles of the neck. The earliest manifestations may be loss of associated arm swings when walking and absence of head rotation when turning the body. There is facial immobility manifested by infrequent blinking and by a paucity of emotional expressions. Tremors are characterized as rhythmic, alternating flexion and extension of the thumbs and other digits (pill-rolling tremor). Tremors are more prominent during rest and tend to disappear during voluntary movement. Seborrhea, oily skin, diaphragmatic spasms, and oculogyric crises are frequent. Dementia and depression are often present.

Treatment of Parkinson disease is designed to increase the concentration of dopamine in the basal ganglia or to decrease the neuronal effects of acetylcholine. Replacement therapy with the dopamine precursor levodopa combined with administration of a decarboxylase inhibitor, which prevents peripheral conversion of levodopa to dopamine and optimizes the amount of levodopa available to enter the central nervous system, is the standard initial medical treatment. Side effects of levodopa include dyskinesia, orthostatic hypotension, nausea, vomiting, confusion, and hallucinations. Amantadine, an antiviral drug, is reported to help control the symptoms of Parkinson disease. The mechanism for its effect is not fully understood. The type B monoamine oxidase inhibitor selegiline can also help control the symptoms of Parkinson disease by inhibiting the catabolism of dopamine in the central nervous system. Selegiline has an advantage over nonspecific monoamine oxidase inhibitors because it is not associated with the occurrence of tyramine-related hypertensive crises.

Surgical treatment of Parkinson disease is reserved for patients with disabling and medically refractory symptoms. Ablative treatments, such as pallidotomy and thalamotomy, have largely been replaced by stimulation of nuclei within the basal ganglia via an implanted deep brain stimulating device. Fetal tissue transplantation for treatment of Parkinson disease is based on the demonstration that implanted embryonic dopaminergic

neurons can survive in recipients. The effectiveness of this treatment is not currently known. Transcranial magnetic resonance-guided focused ultrasound (MRgFUS) thermal ablation, which uses high-intensity ultrasound waves, has also been used to target structures in the thalamus, globus pallidus, and subthalamic nucleus to treat Parkinson disease. Additional clinical trials evaluating the effectiveness of MRgFUS are being performed.

Deep brain stimulator placement is often performed in an awake patient. However, in certain circumstances, such as in patients with developmental delay or those with severe claustrophobia, the procedure is performed with general anesthesia. The procedure begins with placement of a rigid head frame, followed by MRI to allow for coordinate determination relative to fiduciary markers on the head frame. The deep brain electrode is then advanced through a burr hole, often with microelectrode recordings taken since specific nuclei differ in their spontaneous firing patterns. Following successful brain lead placement, a generator pack is implanted below the clavicle or in the abdomen. Of note, deep brain stimulation is currently under investigation for treatment of a variety of other disorders, such as Tourette syndrome, depression, and eating disorders.

Management of anesthesia in patients with Parkinson disease requires an understanding of how this disease is treated. The elimination half-time of levodopa and the dopamine it produces is brief, so interruption of drug therapy for more than 6 to 12 hours can result in an abrupt loss of therapeutic effects. Abrupt drug withdrawal can also lead to skeletal muscle rigidity, which can interfere with ventilation. Therefore levodopa therapy, including the usual morning dose on the day of surgery, must be continued throughout the perioperative period. Oral levodopa can be administered approximately 20 minutes before induction of anesthesia, and the dose may be repeated intraoperatively and postoperatively via an orogastric or nasogastric tube as needed.

The possibility of hypotension and cardiac arrhythmias must be considered, and butyrophenones (e.g., droperidol, haloperidol) must be available to antagonize the effects of dopamine in the basal ganglia. Acute dystonic reactions following administration of alfentanil might indicate an opioid-induced decrease in central dopaminergic transmission. The use of ketamine is controversial because of the possible provocation of exaggerated sympathetic nervous system responses, but ketamine has been administered safely to patients treated with levodopa. The choice of a muscle relaxant is not influenced by the presence of Parkinson disease.

Patients undergoing deep brain stimulator implantation may have been told by the surgeon to refrain from taking the usual morning dose of levodopa to facilitate the return of tremors and enhance sensitivity in detecting the efficacy of deep brain stimulation during the procedure. If that is the case, then establishment of intravenous access may prove challenging in an extremity with a significant tremor. Patients should receive minimal sedation during lead placement to prevent interference with microelectrode recordings and clinical assessment. Since Γ-aminobutyric acid (GABA) is a common neurotransmitter involved in the normal circuitry of the basal ganglia, anesthetic drugs with significant effects on GABA, such as propofol and benzodiazepines, can alter the characteristic microelectrode recordings of specific nuclei and should be avoided. Sedative drugs, such as opioids and dexmedetomidine, are satisfactory alternatives. Excessive sedation should be avoided not only to minimize difficulty obtaining neurologic assessments but more importantly to avoid respiratory depression in a patient in whom there is little access to the airway because of the presence of a head frame. A variety of airway management devices (e.g., fiberoptic bronchoscope, laryngeal mask airway) should be readily available should airway compromise become an issue intraoperatively. In patients having general anesthesia for lead implantation, microelectrode recordings cannot be used to facilitate placement of the lead; thus anesthetic drug choice is not dictated by monitoring. During general anesthesia, lead localization is performed solely by stereotaxis to reach anatomic landmarks.

Lead placement can be a long procedure, so care should be taken to position the patient properly and comfortably. Proper padding should be placed at sites that may be prone to pressure injury.

The procedure is performed with the patient in the sitting position, so there is a risk of air embolism. Precordial Doppler ultrasonographic monitoring can help identify air entrainment. If venous air embolism and oxygen desaturation occur, the patient should not be encouraged to take a deep breath because this can lower intrathoracic pressure and cause the entrainment of even more air. Instead, the surgeon should flood the field with saline and attempt to identify and treat the site of air entrainment. In more severe cases, the patient should be placed supine and hemodynamic support instituted.

Other potential complications of deep brain stimulation placement include hypertension, seizures, and bleeding. Hypertension should be treated to avoid increasing the risk of intracranial hemorrhage. Seizures often spontaneously abate, but very small doses of a barbiturate, propofol, or a benzodiazepine may be required to terminate their activity despite the potentially suppressive effect of administration of these drugs on microelectrode recordings. The effect of these drugs on ventilatory drive must also be appreciated and minimized. A sudden alteration of consciousness could indicate intracranial hemorrhage. Hemorrhage would require aggressive management, such as emergent removal of the head frame, tracheal intubation, and craniotomy after imaging.

For patients having MGgFUS, since there is no incision, the procedure is often performed with minimal if any sedation. A common issue that may arise during this procedure is discomfort due to the cooling helmet used to minimize heat generated on the scalp by the ultrasound emitters. Patients may also experience nausea and vomiting.

Huntington Disease

Huntington disease is a degenerative disease of the central nervous system characterized by marked atrophy of the caudate nucleus and, to a lesser degree, the putamen and globus pallidus. The disorder is due to trinucleotide repeats in the gene for Huntington, a protein expressed in neurons where it has an

unclear function in humans. Huntington disease is transmitted as an autosomal dominant trait with increased penetrance occurring with increased number of trinucleotide repeats and the number of trinucleotide repeats increasing with successive generations.

Manifestations of Huntington disease consist of progressive dementia combined with choreoathetosis. Chorea is usually considered the first sign of Huntington disease. Behavioral changes such as depression, aggressive outbursts, and mood swings may precede the onset of involuntary movements by several years. Involvement of the pharyngeal muscles makes these patients susceptible to pulmonary aspiration. The disease progresses over several years, and accompanying mental depression makes suicide a frequent cause of death. The duration of Huntington disease from clinical onset to death averages 17 years.

Treatment of Huntington disease is supportive and is directed at decreasing the choreiform movements. Haloperidol and other butyrophenones may be administered to control the chorea and emotional lability associated with the disease. The most useful therapy for controlling involuntary movements is drugs that interfere with the neurotransmitter effects of dopamine either by antagonizing dopamine (risperidone, olanzapine) or by depleting dopamine stores (tetrabenazine, deutetrabenazine).

Experience in the management of anesthesia in patients with Huntington disease is limited to case reports and small case series, thus data to guide specific anesthetic drugs or techniques is limited. Preoperative sedation using butyrophenones such as droperidol or haloperidol may be helpful in controlling choreiform movements. The increased likelihood of pulmonary aspiration must be considered. Use of nitrous oxide and volatile anesthetics is acceptable. Propofol and succinylcholine have been administered without adverse effects. Spinal anesthesia has been described in patients with Huntington disease.

Torticollis

Torticollis, or cervical dystonia, is a condition where the muscles of the neck lead to lateral neck flexion and rotation. Trauma may be a contributing factor, but a cause for torticollis is often not identified. Not only does torticollis lead to a disfigurement, but it can impact the patient's respiratory mechanics and ability to perform activities of daily living. Initial treatment consists of physical therapy. Selective injection of botulinum toxin may be considered. Surgery is an option for patients with refractory torticollis. Bilateral anterior rhizotomy at C1 and C3, with a sectioning of the spinal accessory nerve, may be attempted. This operation may cause postoperative paralysis of the diaphragm, resulting in respiratory distress. Selective peripheral denervation of affected cervical musculature is another surgical option. There are no known problems influencing the selection of anesthetic drugs, but spasm of nuchal muscles can interfere with maintenance of a patent upper airway before institution of skeletal muscle paralysis. Awake tracheal intubation may be necessary if chronic skeletal muscle spasm has led to fixation of the cervical vertebrae. The surgeon may utilize electromyography to identify nerves to cervical muscles and the diaphragm. If electromyography is used, drug-induced skeletal muscle paralysis is contraindicated during this part of the procedure. Surgery may be performed with the patient in the sitting position. If so, anesthetic considerations related to use of the sitting position and the potential for venous air embolism will come into play.

The sudden appearance of torticollis after administration of anesthetic drugs has been reported. Administration of diphenhydramine 25 to 50 mg IV produces a dramatic reversal of this drug-induced torticollis.

Transmissible Spongiform Encephalopathies

The human transmissible spongiform encephalopathies are Creutzfeldt-Jakob disease (CJD), kuru, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia. These noninflammatory diseases of the central nervous system are caused by transmissible slow-acting infectious protein pathogens known as prions. Prions differ from viruses in that they lack RNA and DNA and fail to produce a detectable immune reaction. Transmissible spongiform encephalopathies are diagnosed on the basis of clinical and neuropathologic findings, including the presence of diffuse or focal clustered small round vacuoles that may become confluent. Familial progressive subcortical gliosis and some inherited thalamic dementias may also be spongiform encephalopathies. Bovine spongiform encephalopathy (mad cow disease) is a transmissible spongiform encephalopathy that occurs in animals. Infectivity of skeletal muscles, milk, and blood has not been detected.

CJD is the most common transmissible spongiform encephalopathy, with an estimated incidence of one case per million worldwide. Transmission of the prion and the development of clinical disease are still poorly understood. In fact, a significant proportion of the population probably carries the CJD prion, but most do not develop clinical disease. Approximately 10% to 15% of patients with CJD have a family history of the disease, so both infectious and genetic factors probably play a role in disease development. The time interval between infection and development of symptoms is measured in months to years. Rapidly progressive dementia with ataxia and myoclonus suggests the diagnosis, although confirmation currently requires brain biopsy. Reliable noninvasive tests are under development. Alzheimer disease poses the most difficult differential diagnosis. Unlike in toxic and metabolic disorders, myoclonus is rarely present at the onset of CJD, and seizures, when they occur, are a late phenomenon. Also, there may be characteristic electroencephalographic abnormalities associated with CJD, but the sensitivity and specificity are not known. No vaccines or treatments are effective.

Universal infection precautions are recommended when caring for patients with CJD, but other precautions are not necessary. Handling of CSF calls for special precautions (use of double gloves and protective glasses, specimen labeling as "infectious") since CSF has been the only body fluid shown to result in experimental transmission to primates. Performance of biopsies and autopsies requires similar precautions. The main risk of transmitting CJD is during brain biopsy for diagnostic confirmation of the disease. Instruments used should be disposable or should be decontaminated by soaking in sodium

hypochlorite. Alternatively, instruments used for the surgical biopsy can be stored in a freezer and normally sterilized if the biopsy is negative or discarded if the biopsy results are positive for a transmissible spongiform encephalopathy.

Human-to-human transmission has occurred inadvertently in association with surgical procedures (corneal transplantation, stereotactic procedures with previously used electrodes, procedures with contaminated neurosurgical instruments, and human cadaveric dura mater transplantation). Transmission also has been attributed to treatment with human-derived growth hormone and gonadotropic hormones. Although the injection or transplantation of human tissues may result in transmission of infectious prions, the hazards of transmission through human blood are debatable since this disease is not observed more frequently in individuals with hemophilia than in the general population. Nevertheless, transfusion of blood from individuals known to be infected is not recommended.

Management of anesthesia includes the use of universal infection precautions, disposable equipment, and sterilization of any reusable equipment using sodium hypochlorite. Surgery in patients known or suspected to be infected might be better performed at the end of the day to allow thorough cleansing of equipment and the operating room before the next use. The number of personnel participating in anesthesia and surgery is kept to a minimum, and all should wear protective gowns, gloves, and face masks with transparent visors to protect the eyes. Since a proportion of the general population are probably carriers of the prion thought to cause CJD, and both infectious and genetic factors play a role in the development of clinical symptoms, the likelihood of developing CJD after coming in contact with a CJD prion is probably very low.

Multiple Sclerosis

Multiple sclerosis is an autoimmune disease affecting the central nervous system and occurs at a higher rate in individuals who have a first-degree relative with the disease. There are several other risk factors for multiple sclerosis that include female sex, exposure to Epstein-Barr or varicella zoster viruses, autoimmune disorders (i.e., diabetes mellitus type 1, inflammatory bowel disease), low vitamin D levels, and smoking. Geographic latitude was also thought to play a role in modulating risk for multiple sclerosis with higher prevalence of the disease in northern North America and Europe, southeast Australia, and New Zealand. However, the incidence of new disease was found only to be higher in Australia and New Zealand and not in North America and Europe.

Pathologically, multiple sclerosis is characterized by diverse combinations of inflammation, demyelination, and axonal damage in the central nervous system. The loss of myelin covering the axons is followed by formation of demyelinated plaques. Peripheral nerves are not affected by multiple sclerosis. Earlier in the disease process, the disease is characterized by autoreactive lymphocytes, whereas later, microglial activation and neurodegeneration are more common.

Clinical manifestations of multiple sclerosis reflect its multifocal involvement and are always progressive. Manifestations of multiple sclerosis reflect the sites of demyelination in the central nervous system and spinal cord. For example, inflammation of the optic nerves (optic neuritis) causes visual disturbances, involvement of the cerebellum leads to gait disturbances, and lesions of the spinal cord cause limb paresthesias and weakness as well as urinary incontinence and impotence. Optic neuritis is characterized by diminished visual acuity and defective pupillary reaction to light. Ascending spastic paresis of the skeletal muscles can occur. Intramedullary disease of the cervical cord is suggested by an electrical sensation that runs down the back into the legs in response to flexion of the neck (Lhermitte sign). Typically, symptoms develop over the course of a few days, remain stable for a few weeks, and then improve. Because remyelination probably does not occur in the central nervous system, remission of symptoms most likely results from correction of transient chemical and physiologic disturbances that have interfered with nerve conduction in the areas of demyelination. Increases in body temperature can also cause exacerbation of symptoms due to further alterations in nerve conduction in regions of demyelination.

The course of multiple sclerosis is characterized by exacerbations and remissions at unpredictable intervals over a period of several years. Symptoms eventually persist during remissions, leading to severe disability from visual failure, ataxia, spastic skeletal muscle weakness, and urinary incontinence. However, in some patients the disease remains benign, with infrequent, mild episodes of demyelination, followed by prolonged remissions. The onset of multiple sclerosis after 35 years of age is typically associated with slow disease progression.

Multiple sclerosis is primarily a clinical diagnosis and depends strongly on history, physical examination, and findings on MRI of the brain and spinal cord. The diagnosis of multiple sclerosis is based on the McDonald criteria that consider the number of episodes of new onset neurologic findings (i.e., "attacks") and the number of demyelinating lesions on brain or spinal cord MRI. Other findings, such as oligoclonal bands in cerebrospinal fluid, can support the diagnosis.

No treatment is curative for multiple sclerosis, so treatment is directed at symptom control and slowing of disease progression. Treatment primarily involves drugs that attenuate the immune response in the central nervous system, including corticosteroids, immune modulators, and targeted antibodies.

Management of anesthesia in patients with multiple sclerosis must consider the impact of surgical stress on the natural progression of the disease. Regardless of the anesthetic technique or drugs selected for use during the perioperative period, it is possible that symptoms and signs of multiple sclerosis will be exacerbated postoperatively. This may be due to factors such as infection and fever. Any increase in body temperature, even of as little as 1°C, can cause an exacerbation of multiple sclerosis. It is possible that increased body temperature results in complete block of conduction in demyelinated nerves. The unpredictable cycle of clinical exacerbations and remissions that are inherent in multiple sclerosis might lead to erroneous conclusions that there are cause-and-effect relationships between disease severity and drugs or events occurring during the perioperative period.

The changing and unpredictable neurologic presentation of patients with multiple sclerosis during the perioperative period must be appreciated when regional anesthetic techniques are selected. In the past, it was hypothesized that intrathecal administration of local anesthetics promoted demyelination in the spinal cord in patients with multiple sclerosis leading to exacerbation of disease. Alternatively, demyelinated regions of the spinal cord may be more susceptible to the neurotoxic effects of local anesthetics. However, both spinal and epidural analgesia and anesthesia have been used safely in patients with multiple sclerosis and should be considered. The intrathecal dose of local anesthetic drugs should be minimized as much as feasibly possible. Epidural anesthesia may carry less risk than spinal anesthesia because the concentration of local anesthetics in the white matter of the spinal cord is lower than after spinal anesthesia. Peripheral nerve blocks pose no significant increased risk in patients with multiple sclerosis.

General anesthesia is the most frequently used technique in patients with multiple sclerosis. There are no unique interactions between multiple sclerosis and the drugs used to provide general anesthesia, and there is no evidence to support the use of one inhaled or injected anesthetic drug over another. In patients with motor weakness, use of succinylcholine can result in exaggerated potassium release and should be avoided. Prolonged responses to the paralyzing effects of nondepolarizing muscle relaxants would be consistent with coexisting skeletal muscle weakness and decreased skeletal muscle mass. However, resistance to the effects of nondepolarizing muscle relaxants has been observed, which perhaps reflects the proliferation of extrajunctional cholinergic receptors characteristic of upper motor neuron lesions.

Corticosteroid supplementation during the perioperative period may be indicated in patients being treated long term with these drugs. Efforts must be made to recognize and prevent even a modest increase in body temperature, since this change may exacerbate symptoms. Periodic neurologic evaluation during the postoperative period is useful for detection of exacerbations.

Postpolio Sequelae

Poliomyelitis is caused by an enterovirus that initially infects the gut and reticuloendothelial system. In a minority of patients, the virus enters the central nervous system and preferentially targets motor neurons in the brainstem, cerebellum, and anterior horn of the spinal cord. The worldwide incidence of poliomyelitis has significantly decreased since the institution of vaccination against this disease. Because poliomyelitis is so rare at this time in the United States, a clinician will see patients with postpolio sequelae much more commonly than those with acute polio. Postpolio sequelae manifest as fatigue, skeletal muscle weakness, joint pain, cold intolerance, dysphagia, and sleep and breathing problems (i.e., obstructive sleep apnea). Poliovirus may damage the reticular activating system; this accounts for the fact that these individuals may exhibit exquisite sensitivity to the sedative effects of anesthetics as well as delayed awakening from general anesthesia. Sensitivity to nondepolarizing muscle relaxants is common. Severe back pain following surgery may be due to coexisting skeletal muscle atrophy and scoliosis. Postoperative shivering may be profound since these individuals are very sensitive to cold. Postoperative pain perception may be abnormal possibly because of poliovirus damage to endogenous opioid-secreting cells in the brain and spinal cord. Outpatient surgery may not be appropriate for many postpolio patients since they are at increased risk of complications, especially those related to respiratory muscle weakness and dysphagia. There is theoretical concern that the toxic dose of local anesthetic drugs is lower because motor neurons in the dorsal horn of the spinal cord have been either injured or reduced in number due to the original polio infection. However, there are no data to support the notion that neuraxial or peripheral nerve blocks pose increased risk in patients with postpolio syndrome, and the decision to perform regional anesthesia should be made on an individual basis.

Seizure Disorders

Seizures are caused by transient, paroxysmal, and synchronous discharge of groups of neurons in the brain. Seizure is one of the most common neurologic disorders and may occur at any age. Approximately 5% of the population will experience a seizure at some time during their lives. Clinical manifestations depend on the location and number of neurons involved in the seizure discharge and its duration. Transient abnormalities of brain function, such as occur with hypoglycemia, hyponatremia, hyperthermia, and drug toxicity, may result in a seizure. In these cases, treatment of the underlying disorder is usually curative. Epilepsy is defined as recurrent seizures resulting from congenital or acquired factors (e.g., cerebral scarring) and affects approximately 0.6% of the population.

Seizures are grossly classified based on two factors: loss of consciousness and regions of brain affected by the seizure. Simple seizures involve no loss of consciousness, whereas altered levels of consciousness are seen in complex seizures. Partial seizures appear to originate from a limited population of neurons, whereas generalized seizures involve diffuse activation of neurons in both cerebral hemispheres. A partial seizure may initially be evident in one region of the body and may subsequently become generalized, involving both hemispheres, a process known as secondary generalization or the jacksonian march.

MRI is the preferred method for studying brain structure in patients with epilepsy. Standard EEG is used to identify the location(s) of seizure foci as well as to characterize their electrical properties. The use of videography in addition to EEG allows simultaneous documentation of electrical and clinical seizure activity. Electrocorticography, in which electrodes are surgically placed directly on the cerebral cortex, not only permits more accurate focus identification but also allows mapping of electrical events in relation to identifiable brain surface anatomy, a feature that is valuable during surgical resection. Stimulation of various electrocorticographic electrodes can also help identify eloquent brain areas before seizure focus resection so that those areas can be avoided during surgery.

Seizures are treated with antiepileptic drugs, starting with a single drug and achieving seizure control by increasing the

dosage as necessary. Drug combinations may be considered when monotherapy fails. Effective antiepileptic drugs appear to decrease neuronal excitability or enhance neuronal inhibition. Carbamazepine, phenytoin, and barbiturates cause enzyme induction, and long-term treatment with these drugs can alter the rate of their own metabolism as well as that of other drugs. Pharmacokinetic and pharmacodynamic drug interactions are considerations in patients being treated with antiepileptic drugs. Dose-dependent neurotoxic effects are the most common adverse effects of antiepileptic drugs. All antiepileptic drugs can cause depression of cerebral function with symptoms of sedation.

Phenytoin has many side effects, including hypotension, cardiac arrhythmias, gingival hyperplasia, and aplastic anemia. It is associated with various cutaneous manifestations, including erythema multiforme and Stevens-Johnson syndrome. Extravasation or intraarterial injection of phenytoin can induce significant vasoconstriction resulting in purple glove syndrome, which can lead to skin necrosis, compartment syndrome, and gangrene. These side effects make fosphenytoin, a phosphorylated prodrug that does not share the same toxicity profile as phenytoin, a more attractive option for intravenous antiepileptic administration.

Valproate produces hepatic failure in approximately 1 in every 10,000 recipients. The mechanism of this hepatotoxicity is unknown, but it may represent an idiosyncratic hypersensitivity reaction. Pancreatitis has also been observed during valproate therapy. Long-term use of valproate is associated with increased surgical bleeding, especially in children. The mechanism is currently unknown but might involve a combination of thrombocytopenia and valproate-induced decreases in von Willebrand factor and factor VIII.

Carbamazepine can cause diplopia, dose-related leukopenia, and hyponatremia (which is usually clinically unimportant) as well as alterations in the hepatic metabolism of various drugs.

Adverse hematologic reactions associated with antiepileptic drugs range from mild anemia to aplastic anemia and are most commonly associated with the use of carbamazepine, phenytoin, and valproate.

Surgical treatment of seizure disorders is considered in patients whose seizures do not respond to antiepileptic drugs or who cannot tolerate the side effects of pharmacologic therapy. Surgery is now being performed much earlier than in the past, particularly in young patients, to avoid social isolation resulting from medication side effects and persistent seizures. Partial seizures may respond to resection of a pathologic region within the brain such as a tumor, hamartoma, or scar tissue. Corpus callosotomy may help to prevent the generalization of partial seizures to the opposite hemisphere. Finally, hemispherectomy is sometimes needed for persistent catastrophic seizures. These latter two treatments (i.e., corpus callosotomy and hemispherectomy) are currently rarely performed.

In preparation for surgery, the seizure focus is first located by imaging and functional studies. MRI is the imaging modality of choice, especially for detection of mesial temporal sclerosis, a common cause of complex partial seizures. Nuclear medicine–based modalities, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), may demonstrate alterations in metabolism or abnormal blood flow in regions of the brain. Video EEG monitoring can assist in correlating electrical activity and clinical manifestations of seizures.

Electrocorticography, as mentioned earlier, involves placement of electrodes either as a grid directly on the brain surface or deeper within the brain. Electrocorticography offers many advantages over surface EEG recordings, such as increased precision in seizure focus determination, the ability to monitor deep regions of cortex, and the ability to stimulate regions of brain to map eloquent cortex. Electrocorticography can be performed during the same surgical procedure as cortical resection, or electrodes can be placed during one procedure and the patient allowed to return on a different day for seizure focus resection. In the latter case, video monitoring and mapping with grids in place can increase the accuracy of identifying the specific seizure focus for resection. More recently, laser thermal ablation of seizure foci is emerging as a minimally invasive treatment for some forms of epilepsy. Another conservative surgical approach to medically intractable seizures involves the implantation of a left vagal nerve stimulator. The left side is chosen because the right vagal nerve usually has significant cardiac innervation, which could lead to severe bradyarrhythmias. The mechanism by which vagal nerve stimulation produces its effects is unclear. Patients tolerate this treatment well except for the occurrence of hoarseness in some cases, which reflects the vagal innervation of the larynx.

Status Epilepticus

Status epilepticus is a life-threatening condition that manifests as continuous seizure activity or two or more seizures occurring in sequence without recovery of consciousness. The goal of treatment of status epilepticus is prompt establishment of venous access and subsequent pharmacologic suppression of seizure activity combined with support of the airway, ventilation, and circulation. Metabolic causes of acute seizures, including hypoglycemia, can be ruled out within minutes using rapid bedside assessment techniques. If hypoglycemia is present, it can be corrected by intravenous administration of dextrose solution. Routine dextrose administration before confirmation of hypoglycemia is potentially dangerous since hyperglycemia can exacerbate brain injury. Tracheal intubation may be needed to protect the airway and/or optimize oxygen delivery and ventilation. Muscle relaxants should be avoided if muscle movement, rather than electrophysiologic monitoring, is the principal method for assessing therapy effectiveness. Administration of an antiepileptic anesthetic, such as propofol, will temporarily halt seizure activity during tracheal intubation. Ketamine has also been emerging as an effective treatment for refractory status epilepticus.

Monitoring of arterial blood gas levels and pH may be useful for confirming the adequacy of oxygenation and ventilation. Metabolic acidosis is a common sequela of ongoing seizure

activity, and intravenous administration of sodium bicarbonate may be needed to treat extreme acid-base abnormalities. Hyperthermia occurs frequently during status epilepticus and necessitates active cooling.

Management of anesthesia in patients with seizure disorders includes considering the impact of antiepileptic drugs on organ function and the effect of anesthetic drugs on seizures. Sedation produced by antiepileptic drugs may have additive effects with that produced by anesthetic drugs, and enzyme induction by antiepileptic drugs may alter the pharmacokinetics and pharmacodynamics of anesthetic drugs.

When selecting anesthetic induction and maintenance drugs, one must consider their effects on central nervous system electrical activity. Methohexital administration can activate epileptic foci and has been recommended as a method for delineating these foci during electrocorticography in patients undergoing surgical treatment of epilepsy. In selection of muscle relaxants, the central nervous system–stimulating effects of laudanosine, a proconvulsant metabolite of atracurium and cisatracurium, may merit consideration. Various antiepileptic drugs, specifically phenytoin and carbamazepine, shorten the duration of action of nondepolarizing muscle relaxants through both pharmacokinetic and pharmacodynamic means. Topiramate may be the cause of unexplained metabolic acidosis given its ability to inhibit carbonic anhydrase.

It seems reasonable to avoid administering potentially epileptogenic drugs to patients with epilepsy. Instead, propofol, barbiturates, opioids, and benzodiazepines are preferred. Isoflurane, desflurane, and sevoflurane seem to be acceptable choices in patients with seizure disorders. Regardless of the anesthetic drugs used, it is important to maintain treatment with the preoperative antiepileptic drugs throughout the perioperative period.

During intraoperative electrocorticography, monitoring is aimed at identifying interictal epileptiform activity (i.e., the characteristic patterns of electrical activity that occur in the time between seizures). Many anesthetic drugs, such as benzodiazepines, volatile anesthetics, and anesthetic doses of barbiturates and propofol, can significantly suppress epileptiform activity, which renders electrocorticographic monitoring difficult or impossible. During the monitoring period, anesthesia should be managed with drugs such as opioids, nitrous oxide, droperidol, diphenhydramine, and possibly dexmedetomidine. If epileptiform activity remains suppressed or is inadequate for analysis, high-dose short-acting opioids (e.g., alfentanil 50 μg/kg IV bolus) or small intravenous boluses of methohexital (0.3 mg/kg) or etomidate (0.05–0.1 mg/kg) can serve to enhance epileptiform activity. Careful attention to maintaining muscle paralysis during this part of the procedure is important. When the preoperative discussion is held and informed consent is obtained, the patient should be made aware that anesthetic techniques used to improve the quality of electrophysiologic recordings may also increase the risk of awareness during anesthesia.

Despite general anesthesia and muscle relaxation, patients may still exhibit seizure activity. This may manifest as unexplained abrupt changes in heart rate and blood pressure with or without overt clonic movement, depending on the degree of muscle paralysis. Increases in carbon dioxide production from increased brain and muscle metabolism will be reflected in an increased end-expired carbon dioxide concentration and may result in patient respiratory efforts. Seizures can be terminated by the administration of a barbiturate, propofol, or a benzodiazepine that is titrated to seizure cessation. Seizures can also be rapidly terminated by the direct application of cold saline to the brain surface. This is a very useful technique in procedures performed in awake patients because it avoids the use of drugs that could potentially produce somnolence, hypoventilation, airway obstruction, or apnea.

Perioperative Neurocognitive Disorders

Perioperative neurocognitive disorders (PND) consist of alterations in cognition following anesthesia and surgery. PND can be separated into several categories, including postoperative delirium, delayed neurocognitive recovery, and postoperative neurocognitive disorder, based upon timing of events as well as resolution of signs and symptoms. While emergence delirium refers to the relatively common change in behavior immediately following and resolves within minutes of emergence from general anesthesia, postoperative delirium describes behavior changes that persist in the postanesthesia recovery unit and acute postoperative period (up to 1 week postprocedure or until hospital discharge). A patient experiencing postoperative delirium may exhibit waxing and waning agitation (hyperactive delirium) and/or somnolence (hypoactive delirium). Cognitive changes that persist until 30 days postoperatively are labeled as delayed neurocognitive recovery. The term *postoperative neurocognitive disorder* is used to describe continued cognitive concerns beyond 30 days and up until 1 year. Beyond 1 year, the "postoperative" descriptor is no longer used to describe the persistent neurocognitive concerns. Neurocognitive disorders can be further classified into minor and major based upon the decline observed on neuropsychological testing and impairment of ability to perform activities of daily living. Of note, *postoperative cognitive dysfunction* is another term used in research to define objective changes in cognition based upon an individual's preoperative and postoperative neuropsychological testing.

The pathophysiology of PND is not fully known and is thought to be multifactorial with both patient- and procedural-related factors contributing to its cause. It is possibly related to the systemic and neuroinflammatory response that results from the surgical procedures. Preoperative risk factors include preexisting cognitive impairment, older age, as well as lower educational levels and lower preoperative intelligence quotient. Postoperative risk factors include uncontrolled pain, medications such as benzodiazepines and opioids, electrolyte abnormalities, sleep deprivation, dehydration, and intensive care unit admission.

At this time, there are no formal recommendations regarding anesthetic techniques to minimize the occurrence of PND. Studies evaluating the impact of type of anesthetic, including comparisons between general and neuraxial anesthetics, on the

development of PND have demonstrated mixed results. Inhalation versus intravenous anesthetics have also been compared without definite superiority of one over the other. However, increasing anesthetic depth has been correlated with increased incidence postoperative delirium, and using age-adjusted anesthetic dosages is important. Maintenance of adequate cerebral perfusion can also not be underestimated. The use of specialized monitors, including processed EEG and near-infrared spectroscopy, have been investigated as strategies to mitigate risk of PND. Benzodiazepines, opioids, and ketamine have also been associated with increased risk of PND, while there are some data to support use of intraoperative dexmedetomidine to reduce the risk of postoperative delirium.

NEUROOCULAR DISORDERS

Disorders involving the visual system discussed in this section are limited to those affecting the retina, optic nerve, and intracranial optic system. Degenerative diseases involving this part of the visual system include Leber optic atrophy, retinitis pigmentosa, and Kearns-Sayer syndrome. The most common cause of new-onset blindness during the postoperative period is ischemic optic neuropathy. Other causes of postoperative visual defects are cortical blindness, retinal artery occlusion, and ophthalmic vein obstruction.

Leber Optic Atrophy

Leber optic atrophy, or Leber hereditary optic neuropathy, is characterized by degeneration of the retina and atrophy of the optic nerves, resulting in blindness. This disorder was the first human disorder for which a mitochondrial pattern of inheritance was definitively described. This rare disorder usually presents as loss of central vision in adolescence or early adulthood and is often associated with other neuropathologic conditions, including multiple sclerosis and dystonia.

Retinitis Pigmentosa

Retinitis pigmentosa refers to a genetically and clinically heterogeneous group of inherited retinopathies characterized by degeneration of the retina. These debilitating disorders collectively represent a common form of human visual handicap, with an estimated prevalence of approximately 1 in 3000. Examination of the retina shows areas of pigmentation, particularly in the peripheral regions. Vision is lost from the periphery of the retina toward the center until total blindness occurs.

Kearns-Sayer Syndrome

Kearns-Sayer syndrome, a mitochondrial myopathy, is characterized by retinitis pigmentosa associated with progressive external ophthalmoplegia, typically manifesting before 20 years of age. Cardiac conduction abnormalities, ranging from bundle branch block to complete atrioventricular heart block, are common. Complete heart block can occur abruptly, leading to sudden death. Generalized degeneration of the central nervous system has been observed. Although Kearns-Sayer syndrome is rare, it is possible that patients with this disorder will require anesthesia for insertion of implantable cardiac pacemakers.

Management of anesthesia requires a high index of suspicion for, and preparation to treat, third-degree atrioventricular heart block. Transthoracic pacing capability must be available. Experience is too limited to recommend specific drugs for induction and maintenance of anesthesia. Presumably, the response to succinylcholine and nondepolarizing muscle relaxants is not altered, since this disease does not involve motor neurons or the neuromuscular junction.

Ischemic Optic Neuropathy

Ischemic optic neuropathy should be suspected in patients who complain of visual loss during the first week following surgery of any form. Ischemic injury to the optic nerve can result in loss of both central and peripheral vision.

The optic nerve can be functionally divided into an anterior and a posterior segment based on differences in blood supply (Fig. 13.5). Blood supply to the anterior portion is derived from both the central retinal artery and small branches of the ciliary artery. In contrast, blood supply to the posterior segment of the optic nerve is derived from small branches of the ophthalmic and central retinal arteries. Baseline blood flow to the posterior segment of the optic nerve is significantly less than that to the anterior segment. Because of this difference, ischemic events in the anterior and posterior segments of the optic nerve are associated with different risk factors and physical findings. However, the prognosis, in terms of improvement of vision, is poor in either case. If ischemic optic neuropathy is suspected, urgent ophthalmologic consultation should be obtained so that other treatable causes of perioperative blindness can be ruled out.

Anterior Ischemic Optic Neuropathy

The visual loss associated with anterior ischemic optic neuropathy is due to infarction within the watershed perfusion zones between the small branches of the short posterior ciliary arteries. The usual presentation is a sudden, painless, monocular visual deficit varying in severity from a slight decrease in visual acuity to blindness. Asymptomatic optic disk swelling may be the earliest sign. A congenitally small optic disk is often present. The prognosis varies, but the most common outcome is minimal recovery of visual function.

The nonarteritic form of anterior ischemic optic neuropathy is more likely than the arteritic form to manifest during the postoperative period. It is usually attributed to decreased oxygen delivery to the optic disk in association with hypotension and/or anemia. This form of visual loss has been associated with hemorrhagic hypotension (e.g., from gastrointestinal hemorrhage), anemia, cardiac surgery, head and neck surgery, cardiac arrest, and hemodialysis. It may also occur spontaneously. Arteritic anterior ischemic optic neuropathy, which is less common than the nonarteritic form, is associated with inflammation and thrombosis of the short posterior ciliary arteries. The diagnosis is confirmed by demonstration of giant cell arteritis on a biopsy sample from the temporal artery. High-dose corticosteroids are used to treat arteritic anterior ischemic optic neuropathy and to provide prophylaxis against disease manifestation in the contralateral eye.

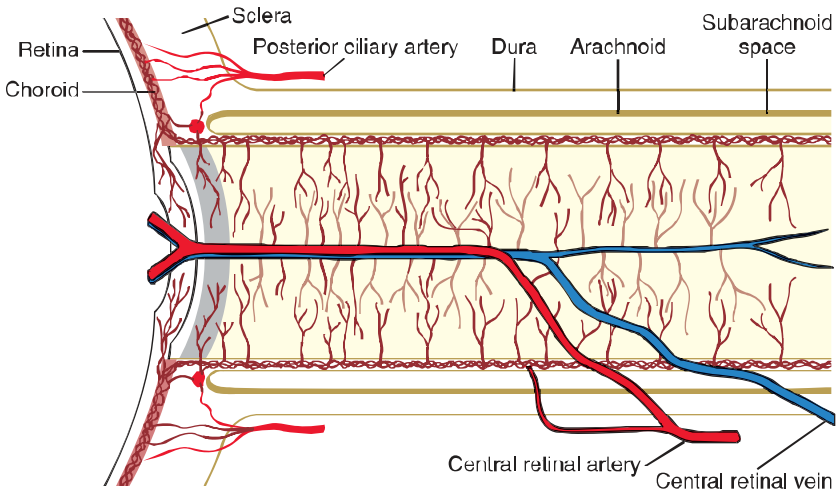

Fig. 13.5 Blood supply to retina and optic nerve. Note the greater supply to the anterior portion of the optic nerve via the central retinal artery. Blood flow to the posterior portion of the optic nerve is supplied by pial perforators and is much less than blood flow to the anterior segment. (Adapted from Hayreh SS. Anatomy and physiology of the optic nerve head. *Trans Am Acad Ophthalmol Otolaryngol.* 1974;78:240–254.)

Posterior Ischemic Optic Neuropathy

Posterior ischemic optic neuropathy presents as acute loss of vision and visual field defects similar to those in anterior ischemic optic neuropathy. It is presumed to be caused by decreased oxygen delivery to the posterior portion of the optic nerve between the optic foramen and the point of entry of the central retinal artery. However, recent data suggest that impedance of venous outflow from the optic nerve may contribute. Spontaneous occurrence is less frequent than with anterior ischemic optic neuropathy. However, posterior ischemic optic neuropathy is more common than anterior ischemic optic neuropathy as a cause of visual loss in the perioperative period. There may be no abnormal ophthalmoscopic findings initially, which reflects retrobulbar involvement of the optic nerve. Mild disk edema is present after a few days, and CT of the orbits may reveal enlargement of the intraorbital optic nerve.

Posterior ischemic optic neuropathy has been described following prolonged spine surgery performed in the prone position, cardiac surgery, radical neck dissection, hip arthroplasty, and robotic prostatectomy. The etiology of posterior ischemic optic neuropathy appears to be multifactorial. Factors associated with increased risk for posterior ischemic optic neuropathy include male sex, obesity, use of the Wilson frame, long-duration procedures, and increased blood loss during surgery. Use of colloid solutions seems to be protective. Other associations, such as anemia, hypotension, excessive fluid administration, and excessive use of vasopressors, are speculative with no formal data to support an association.

Cortical Blindness

Cortical blindness may follow profound hypotension or circulatory arrest/cardiac arrest as a result of hypoperfusion and infarction of watershed areas in the parietal or occipital lobes. This form of blindness has been observed after many different kinds of surgical procedures, such as cardiac surgery, craniotomy, laryngectomy, and cesarean section, and can result from air or particulate emboli during cardiopulmonary bypass. Cortical blindness is characterized by loss of vision but retention of pupillary reactions to light and normal findings on funduscopic examination. Patients may not be aware of focal vision loss, which usually improves with time. The presence of abnormalities in the parietal or occipital lobes on CT or MRI scans confirms the diagnosis.

Retinal Artery Occlusion

Central retinal artery occlusion presents as painless monocular blindness. It is due to occlusion of a branch of the retinal artery. Visual field defects are often severe initially, but unlike with ischemic optic neuropathy they improve with time. Ophthalmoscopic examination reveals a pale edematous retina. Also unlike ischemic optic neuropathy, central retinal artery occlusion is often caused by emboli from an ulcerated atherosclerotic plaque in the ipsilateral carotid artery. Many retinal artery occlusions are due to emboli during open-heart surgery, and these resolve promptly. Vasospasm or thrombosis may also cause central retinal artery occlusion following radical neck surgery complicated by hemorrhage and hypotension. The condition can also occur following intranasal injection of Γ-adrenergic agonists. Stellate ganglion block improves vision in some patients.

Ophthalmic Venous Obstruction

Obstruction of venous drainage from the eyes may occur intraoperatively when patient positioning results in external pressure on the orbits. Placement in the prone position and use of headrests during neurosurgical procedures require careful attention to ensure that the eyeballs and orbits are free from external compression. Ophthalmoscopic examination reveals engorgement of the veins and edema of the macula.

KEY POINTS

- Major goals when providing anesthesia care for patients undergoing neurologic surgery include maintenance of adequate cerebral oxygen delivery, optimization of operative conditions, and facilitation of a rapid, smooth emergence from anesthesia to allow for immediate assessment of neurologic function.
- In the perioperative period, factors affecting CBF include Pao_2 and $Paco_2$, systemic blood pressure, ICP, cerebral autoregulation, and various drugs.
- Major techniques to decrease ICP include head elevation, hyperventilation, CSF drainage, and administration of hyperosmotic drugs, diuretics, corticosteroids, and cerebral vasoconstrictors.
- Venous air embolism can occur in a variety of circumstances, most commonly in patients who are placed in the sitting (or other head-up) position. Techniques available to monitor for the entrainment of air include precordial Doppler ultrasonography, transesophageal echocardiography, and measurement of end-expired carbon dioxide content. Treatment includes discontinuation of nitrous oxide administration, flooding of the surgical field with fluid, aspiration of air via a central venous catheter, and hemodynamic support.
- Succinylcholine should be used with caution in patients with neurologic diseases because of its potential to produce a transient increase in ICP and because of the risk of hyperkalemia in the setting of denervating diseases that cause an upregulation of acetylcholine receptors at the neuromuscular junction.

RESOURCES

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14

Disorders of the Spine and Spinal Cord

Benjamin T. Daxon, Jeffrey J. Pasternak

OUTLINE

ANATOMY OF THE VERTEBRAL COLUMN AND SPINAL CORD

The vertebral column consists of 24 individual vertebrae (7 cervical, 12 thoracic, and 5 lumbar), in addition to the sacrum and coccyx. Basic anatomy of individual vertebrae and the vertebral column is illustrated in Fig. 14.1. Briefly, the anterior section of vertebrae consists of a body and adjacent vertebral bodies that are separated in intervertebral disks. Posteriorly, vertebrae consist of one midline spinous process and two lateral transverse processes. The lamina is the region of bone between spinous and transverse processes and the pedicle is the segment of bone connecting transverse processes with the vertebral body. Posteriorly, adjacent vertebrae articulate at facet joints. The spinal cord is contained within the bony confines of the central canal of the vertebral column.

The spinal cord extends from the medulla oblongata of the brainstem to the lumbar region of the vertebral column. The cross-sectional anatomy of the spinal cord is illustrated in Fig. 14.2. At each vertebral level, the spinal cord gives off bilateral nerve roots. Posterior nerve roots carry afferent information from the periphery to the spinal cord. Deep touch and vibration sensation is carried by the spinal cord to the brain via the posterior columns, whereas pain and temperature information is carried to the brain via the lateral spinothalamic tracts. The corticospinal tract carries efferent information from the brain through the spinal cord, and this information leaves the anterior roots of the spinal cord. Innervation of muscles by spinal roots is summarized in Table 14.1. Blood is supplied to the spinal cord by two posterior spinal arteries that predominantly supply the posterior spinal roots and posterior columns, and an anterior spinal artery that supplies the remainder of the spinal cord.

SPINAL CORD INJURY

Acute Spinal Cord Injury

The mobility of the cervical spine makes it vulnerable to injury, especially hyperextension injury. It is estimated that cervical spine injury occurs in 1.5% to 3% of all major trauma victims. Approximately 4% to 5% of patients with traumatic head injury have a concurrent injury of the spine, typically occurring in the upper cervical spine (i.e., C1–C3). Trauma can also injure the thoracic and lumbar spinal cord segments.

The clinical manifestations of acute spinal cord injury depend on both the extent and the site of injury. Acute spinal cord injury initially produces a state of spinal shock that is characterized by flaccid muscle paralysis with loss of sensation below the level of injury. It should be noted that spinal shock refers to the loss of neurologic function following spinal cord injury, whereas neurogenic shock refers to the manifestations of autonomic nervous system impairment that can result following central nervous system injury.

The extent of injury is commonly described in terms of the American Spinal Injury Association (ASIA) classification system (Table 14.2), which characterizes the injury in terms of both motor and sensory impairment. A score of A indicates a "complete" injury in which all motor and sensory function is

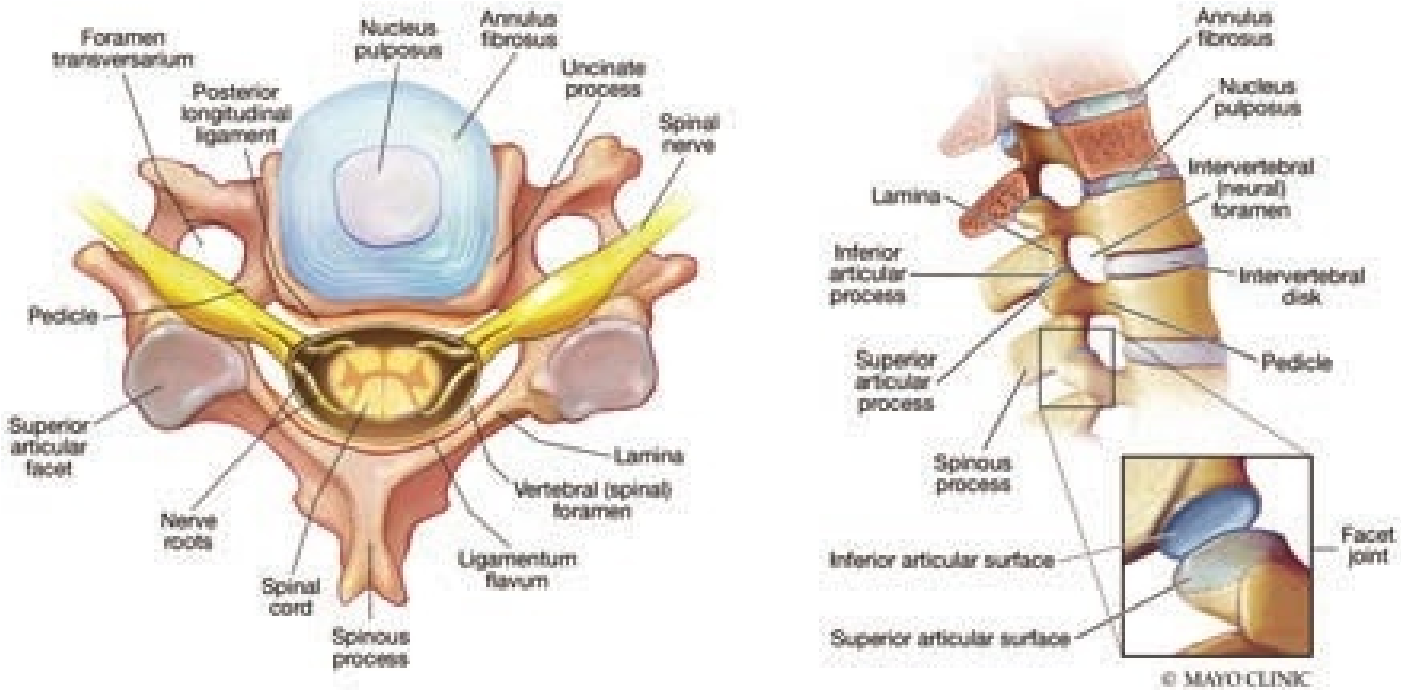

Fig. 14.1 Anatomy of the vertebra and the vertebral column.

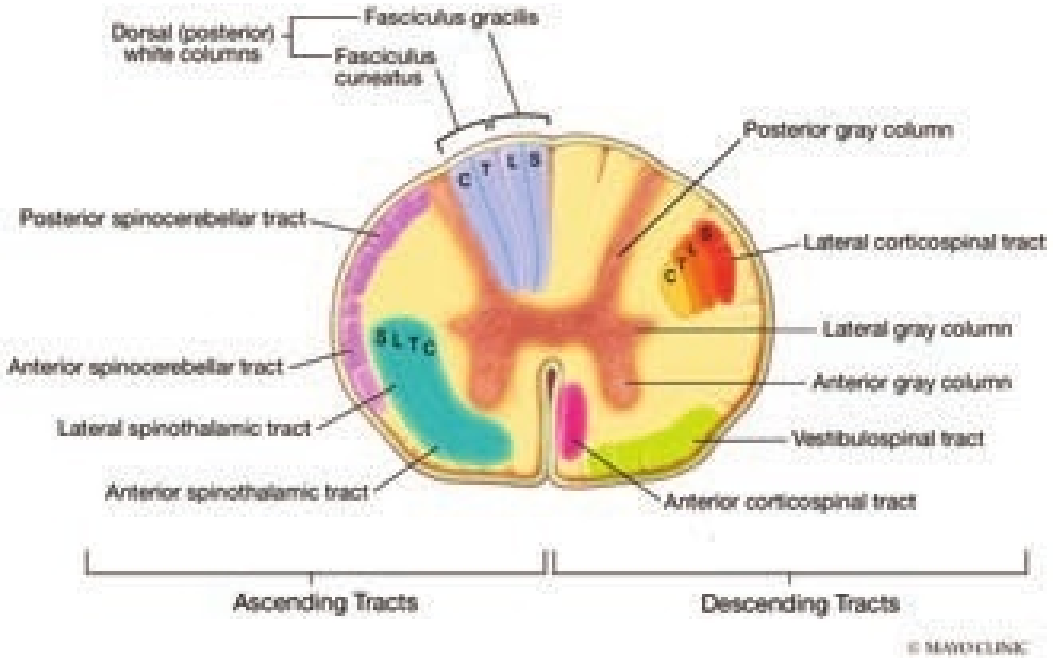

Fig. 14.2 Cross-sectional anatomy of the spinal cord illustrating the location of major tracts.

lost below the level of the lesion, including function at the lower sacral segments of S4 and S5. Lower sacral neurologic function is determined by assessing rectal tone and sensation. Scores of B through D are assigned to "incomplete" lesions in which some degree of spinal cord integrity is maintained below the level of injury. A score of E indicates "normal" spinal cord function.

The extent of physiologic effects from spinal cord injury depends on the level and extent of injury, with the most severe physiologic derangements occurring with complete injury to the cervical cord and lesser perturbations occurring with less complete injury and more caudal cord injuries. Reductions in blood pressure are common, especially with cervical cord injury, and are influenced by (1) loss of sympathetic nervous system activity and a decrease in systemic vascular resistance, and (2) bradycardia resulting from loss of the T1 through T4 sympathetic innervation to the heart (i.e., loss of cardiac accelerator innervation).

TABLE 14.1 Major Muscle Innervations

Muscle	Action	Roots	Nerve
Serratus anterior	Anterior movement of shoulder	C5, C6, C7	Long thoracic
Rhomboids	Scapula adduction	C4, C5	Dorsal scapular
Deltoid	Arm abduction	C5, C6	Axillary
Biceps brachii	Forearm flexion and supination	C5, C6	Musculocutaneous
Flexor carpi ulnaris	Hand flexion	C7, C8, T1	Ulnar
Adductor pollicis	Thumb adduction	C8, T1	Ulnar
Pronator teres	Forearm pronation	C6, C7	Median
Abductor pollicis	Thumb metacarpal abduction	C8, T1	Median
Triceps brachii	Forearm extension	C6, C7, C8	Radial
Extensor carpi radialis	Hand extension	C5, C6	Radial
Iliopsoas	Hip flexion	L1, L2, L3	Femoral
Quadriceps femoris	Knee extension	L2, L3, L4	Femoral
Adductor longus	Thigh adduction	L2, L3, L4	Obturator
Gluteus medius	Thigh abduction and medial rotation	L4, L5, S1	Superior gluteal
Gluteus maximus	Thigh abduction	L5, S1, S2	Inferior gluteal
Biceps femoris	Leg flexion	L5, S1, S2	Sciatic
Tibialis anterior	Foot dorsiflexion	L4, L5, S1	Deep peroneal
Tibialis posterior	Foot plantar flexion	L4, L5	Tibial
Gastrocnemius	Knee flexion and foot plantar flexion	S1, S2	Tibial
Soleus	Foot plantar flexion	S1, S2	Tibial
Rectal sphincter	Rectal sphincter contraction	S2, S3, S4	Pudendal

TABLE 14.2 American Spinal Injury Association Impairment Scale

Category	Description	Definition
A	Complete	No motor function below level of lesion or in sacral segments S4 and S5
B	Incomplete	Sensory but not motor function is preserved below neurologic level and includes S4–S5 segments
C	Incomplete	Motor function is preserved below level of injury and more than half of key muscles below neurologic level have a grade less than 3
D	Incomplete	Motor function is preserved below level of injury and more than half of key muscles below neurologic level have a grade of 3 or more
E	Normal	Sensory and motor function are intact

Hypotension can also occur with thoracic and lumbar cord injuries, although typically it is less severe than with cervical injuries. With cervical and upper thoracic cord injury, the major cause of morbidity and mortality is alveolar hypoventilation combined with an inability to clear bronchial secretions. Respiratory muscles are not affected with lumbar and low thoracic injuries, so minimal respiratory impairment can be expected with these injuries. Aspiration of gastric contents, pneumonia, and pulmonary embolism can also occur.

Cervical spine radiographs are obtained for a large percentage of patients who come for treatment of various forms of trauma and are intended to identify both suspected and occult cervical spine injuries. However, the probability of cervical spine injury is minimal in patients younger than 60 years of age who meet the following five criteria: (1) no midline cervical spine tenderness, (2) no focal neurologic deficits, (3) normal sensorium, (4) no intoxication, and (5) no painful distracting injury. Patients who meet these criteria do *not* require routine imaging studies to rule out occult cervical spine injury.

An estimated two-thirds of trauma patients have multiple injuries that can interfere with cervical spine evaluation. Evaluation ideally includes computed tomography (CT) or magnetic resonance imaging (MRI), but imaging may not be practical in some cases because of the risk of transporting patients in an unstable condition. For this reason, standard radiographic views of the cervical spine, often taken with a portable x-ray machine, are frequently relied upon to evaluate for the presence of cervical spine injury and associated instability. For cervical spine imaging to have greatest utility, the entire cervical spine (including the body of the first thoracic vertebra) must be visible. Images are analyzed for alignment of the vertebrae (lateral view) and presence of fractures (all views), and the disk and soft tissue spaces are evaluated. The sensitivity of plain radiographs for detecting cervical spine injury is less than 100%, so the likelihood of cervical spine injury must be interpreted in conjunction with other clinical signs, symptoms, and risk factors. If there is any doubt, it is prudent to treat all acute cervical spine injuries as potentially unstable until proven otherwise.

Treatment of a cervical fracture or dislocation entails immediate immobilization to limit neck motion. Soft neck collars have little effect in limiting movement of the neck. Hard neck collars limit neck flexion and extension, but only by about 25%; therefore halo-thoracic devices are often needed to provide effective immobilization and traction to prevent cervical spine movement. During direct laryngoscopy with manual inline stabilization (MILS), any cervical collars are removed and an assistant's hands are placed on each side of the patient's face while downward pressure is applied against a firm table surface to hold the head immobile in a neutral position and minimize cervical flexion and extension. MILS can be done with the assistant either behind the patient adjacent to the intubator or with the assistant orthogonal to the patient and the assistant's forearms resting on the patient's chest or clavicles. Hard collars tend to limit mouth opening, but with their removal and application of MILS 56% of patients will improve their Cormack-Lehane grade. Attention must be paid while grasping the head not to apply traction and elongate the cord, which may compromise cord perfusion. Not only can movement of the neck in the presence of cervical spine injury cause mechanical deformation of the spinal cord, but there is an even greater risk that neck motion that elongates the cord will compromise spinal cord blood supply as a result of narrowing the longitudinal blood vessels. In fact, maintenance of spinal cord perfusion pressure may be of more importance than positioning for prevention of spinal cord injury in the presence of cervical spine injury.

Management of Anesthesia

Patients with acute spinal cord injury often require special precautions during airway management. When laryngoscopy is performed, neck movement must be minimized and hypotension avoided so that spinal cord perfusion pressure can be maintained. However, fear of possible spinal cord compression must not prevent necessary airway interventions. Extensive clinical experience supports the use of direct laryngoscopy for orotracheal intubation provided that (1) maneuvers are taken to stabilize the head during the procedure and thus to avoid hyperextension of the neck, (2) prior evaluation of the airway did not suggest the likelihood of any associated technical difficulties, and (3) adequate blood pressure and oxygenation are maintained during airway management. Otherwise, video laryngoscopes are reasonable alternates to direct laryngoscopy. Awake fiberoptic laryngoscopy with topical anesthesia is another alternative to direct laryngoscopy if the patient is cooperative and airway trauma—with associated blood, secretions, and anatomic deformities—does not preclude visualization with the fiberscope. It is important to remember that coughing during topical anesthetization of the airway and fiberoptic intubation may result in cervical spine movement. It is reasonable to have an assistant maintain MILS during *all* airway manipulations. There is no evidence of increased neurologic morbidity after elective or emergency orotracheal intubation of anesthetized or awake patients who have an unstable cervical spine if appropriate steps are taken to minimize neck movement. Awake tracheostomy is reserved for the most challenging airway conditions, in which neck injury, combined with facial fractures or other severe anomalies of airway anatomy, makes securing the airway by nonsurgical means difficult or unsafe. Airway management in the presence of cervical spine injury should be dictated by common sense, not dogmatic approaches. Certainly, clinical experience supports the safety of a variety of airway management techniques.

The absence of compensatory sympathetic nervous system responses in patients with cervical or high thoracic spinal cord injury makes these patients particularly vulnerable to significant decreases in blood pressure following changes in body position, blood loss, or positive pressure ventilation. To minimize these effects, liberal intravenous infusion of crystalloid solutions may be necessary to maintain intravascular volume, which has been compromised by vasodilation. Acute blood loss should be treated promptly. Electrocardiographic abnormalities are common during the acute phase of spinal cord injury, especially with cervical cord injuries. Breathing is best managed by mechanical ventilation, since abdominal and intercostal muscle weakness or paralysis is exacerbated by general anesthesia and increases the likelihood of respiratory failure with ensuing hypoxemia and hypercapnia. Body temperature should be monitored and manipulated because patients tend to become poikilothermic in dermatomes below the level of the spinal cord lesion. Maintenance of anesthesia is targeted at ensuring physiologic stability and facilitating tolerance of the endotracheal tube. Volatile and intravenous anesthetics are both satisfactory. Nitrous oxide should be used with great caution, if at all, given concerns for coexisting trauma and air entrainment in closed spaces, as can occur with basilar skull fracture or rib fracture. Arterial hypoxemia is common following spinal cord injury, which emphasizes the need for continuous pulse oximetry and oxygen supplementation.

Muscle relaxant use should be based on the operative site and the level of spinal cord injury. Succinylcholine does not provoke excessive release of potassium during the first few hours after spinal cord injury. Use of a nondepolarizing relaxant, with mask ventilation and possible cricoid pressure, is another alternative to airway management during anesthetic induction and before laryngoscopy. A nondepolarizing relaxant may also facilitate patient positioning.

Chronic Spinal Cord Injury

Sequelae of chronic spinal cord injury include impaired alveolar ventilation, autonomic hyperreflexia, chronic pulmonary and genitourinary tract infections, renal stones and possible renal dysfunction, anemia, and altered thermoregulation. Injuries that occur more rostral along the spinal cord tend to have more significant systemic effects. Chronic urinary tract infection reflects the inability to empty the bladder completely and predisposes to calculus formation. As a result, renal failure may occur and is a common cause of death in patients with chronic spinal cord injury. Prolonged immobility leads to osteoporosis, skeletal muscle atrophy, and decubitus ulcers. Immobility also predisposes patients to deep venous thrombosis, so prophylactic measures such as use of compression stockings, low-dose anticoagulant therapy, and insertion of inferior vena cava filters may be indicated. Pathologic fractures can occur when these patients are moved. Pressure points should be well protected

and padded to minimize the likelihood of trauma to the skin and the development of decubitus ulcers.

Chronic pain and depression are common problems following spinal cord injury. Nerve root pain is localized at or near the level of injury. Visceral pain is produced by distention of the bladder or bowel. Phantom pain can occur in areas of complete sensory loss. There may also be a loss of lifestyle and ability that frustrates and depresses many. As a result, many patients are often treated with antidepressants and analgesics, including opioids that require attention when anesthetic management is planned (e.g., avoidance of serotonin syndrome by judicious use of serotonergic agents such as ondansetron or fentanyl for patients on selective serotonin reuptake inhibitors [SSRIs] or monoamine oxidase inhibitors [MAOIs]).

Several weeks after acute spinal cord injury, spinal cord reflexes gradually return, and patients enter a more chronic stage characterized by overactivity of the sympathetic nervous system and involuntary skeletal muscle spasms. Baclofen, which potentiates the inhibitory effects of γ-aminobutyric acid (GABA), is useful for treating spasticity. Abrupt cessation of baclofen therapy, as may occur with hospitalization for an unrelated problem, may result in withdrawal reactions that can include seizures. Diazepam and other benzodiazepines also facilitate the inhibitory effects of GABA and may have utility in the management of a patient receiving baclofen. Spasticity refractory to pharmacologic suppression may require surgical treatment via dorsal rhizotomy or myelotomy, but usually implantation of a spinal cord stimulator or subarachnoid baclofen pump will be undertaken before rhizotomy is considered.

Spinal cord injury at or above the fifth cervical vertebra may result in apnea caused by denervation of the diaphragm ("C three, four, and *five* to keep the diaphragm *alive*"). With function of the diaphragm intact, tidal volumes are likely sufficient, but coughing and secretion clearance are often impaired because of decreased expiratory reserve volumes from denervation of intercostal and abdominal muscles. Indeed, acute spinal cord injury at the cervical level is accompanied by marked decreases in vital capacity. Arterial hypoxemia is a consistent early finding following cervical spinal cord injury. Tracheobronchial suctioning has been associated with bradycardia and even cardiac arrest in these patients, so it is important to optimize arterial oxygenation before suctioning the airway.

Management of Anesthesia

Anesthetic management in patients with chronic spinal cord injury should focus on preventing autonomic hyperreflexia. When general anesthesia is selected, administration of muscle relaxants is useful to facilitate tracheal intubation and prevent reflex skeletal muscle spasms in response to surgical stimulation. Nondepolarizing muscle relaxants are the primary choice in this circumstance, since succinylcholine may provoke hyperkalemia, most commonly during the initial 6 months after spinal cord injury. Indeed, it seems reasonable to avoid succinylcholine after 24 hours from spinal cord injury.

The anesthesiologist must be aware of the potential for altered hemodynamics, especially with cervical and high thoracic cord lesions. These can manifest as wide alterations in both blood pressure and heart rate. In chronically immobile patients, the index of suspicion for pulmonary thromboembolism, which can manifest as alterations in hemodynamics and oxygenation, must be high. If intercostal muscle function is impaired, patients may be at high risk of postoperative hypoventilation and may have an impaired cough and a corresponding accumulation of secretions. Baclofen and benzodiazepines should be continued throughout the perioperative period to avoid withdrawal symptoms. Patients with impaired renal function may require close attention to fluid administration, serum electrolyte concentrations, and potential altered pharmacology of drugs eliminated by the kidney. Prophylaxis against deep venous thrombosis should be continued.

Autonomic Hyperreflexia

Autonomic hyperreflexia appears following spinal shock and in association with return of spinal cord reflexes. This reflex response can be initiated by cutaneous or visceral stimulation below the level of spinal cord injury. Surgery and distention of a hollow viscus such as the bladder or rectum are common stimuli.

Stimulation below the level of spinal cord injury initiates afferent impulses that enter the spinal cord (Fig. 14.3). Because of reflexes entirely within the spinal cord itself, these impulses elicit an increase in sympathetic nervous system activity along the splanchnic outflow tract. In neurologically intact individuals, this outflow would be modulated by inhibitory impulses from higher centers in the central nervous system, but in the presence of a spinal cord lesion this outflow is isolated from inhibitory impulses from above, so generalized vasoconstriction occurs below the level of the spinal cord injury. Because of the intense vasoconstriction, reflex bradycardia and cutaneous vasodilation occur above the level of the spinal cord injury, which is often inadequate to overcome the increased blood pressure. Nasal stuffiness reflects the vasodilation, while headaches and blurred vision reflect severe hypertension. This increase in blood pressure can result in cerebral, retinal, or subarachnoid hemorrhage as well as increased operative blood loss. Loss of consciousness and seizures may also occur, and cardiac arrhythmias are often present. Pulmonary edema reflects acute left ventricular failure resulting from dramatically increased afterload.

The incidence of autonomic hyperreflexia depends on the level of spinal cord injury. Approximately 85% of patients with lesions above T6 exhibit this reflex. It is unlikely to be associated with spinal cord lesions below T10. Also, in patients with cervical or high thoracic spinal cord lesions, those with complete lesions are more likely to exhibit autonomic hyperreflexia than those with incomplete lesions. The incidence and severity also diminish the further out from injury.

Management of patients at risk should begin with efforts to prevent the development of autonomic hyperreflexia. Patients who have no history of this reflex are still at risk of its occurrence during surgery simply because of the intense stimuli that surgery can produce. Before surgical or other stimulation is initiated in locations that lack sensory innervation, general, neuraxial, or regional anesthesia should be instituted. Epidural

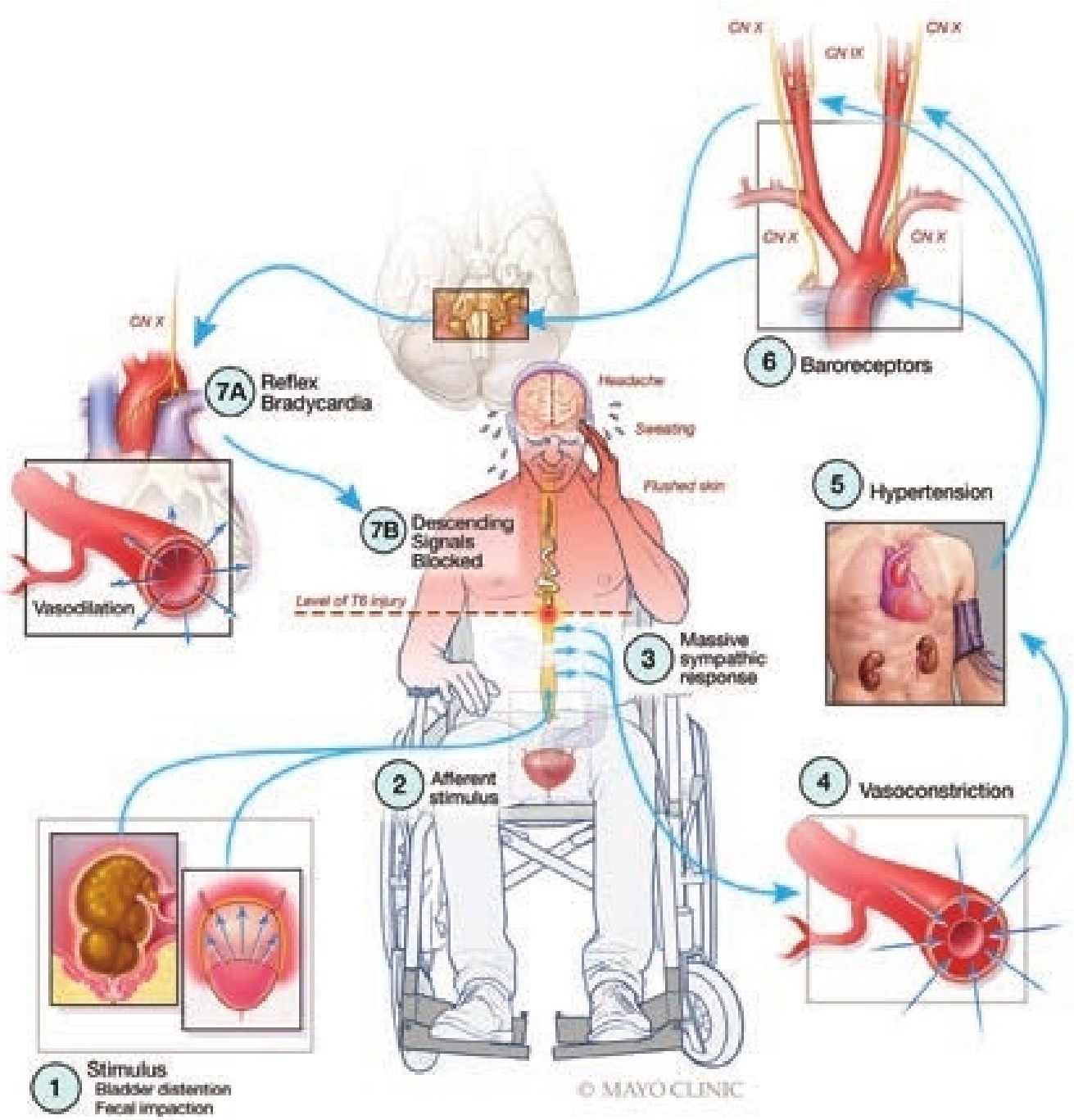

Fig. 14.3 Pathophysiology of autonomic hyperreflexia.

anesthesia has been described for the treatment of autonomic hyperreflexia provoked by uterine contractions during labor. However, epidural anesthesia may be less effective than spinal anesthesia in preventing autonomic hyperreflexia because of its relative sparing of the sacral segments and lesser block density. Blocking afferent pathways with topical local anesthetics applied to the urethra for a cystoscopic procedure does not prevent autonomic hyperreflexia because this form of anesthesia does not block the bladder muscle proprioceptors that are stimulated by bladder distention.

Regardless of the anesthesia technique selected, vasodilator drugs having a short half-life (e.g., clevidipine) should be readily available to treat sudden-onset severe hypertension. Persistence of hypertension requires continuous infusion of vasodilators, perhaps supplemented with longer-acting drugs such as hydralazine. It is important to note that autonomic hyperreflexia may first manifest postoperatively when the effects of the anesthetic drugs begin to wane.

ELECTIVE SPINE SURGERY

The indications and populations of patients requiring surgery on the spine are very diverse and represent a variety of indications in a wide range of patient ages. Some of the major indications for

spine surgery include disk disease, spinal stenosis, spondylolisthesis, scoliosis, and spinal cord tumors.

Indications for Elective Spine Surgery

Disk Disease

A common cause of back and neck pain is intervertebral disk disease. The intervertebral disk is composed of a compressible nucleus pulposus surrounded by a fibrocartilaginous annulus fibrosis. The disk acts as a shock absorber between vertebral bodies. Trauma or degenerative processes lead to changes in the intervertebral disk. Nerve root or spinal cord compression results when the nucleus pulposus protrudes through the annulus fibrosis. With compression of a single nerve root (i.e., a radiculopathy), patients usually complain of pain in a single dermatomal distribution or localized muscle weakness. Spinal cord compression can lead to complex sensory, motor, and autonomic symptoms at and below the level of the insult. CT or MRI confirms the diagnosis and the location of intervertebral disk herniation. Initial treatment of cervical disk protrusion is typically conservative and includes rest, pain control, and possibly epidural administration of steroids. Surgical decompression is necessary if symptoms do not abate with conservative treatment or if there is significant motor involvement.

Spondylosis and Spondylolisthesis

Spondylosis is a common acquired degenerative disorder that leads to osteophyte formation and degenerative disk disease. The term *spondylosis* is used synonymously with spinal stenosis. There is narrowing of the spinal canal and compression of the spinal cord by transverse osteophytes or nerve root compression by bony spurs in the intervertebral foramina. Spinal cord dysfunction can also reflect ischemia of the spinal cord caused by bony compression of the spinal arteries. Symptoms typically develop insidiously after age 50 years. With cervical spondylosis, neck pain and radicular pain in the arms and shoulders are accompanied by sensory loss and skeletal muscle atrophy. Later, sensory and motor signs may appear in the legs producing an unsteady gait. Lumbar spondylosis usually leads to radicular pain and muscle atrophy in the lower extremities. Sphincter disturbances are uncommon regardless of the location of spondylosis. Radiographs of the spine often demonstrate osteoarthritic changes, but these changes correlate poorly with neurologic symptoms. Surgery may be necessary to arrest progression of the symptoms, especially if there is evidence of motor loss.

Spondylolisthesis refers to anterior subluxation of one vertebral body on another. This most commonly occurs at the lumbosacral junction. Radicular symptoms usually involve the nerve root inferior to the pedicle of the anteriorly subluxed vertebra. Treatment includes analgesics, antiinflammatory medications, and physical therapy if low back pain is the only symptom. Surgery is reserved for patients who have myelopathy, radiculopathy, or neurogenic claudication.

Scoliosis

Scoliosis refers to the sideward bending or rotation of the vertebral column. In most circumstances, scoliosis is an incidental finding and is asymptomatic. A greater curvature can result in pain or physical deformity, and severe cases can impact chest wall dynamics during breathing. In most circumstances, scoliosis is idiopathic with no attributable cause but is associated with a family history of scoliosis. Idiopathic scoliosis often presents before or during early adolescence with an equal rate among males and females. However, mild asymptomatic scoliosis is approximately 10 times more likely to increase in severity among females. Other conditions associated with an increased incidence of scoliosis include but are not limited to cerebral palsy, Marfan syndrome, muscular dystrophy, spinal muscular atrophy, Ehlers-Danlos syndrome, dwarfism, and prior vertebral column trauma. Conservative treatment for mild scoliosis includes exercise and physical therapy focused at strengthening the paraspinal musculature and bracing. For progressive or severe cases, spinal fusion surgery may be required.

Spinal Cord Tumors

Spinal cord tumors can be divided into two broad categories. (1) Intramedullary tumors are located within the spinal cord and account for approximately 10% of tumors affecting the spinal column. Gliomas and ependymomas account for the vast majority of intramedullary tumors. (2) Extramedullary tumors can be either intradural or extradural. Neurofibromas and meningiomas account for most of the intradural tumors. Metastatic lesions, usually from lung, breast, or prostate cancer or myeloma, are the most common extradural lesions. Other mass lesions of the spinal cord, including abscesses and hematomas, share many of the clinical signs and symptoms of tumors.

Spinal cord tumors typically present with symptoms of cord compression. Pain is common and usually aggravated by coughing or straining. Sometimes spinal tenderness may be present. Motor symptoms and sphincter disturbances may occur. Diagnosis is usually based on symptoms and imaging of the spinal cord. MRI is the technique of choice. Treatment and prognosis depend on the nature of the lesion, and treatment may include corticosteroids, radiation therapy, chemotherapy, or surgical decompression or excision.

Management of Anesthesia

Elective surgical procedures on the spine can range in complexity from simple procedures, such a microdiskectomy that can be performed as an outpatient procedure, to complex procedures involving fusion of multiple vertebral levels or staged procedures involving access to both the anterior and posterior vertebral elements. Further, patients can vary in age from adolescents to elderly and vary in medical complexity from healthy patients to those with severe medical illnesses. As such, anesthesia for each spine procedure must be individualized to address patient characteristics and both surgical requirements and complexity.

General anesthesia is often used for patients having spine surgery, although simple lumbar diskectomies can be performed with spinal anesthesia if the patient is motivated, is able to remain in the prone position for the duration of surgery, and does not have any contraindications for neuraxial anesthesia. Also, regional anesthesia might not be optimal for patients with suspected or known difficult airway and those who are obese or

claustrophobic. Intrathecal drugs should include a local anesthetic, such as bupivacaine, with or without a shorter-acting opioid, such as fentanyl. Long-acting opioids should be used with caution, as simple diskectomies may be performed as an outpatient procedure, and patients who received intrathecal doses on long-acting opioids are at risk for delayed respiratory depression. If mild sedation is administered intravenously, supplemental oxygen may be considered.

For patients having general anesthesia, disease of the cervical spine can impact airway management plan. For those with an unstable cervical spine, awake fiberoptic intubation with MILS or asleep intubation with MILS via either direct or video laryngoscopy can be considered. Airway management technique should be dictated by patient status and clinician experience, not by dogmatic ideas. For surgeries involving an anterior approach to the cervical spine, traction of the airway can injure the recurrent laryngeal nerve, a phenomenon that may be due in part to pressure on submucosal branches of the recurrent laryngeal nerve by the endotracheal tube on the convex surface of the retracted trachea. It is recommended that during these procedures, following airway retraction, air should be removed from the endotracheal tube cuff with subsequent replacement of just enough air so that a leak around the cuff does not exist. This will mitigate the pressure by the cuff and tracheal tube on the convex surface of the trachea.

Although most spine procedures are performed with the patient in the prone position, occasionally procedures may be performed in the supine, sitting, or rarely even the lateral decubitus position. For patients having surgery in the prone position, their face should be positioned in a face pillow with care to avoid compression of the eyes or pressure on the nose, chin, or forehead. Alternatively, in those with limited cervical range of motion or who are undergoing a prolonged procedure in the prone position, a Mayfield head-holder may be considered to allow for flexibility in neck positioning and to avoid compression of the eyes and other facial pressure points. Depending on the nature of surgery and flexibility of the patient's shoulders, the arms may be up in the superman or surrender position or tucked at the patient's sides. Care must be exercised to avoid excessive (>90-degree) arm abduction and excessive traction on shoulder musculature, as this can result in nerve damage. Pressure points at the elbow, to avoid ulnar nerve compression, and at the hips and knees should be padded. In those having surgery supine, such as during the anterior approach to the cervical or lumbar spine, the patient's arms are often tucked at the sides. Anesthetic management of patients having surgery in the sitting position is discussed in detail in Chapter 13.

Induction of general anesthesia can be accomplished with short-acting opioids, such as fentanyl, in addition to intravenous hypnotic drugs, such as propofol, ketamine, or etomidate. In most circumstances of patients undergoing tracheal intubation following induction of anesthesia, a muscle relaxant is often used to facilitate this procedure and assist with patient positioning. Succinylcholine should be avoided in patients with preexisting neurologic deficits due to risk for hyperkalemia. In patients in whom baseline motor evoked potentials are being measured prior to and following positioning, a nondepolarizing muscle relaxant used for intubation will interfere with this process. In these patients, if not contraindicated, succinylcholine can be considered. Alternatively, remifentanil, administered as a 3- to 5-μg/kg intravenous bolus following loss of consciousness, can facilitate tracheal intubation, though attention must be given to potential bradycardia with this technique.

General anesthesia can be maintained with inhaled, injectable, or a combination of inhaled or injectable hypnotic drugs. Monitoring should consist of American Society of Anesthesiologists standard monitors. An intraarterial line can be helpful during more complex and invasive procedures to monitor blood pressure and to obtain blood samples. A urinary catheter should be considered for any case expected to be longer that 1 to 2 hours. Central venous access should be considered for any patient expected to have significant blood loss.

Frequently, electromyography, somatosensory-evoked potential monitoring, and motor-evoked potential monitoring may be used to monitor spinal cord or nerve root integrity and have a variety of anesthetic implications. The preferred approach may vary among institutions. In procedures employing only electromyography, pharmacologic paralysis should be avoided, and a deeper plane of anesthesia may be needed to minimize the risk of patient movement. If somatosensory-evoked potentials are used alone, nitrous oxide should be avoided, and other inhaled anesthetics should be minimized to less than 1 minimum alveolar concentration (MAC) or avoided. Maintenance of anesthesia in these cases will likely need supplementation with propofol and opioids. Muscle relaxation will not interfere with somatosensory-evoked potentials. When motor-evoked potential monitoring is employed alone or in combination with electromyography or somatosensory-evoked potentials, muscle relaxation should be avoided. Inhaled anesthetics, including nitrous oxide, can suppress motor-evoked potential waveforms and should either be minimized or avoided. Anesthesia can be maintained with a combination of propofol and opioids. Given the risk for tongue laceration due to jaw contraction during motor-evoked potential stimulation, a bite block should be placed. It is important to note that evoked potential waveforms may be more sensitive to anesthetic drug suppression in patients with preexisting neurologic deficits compared to those who are neurologically intact prior to surgery. This may require avoiding inhaled anesthetic drugs and minimizing propofol dosing to within reason. To compensate, opioid dosing can be increased, as opioids tend to have less of a suppressant effect on somatosensory- and motor-evoked potential waveforms compared to inhaled or injected hypnotic drugs.

Blood pressure should be maintained within 20% of the patient's preoperative values. Excessive hypertension can increase risk for bleeding, and hypotension can impair spinal cord perfusion and may impair optic nerve perfusion in those having prolonged procedures in the prone position. Oxygen should be administered to maintain normoxia, and ventilation should be adjusted to maintain normocapnia. Temperature should be monitored, and normothermia should be maintained. Intravenous fluids should consist of balanced crystalloid solutions administered to maintain euvolemia and adequate urine output

for those patients with a urinary catheter in place. Colloid solutions, such as 5% albumin, may be considered in addition to crystalloid solutions, especially in patients at significant risk for ischemic optic neuropathy, as albumin administered to treat bleeding and hypovolemia has been shown to be protective against ischemic optic neuropathy. Ischemic optic neuropathy is discussed in detail in Chapter 13.

Blood products should be administered to treat excessive blood loss, anemia, and coagulopathy. In most patients without significant systemic diseases, hemoglobin should be maintained at or above 7 to 8 g/dL. For patients at increased risk for bleeding or those sustaining significant intraoperative blood loss, intraoperative cell salvage and tranexamic acid can be considered. A variety of dosing strategies for tranexamic acid are described in the literature, including a 10-mg/kg bolus followed by an infusion of 2 mg/kg/hr during the procedure. Induced hypotension to minimize bleeding is *not* recommended, as it may impair perfusion to other vital organs such as the brain, coronary circulation, kidneys, and optic nerves.

Analgesic management of patients having spine surgery can vary significantly depending on the procedure and the patient's preoperative tolerance to opioids. However, in all circumstances, a multimodal approach is preferred. For simpler procedures, such as single-level microdiskectomy, short-acting opioids such as fentanyl in combination with acetaminophen may be sufficient. For patients undergoing complex spine surgery or in those with opioid tolerance, a more complex analgesic plan will be required. Preoperative gabapentin or pregabalin may be considered but should be used with caution as it may lead to excessive sedation at the end of the procedure. A combination of long-acting opioids and acetaminophen should be considered. Other nonsteroidal antiinflammatories, such as ketorolac, may increase risk for bleeding and are associated with a theoretical risk for impairment of ossification at spinal fusion sites; therefore they should be used with caution, if at all. Low-dose ketamine, administered as intermittent boluses or by continuous infusion, may reduce opioid requirements and minimize any risk of opioid-induced hyperalgesia. Like ketamine, dexmedetomidine, administered as an intraoperative infusion, can also provide analgesia without impacting ventilation postoperatively and likely decreases opioid requirements. Intravenous methadone may also be considered for more complex surgeries and pain-prone patients, as its long half-life provides continuous analgesia for several days. Furthermore, it provides both opioid agonism and glutamate antagonism (among other actions), offering multimodal treatment of pain in a single drug. Other analgesic techniques include infiltration of the incision site with local anesthetics or liposomal bupivacaine, administration of intrathecal opioids, or even epidural analgesia. Use of a local anesthetic for intrathecal injection or for epidural infusion may impair the ability to obtain a postoperative neurologic exam after surgery and should be used only after discussion with the surgical team.

Following simple spine procedures, the patient is frequently extubated in the operating room and transferred to the recovery room. Delay of extubation should be considered in patients at risk for significant airway edema, such as those who were in the prone position for a long duration, those who required fluid resuscitation due to significant intraoperative blood loss, and obese patients due to impaired venous return from increased intrathoracic pressure while in the prone position that can result in venous congestion. In patients at risk for airway edema, checking a cuff leak or assessing the degree of airway edema with point-of-care ultrasound can be useful. Additionally, extubation over a tube exchanger in those at risk for airway edema may allow for oxygenation if edema leads to airway compromise while means to resecure the airway are planned and executed.

CONGENITAL ANOMALIES AND DEGENERATIVE DISEASES OF THE VERTEBRAL COLUMN

Spina Bifida Occulta

Spina bifida occulta results from the incomplete formation of a single lamina in the lumbosacral spine without other abnormalities (Fig. 14.4). It is a congenital defect that is present in an estimated 5% of individuals. It usually produces no symptoms and is often discovered as an incidental finding on radiographic

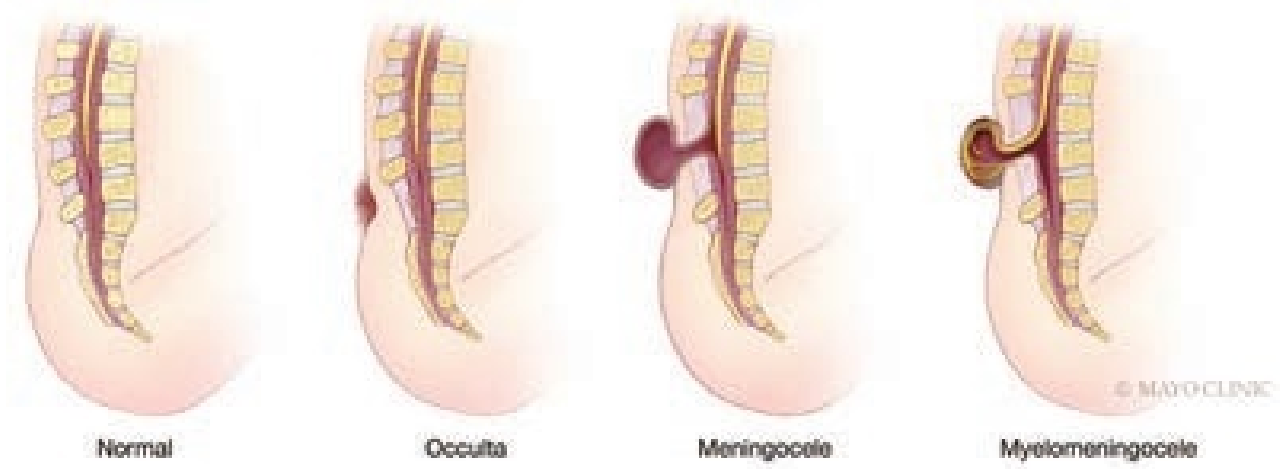

Fig. 14.4 Major caudal neural tube defects.

examination during evaluation of some other unrelated disease process. Because there are no associated abnormalities, an increased risk with spinal anesthesia is not expected, and large numbers of these patients have undergone spinal anesthesia safely.

Meningocele and Myelomeningocele

During fetal development, closure of the neural tube is required for normal formation of the brain, spinal cord, and their enclosing structures: the cranium and vertebral canal. Failure of the neural tube to appropriately close in the caudal segments results in neural tube defects. Herniation of contents of the spinal canal result in meningocele and myelomeningocele if the herniated contents contain only meninges and cerebrospinal fluid versus meninges, cerebrospinal fluid, and neural elements, respectively (see Fig. 14.4). This is opposed to a pseudomeningocele that refers to a collection of cerebrospinal fluid that does not contain meninges or neural elements and usually results from trauma or surgery. Meningocele is relatively rare and usually associated with a lower incidence and severity of neurologic deficits. Myelomeningocele is the most common severe congenital anomaly of the spine. Although it usually occurs in the lumbosacral region, myelomeningocele can also occur in cervical or thoracic regions of the vertebral column and cord. Increased risk is associated with maternal folate deficiency and can occur in the setting of other congenital anomalies such as trisomy 13, trisomy 18, and type II Chiari malformations. Hydrocephalus can also occur, especially if a type II Chiari malformation is coexistent. A myelomeningocele often results in sensory and motor deficits that can be severe. Patients often also have bowel and bladder dysfunction. Due to frequent and multiple exposures from a very early age to medical products containing latex, patients with myelomeningocele often develop latex sensitivity; thus perioperative exposure to latex should be avoided. Perioperative management should include avoidance of succinylcholine due to increased risk for hyperkalemia in the setting of motor deficits. Resistance to nondepolarizing muscle relaxants can occur in weak extremities, thus titration of muscle relaxant dose should not be based on monitoring of the lower extremities. The clinician should also be aware of other neurologic deficits that may be related to hydrocephalus, such as the presence of a cerebrospinal fluid–diverting shunt or a Chiari malformation. In utero surgical repair of a myelomeningocele may reduce the incidence of associated hydrocephalus and improve overall neurologic function.

Tethered Spinal Cord Syndrome

During fetal development, the vertebral column develops and elongates at a rate greater than the spinal cord. Abnormal attachments of the spinal cord to the vertebral column can result in stretching of the spinal cord and the development of tethered spinal cord syndrome. These abnormal attachments can occur in the setting of myelomeningocele, dermal sinus tracts, lipomatous tissue in the spinal canal, diastematomyelia (or a bifurcated spinal cord), or a filum terminale of reduced elasticity. Also, trauma or injury to the spinal cord and vertebral column can cause scar formation that can lead to cord tethering. Spinal cord stretch leads to dysfunction. Depending on the cause and severity, tethered spinal cord syndrome can present at any stage of life, from early childhood through adulthood. Many individuals with a tethered spinal cord have cutaneous manifestations overlying the anomaly, including tufts of hair, hyperpigmented areas, cutaneous lipomas, and skin dimples. Scoliosis and foot deformities such as clubfoot may also occur. Performance of spinal anesthesia in patients with a tethered spinal cord may increase the risk of cord injury. Normally, the conus medullaris lies at the level of L1 to L2 in adults. Patients with tethered spinal cord syndrome often have a conus medullaris that lies lower than the L2 level, but the absence of a low-lying conus medullaris does not rule out the diagnosis. This latter effect may be due to stretch of the cord without associated lengthening of the cord or a functional cord stretch that may occur only with changes in position. Patients may present with motor and sensory deficits with bladder and bowel incontinence. Surgical management often involves release of tethering if possible. Spinal anesthesia should be avoided in these patients to reduce risk for exacerbation of neurologic deficits. In patients with motor deficits, succinylcholine should be avoided due to risk for hyperkalemia. Resistance to nondepolarizing muscle relaxants can also occur.

Syringomyelia

Syringomyelia, also known as syrinx, is a disorder in which there is cystic cavitation of the spinal cord. The condition is often congenital, but it can also occur following spinal cord trauma or in association with various neoplastic conditions such as gliomas. Rostral extension into the brainstem is called syringobulbia. Two main forms of syringomyelia occur depending on whether there is communication of the cystic regions with the subarachnoid space or central canal. In communicating syringomyelia, either there is only dilation of the central canal of the cord, known as hydromyelia, or there is communication between the abnormal cystic lesions in the spinal cord proper and the cerebrospinal fluid spaces. Communicating syringomyelia is usually associated with either a history of basilar arachnoiditis or Chiari malformation. In contrast, the presence of cysts that have no connection to the cerebrospinal fluid spaces is called noncommunicating syringomyelia and is often associated with a history of trauma, neoplasms, or arachnoiditis.

Signs and symptoms of congenital syringomyelia usually begin during the third or fourth decade of life. Early complaints are those of sensory impairment involving pain and temperature sensation in the upper extremities. This reflects compromise of pain and temperature neuronal pathways that cross within the spinal cord near the central canal. As cavitation of the spinal cord progresses, destruction of lower motor neurons ensues with the development of skeletal muscle weakness and wasting as well as loss of reflexes. Thoracic scoliosis may result from weakness of paravertebral muscles. Syringobulbia is characterized by paralysis of the palate, tongue, and vocal cords and loss of sensation over the face. MRI is the preferred procedure to diagnose syringomyelia.

There is no known treatment that is effective in arresting the progressive degeneration of the spinal cord or medulla. Surgical

procedures designed to restore normal cerebrospinal fluid flow have not been predictably effective.

Management of anesthesia in patients with syringomyelia or syringobulbia should consider the neurologic deficits associated with this disease. Thoracic scoliosis can contribute to pulmonary ventilation/perfusion mismatching. Lower motor neuron disease with skeletal muscle wasting suggests the possibility that hyperkalemia can develop after administration of succinylcholine. Altered responses to nondepolarizing muscle relaxants can be observed. Thermal regulation may be impaired. The selection of drugs for induction and maintenance of anesthesia is not influenced by this disease. With syringobulbia, any decrease in or absence of protective airway reflexes may influence the timing of endotracheal tube removal postoperatively.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a degenerative disease involving (1) the lower motor neurons in the anterior horn gray matter of the spinal cord and (2) the upper motor neurons of corticospinal tracts. Therefore this disease process produces both upper and lower motor neuron degeneration. It most commonly affects men 40 to 60 years of age (it is colloquially known as Lou Gehrig disease after the New York Yankees first baseman who died from the disease at age 37, and has more recently been associated with the ice bucket challenge to raise money and awareness). When the degenerative process is limited to the motor cortex of the brain, the disease is called primary lateral sclerosis; limitation to the brainstem nuclei is known as pseudobulbar palsy. Werdnig-Hoffmann disease resembles ALS except that it occurs during the first 3 years of life. Although the cause of ALS is unknown, occasionally a genetic pattern is present with defects in the gene for superoxide dismutase occurring in up to 20% of patients with ALS.

Signs and symptoms of ALS reflect upper and lower motor neuron dysfunction. Initial manifestations often include skeletal muscle atrophy, weakness, and fasciculations, frequently beginning in the intrinsic muscles of the hands. With time, atrophy and weakness involve most of the skeletal muscles, including the tongue, pharynx, larynx, and chest. Early symptoms of bulbar involvement include fasciculations of the tongue plus dysphagia, which leads to pulmonary aspiration. The ocular muscles are generally spared. Autonomic nervous system dysfunction can be manifested as orthostatic hypotension and resting tachycardia. Complaints of cramping and aching sensations, particularly in the legs, are common. Plasma creatine kinase concentrations are normal, which distinguishes this disease from chronic polymyositis. Carcinoma of the lung has been associated with ALS. ALS has no known treatment, and death is likely within 6 years after the onset of clinical symptoms, usually resulting from respiratory failure.

General anesthesia in patients with ALS may be associated with exaggerated respiratory depression, and consideration should be given to minimization or narcotics and other respiratory depressants and avoidance of deep extubation. ALS patients are also vulnerable to hyperkalemia following administration of succinylcholine as a result of lower motor neuron disease, and these patients may show prolonged responses to nondepolarizing muscle relaxants. Bulbar involvement with dysfunction of pharyngeal muscles may predispose to pulmonary aspiration. There is no evidence that any specific anesthetic drug or combination of drugs is ideal in these patients. Epidural anesthesia has been used successfully in patients with ALS without neurologic exacerbation or impairment of pulmonary function.

Friedreich Ataxia

Friedreich ataxia is an autosomal recessive condition characterized by degeneration of the spinocerebellar and pyramidal tracts. Cardiomyopathy is present in 10% to 50% of patients with this disease. Kyphoscoliosis, producing a progressive deterioration in pulmonary function, is seen in nearly 80% of affected individuals. Ataxia is the typical presenting symptom. Dysarthria, nystagmus, skeletal muscle weakness and spasticity, and diabetes mellitus may be present. Friedreich ataxia is usually fatal by early adulthood, most often because of heart failure.

Management of anesthesia in patients with Friedreich ataxia is similar to that described for patients with ALS. If cardiomyopathy is present, the negative inotropic effects of anesthetic drugs must be considered when selecting a technique. Kyphoscoliosis may make epidural anesthesia technically difficult. Spinal anesthesia has been used successfully. The likelihood of postoperative ventilatory failure may be increased, especially in the presence of kyphoscoliosis.

KEY POINTS

- The extent of physiologic effects from spinal cord injury depends on the level of injury, with the most severe physiologic derangements occurring with injury to the cervical cord. Hypotension is a result of (1) loss of sympathetic nervous system activity and a decrease in systemic vascular resistance, and (2) bradycardia resulting from loss of the T1 through T4 sympathetic innervation to the heart. These hemodynamic changes are collectively known as neurogenic shock and typically last 1 to 3 weeks.
- Major goals in caring for patients who have spinal cord disease or are undergoing surgical procedures involving the spinal cord or vertebral column are maintenance of adequate blood flow and oxygen delivery to vulnerable neurologic tissues, optimization of operative conditions, and facilitation of a rapid and smooth emergence from anesthesia to allow immediate assessment of neurologic function.
- Succinylcholine should be used with caution in patients with motor deficits because of the potential risk of hyperkalemia.
- In acute spinal cord injury, care must be taken during airway manipulation to avoid excessive neck movement. Succinylcholine can be used without significant risk of hyperkalemia in the first few hours following spinal cord injury.
- Sequelae of chronic spinal cord injury include impaired alveolar ventilation, cardiovascular instability manifested as

autonomic hyperreflexia, chronic pulmonary and genitourinary tract infections, anemia, and altered thermoregulation.

- Patients with cervical and thoracic spinal cord injuries are at risk of developing autonomic hyperreflexia in response to various stimuli, including surgery, bowel distention, and bladder distention. Autonomic hyperreflexia can be prevented by either general or spinal anesthesia, since both methods are effective in blocking the afferent limb of the pathway. Use of topical anesthesia for cystoscopic procedures does not prevent autonomic hyperreflexia, and epidural anesthesia is not reliably effective in preventing autonomic hyperreflexia.

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15

Diseases of the Autonomic and Peripheral Nervous Systems

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OUTLINE

INTRODUCTION

The peripheral nervous system consists of nerve elements outside the brain and spinal cord. It contains both peripheral nerves and elements of the autonomic nervous system. Disorders of the autonomic nervous system can result in significant hemodynamic changes as well as abnormal responses to drugs that work via adrenergic receptors. Diseases affecting peripheral nerves often have perioperative implications, including choice of muscle relaxants and management of neuropathic pain.

OVERVIEW OF THE AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system is a part of the peripheral nervous system that acts involuntarily to regulate multiple bodily functions. The autonomic nervous system has two divisions: the sympathetic and parasympathetic nervous systems. A brief overview of the structure, end-organ innervation, and functions of the sympathetic and parasympathetic nervous systems are illustrated in Fig. 15.1.

AUTONOMIC NERVOUS SYSTEM DISORDERS

Multiple System Atrophy

Multiple system atrophy involves degeneration and dysfunction of diverse central nervous system structures such as the basal ganglia, cerebellar cortex, locus coeruleus, pyramidal tracts, inferior olivary nuclei, vagal motor nuclei, and spinocerebellar tracts. The extent of degeneration of these structures, individually or in aggregate, results in different clinical manifestations that were considered different disease states in the past. Examples include striatonigral degeneration associated with parkinsonian features, olivopontocerebellar atrophy associated with cerebellar dysfunction, and Shy-Drager syndrome associated with autonomic dysfunction. These disorders are now all categorized as multiple system atrophy.

Autonomic manifestations include orthostatic hypotension, syncope, urinary retention, sluggish pupillary reflexes, and sexual dysfunction. Baroreceptor function may also be impaired, resulting in the inability to appropriately produce tachycardia and vasoconstriction in response to systemic hypotension. Control of breathing may be compromised, especially later in the course of the disease. Nonautonomic manifestations of multisystem atrophy include ataxia and parkinsonism.

Treatment includes use of elastic stockings, consumption of a high-sodium diet to expand plasma volume, and administration of vasoconstricting α_1-adrenergic agonists or α_2-adrenergic antagonists. If symptoms of parkinsonism are present, they can be treated with drugs such as levodopa and anticholinergics. Patients with multisystem atrophy have an ominous prognosis, with death generally occurring within 8 years of diagnosis, usually due to cerebral ischemia from prolonged hypotension.

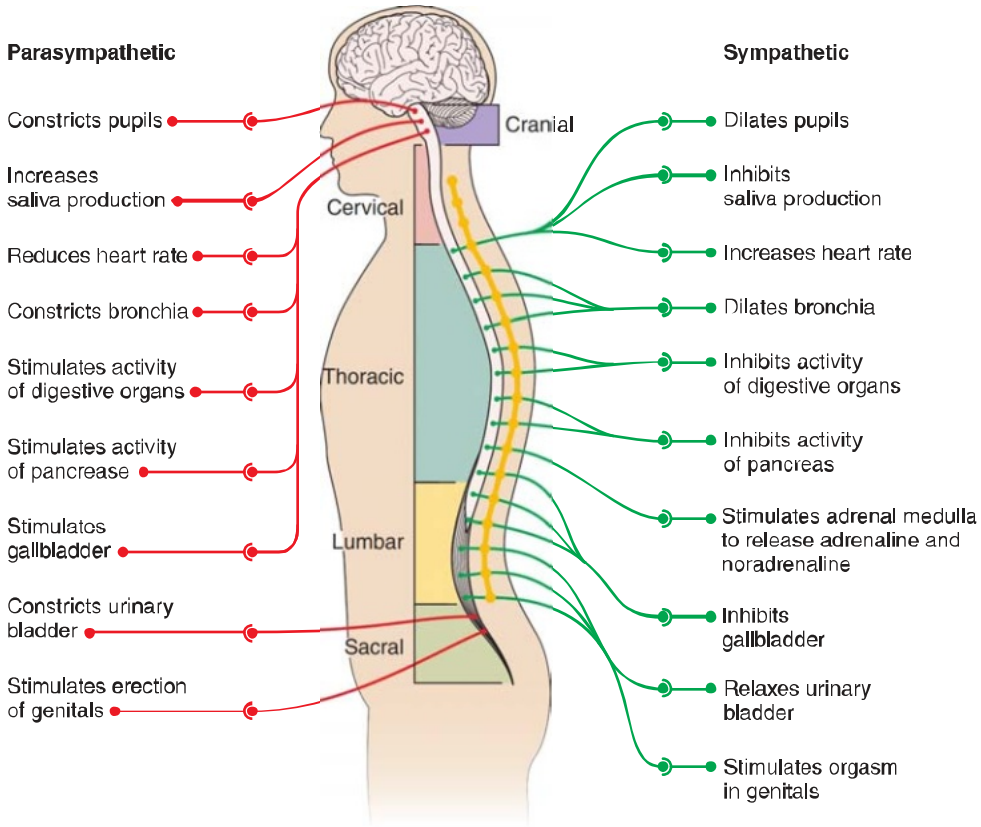

Fig. 15.1 Anatomy and functions of the autonomic nervous system.

Management of Anesthesia

The keys to management of autonomic dysfunction include continuous monitoring of systemic blood pressure and prompt correction of hypotension. Fluids and vasopressors can be used to treat hypotension. If vasopressors are needed, a direct-acting vasopressor such as phenylephrine is preferred. Small doses of phenylephrine should be used initially until the response can be assessed, because upregulated expression of α-adrenergic receptors in the setting of chronic relative autonomic denervation can produce an exaggerated hypertensive response. Spinal or epidural anesthesia can be considered, although the risk of hypotension demands diligence and caution. Impaired baroreceptor function can impair physiologic responses to anesthetic-induced vasodilation, potentiating hypotension. Intravenous ketamine is associated with less hypotension. Administration of a muscle relaxant that has little or no effect on hemodynamics, such as vecuronium or cisatracurium, is preferred. Signs of light anesthesia may be less apparent in these patients because the sympathetic nervous system is less responsive to noxious stimulation. Any antiparkinson medications should be continued in the perioperative period.

Postural Orthostatic Tachycardia Syndrome

Postural orthostatic tachycardia syndrome (POTS) is a chronic idiopathic disorder of the autonomic nervous system characterized by episodic and position-related hypotension. POTS is most often observed in young women. Symptoms include palpitations, tremulousness, lightheadedness, fatigue, and syncope. The pathophysiology is unclear, although possible explanations include enhanced sensitivity of β_1-adrenergic receptors, hypovolemia, excessive venous pooling during standing, primary dysautonomia, and lower extremity sympathetic denervation. Treatment includes increasing intravascular fluid volume and use of α_1-adrenergic agonists, such as midodrine.

Management of Anesthesia

Management of anesthesia for patients with POTS includes preoperative administration of fluids to expand intravascular fluid volume. Low-dose phenylephrine infusions may be cautiously administered, with recognition that lower extremity sympathetic nervous system denervation may cause upregulation of α_1-adrenergic receptors and contribute to receptor hypersensitivity. β-adrenergic blocking drugs may be used to blunt tachycardia if needed, but care must be taken to avoid excessive hypotension.

Paraganglioma

Paragangliomas are neuroendocrine tumors that arise from neural crest cells. Distinct terminology based on tumor location, such as carotid body tumor and glomus jugulare, are currently falling out of favor. These tumors have a somewhat similar origin to pheochromocytoma except that paragangliomas exist in extraadrenal locations. They can develop within neuroendocrine tissues surrounding the aorta or within the lung, as well as in the head and neck. Paragangliomas rarely secrete vasoactive substances, but when they do, norepinephrine secretion is the

most common one (mimicking a pheochromocytoma). Paragangliomas typically lack the enzyme that converts norepinephrine to epinephrine, thus epinephrine secretion is even less common than norepinephrine secretion. Other hormones that can be produced include cholecystokinin, thought to play a role in the high incidence of postoperative ileus following tumor resection; serotonin or kallikrein, which can cause carcinoid-like symptoms; and histamine or bradykinin, causing bronchoconstriction and hypotension. Small tumors are most often treated with radiation or embolization. Surgery may be required for large or invasive tumors.

Management of Anesthesia

Preoperative determination of urinary catecholamine metabolites and serum 5-hydroxyindoleacetic acid (5-HIAA) may be useful to determine if the tumor is likely to secrete catecholamines or serotonin, respectively. Phenoxybenzamine or prazosin may be administered to patients with elevated urinary catecholamine metabolites, and octreotide should be given preoperatively to patients with elevated 5-HIAA concentration in serum.

Invasive arterial monitoring should be considered, especially in patients with vasoactive substance-secreting tumors. Given the risk of pheochromocytoma-like and carcinoid-like signs occurring intraoperatively, drugs used to treat both hypertension (e.g., rapidly titratable antihypertensive agents such as clevidipine, sodium nitroprusside, nicardipine) and carcinoid crisis (e.g., octreotide) should be immediately available.

With paragangliomas in the head and neck, cranial nerve deficits (vagus, glossopharyngeal, hypoglossal) may be present preoperatively or may occur as a result of tumor resection. Unilateral vocal cord paralysis is a risk after cranial nerve injury. In adults, this does not usually result in complete airway obstruction by itself but could produce airway obstruction in combination with airway edema or laryngeal distortion. Other complications can include impaired gastric emptying as a consequence of vagal nerve dysfunction and subsequent pulmonary aspiration.

Venous air embolism is a risk in head and neck surgery, especially if the internal jugular vein is opened to remove tumor. Appropriate monitoring to detect venous air is indicated when embolism is considered a risk. Sudden, unexplained cardiovascular collapse and death during resection of these tumors may reflect the presence of a venous air or tumor embolism.

If the surgeon finds it necessary to identify cranial nerves, skeletal muscle paralysis should be avoided to allow for monitoring of nerve integrity during surgery.

Carotid Sinus Hypersensitivity

Carotid sinus hypersensitivity, exaggerated activity of baroreceptors in response to mechanical stimulation, is an uncommon entity. Stimulation of the carotid sinus by external massage, which in normal individuals produces modest decreases in heart rate and systemic blood pressure, can produce syncope in those with carotid sinus hyperactivity. Affected individuals have an increased incidence of peripheral vascular disease. Carotid sinus hypersensitivity is a recognized (although transient) complication following carotid endarterectomy.

Two distinct cardiovascular responses may be noted in the presence of carotid sinus hypersensitivity. In approximately 80% of affected individuals, a cardioinhibitory reflex, mediated by the vagus nerve, produces profound bradycardia. In approximately 10% of affected individuals, a vasodepressor reflex, mediated by inhibition of vasomotor tone, produces decreases in systemic vascular resistance and profound hypotension. The remaining 10% exhibit components of both reflexes.

Carotid sinus hypersensitivity may be treated with medications, implantation of a cardiac pacemaker, or ablation of the carotid sinus.

Management of Anesthesia

Anesthetic management in patients with carotid sinus hypersensitivity is often complicated by hypotension, bradycardia, and cardiac arrhythmias. Continuous invasive monitoring of arterial blood pressure can be valuable. Drugs to treat hypotension and bradycardia should be available. Further, external cardiac pacing can be useful to treat bradycardia that is unresponsive to pharmacologic therapy.

Hyperhidrosis

Hyperhidrosis is a rare disorder where individuals produce an excessive amount of sweat. The disorder can be either idiopathic or secondary to other conditions such as hyperthyroidism, pheochromocytoma, hypothalamic disorders (including that following central nervous system trauma), spinal cord injury, parkinsonism, or menopause. The disorder results from overactivity of sudomotor nerve fibers innervating eccrine sweat glands. Conservative treatments include topical astringents or antiperspirants. Although these sudomotor nerve fibers belong to the sympathetic nervous system, the primary neurotransmitter in sweat glands is acetylcholine. Thus patients may respond to anticholinergic drugs or to botulinum toxin injections. Severe cases may require surgical sympathectomy.

Management of Anesthesia

The sympathetic chain is most commonly accessed in the thoracic cavity via video-assisted thoracoscopy. One-lung ventilation will be required and is facilitated by placement of a double-lumen endotracheal tube. Successful sympathectomy will produce vasodilation in the ipsilateral upper extremity. This can be documented by an increase in ipsilateral hand skin temperature by more than 1°C or increase in cutaneous blood flow measured by laser Doppler flowmetry. In otherwise healthy patients, this surgery can be performed as an outpatient procedure. Patients often have minimal pain postoperatively, which responds well to opioids and nonsteroidal antiinflammatory drugs (NSAIDs). Common surgical complications include infection, Horner syndrome (resulting from injury to the stellate ganglion during the ablative procedure), and a compensatory hyperhidrosis elsewhere (e.g., trunk or lower extremity).

Paroxysmal Sympathetic Hyperactivity

Paroxysmal sympathetic hyperactivity (PSH) is a phenomenon that can occur in up to 33% of patients with traumatic brain injuries and can persist for weeks or months after injury. This

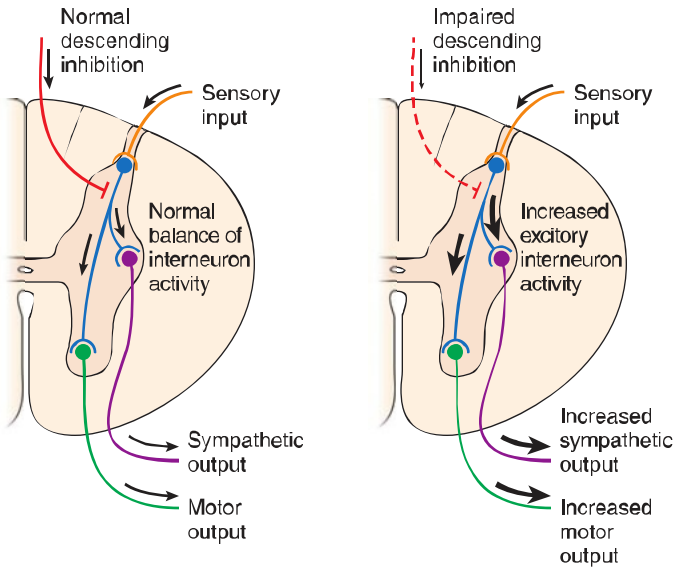

Fig. 15.2 Normal versus impaired descending inhibition in pathophysiology of paroxysmal sympathetic hyperactivity.

syndrome has also been referred to as autonomic storm, sympathetic storm, and dysautonomia. Symptoms include tachycardia, hyperthermia, hypertension, tachypnea, diaphoresis, hypertonia, and posturing. The pathophysiology of this syndrome remains unclear but may be attributed to disconnection of cortical inhibitory networks that control efferent sympathetic pathways leading to sympathetic disinhibition (Fig. 15.2).

The main therapeutic goals of treating patients with PSH are to avoid triggers that provoke the syndrome, alleviate the sympathetic outflow, and provide supportive therapy. A major portion of patients experience paroxysms in response to stimuli such as pain, movement, or urinary retention. Thus it is important to avoid these triggers when they can be identified.

Opioids are most frequently used to mitigate pain responses. Other sedative agents such as benzodiazepines have anxiolytic effects and have also been used in treating PSH symptoms. β-adrenergic antagonists are commonly used to suppress central and peripheral adrenergic outflow. Propranolol is often chosen due to its lipophilicity and its ability to cross the blood-brain barrier and act centrally. α_2-adrenergic drugs such as clonidine or dexmedetomidine can also be used in these patients to suppress adrenergic outflow. Dopaminergic agonists, such as bromocriptine, can decrease temperature and sweating in patients with PSH. Finally, dantrolene has been used to diminish fever caused by prolonged muscle contractions.

Another aspect of treatment of patients with PSH is supportive therapy to ensure that long-term sequela of the syndrome is avoided. Physiotherapy, nutritional management, and temperature control are all important things to consider.

Management of Anesthesia

Anesthetic management of patients with PSH includes avoiding triggers that would precipitate catecholamine outflow. Proper management of pain intraoperatively with appropriate opioids and anesthetic agents is crucial. Dexmedetomidine, if used intraoperatively, can be continued postoperatively in the intensive care unit setting to further prevent sympathetic storms. If hypertension, hyperthermia, and tachycardia were to manifest intraoperatively, symptoms can be managed with β-adrenergic antagonists such as propranolol or labetalol and cooling the body with forced air blankets.

Familial Dysautonomia

Familial dysautonomia, also known as Riley-Day syndrome, is a hereditary disorder of the autonomic nervous system. It is transmitted via an autosomal recessive inheritance pattern and occurs most commonly in people of Ashkenazi Jewish descent. Neurologic symptoms are usually apparent at birth and present as poor suckling, hypotonia, and failure to respond to painful stimuli. Neurologic function declines with age, and manifestations later in life include frequent vomiting, recurrent aspiration pneumonia, failure to thrive, unsteady gait, and scoliosis. The most distinctive clinical features of familial dysautonomia include dysautonomic crises in response to stress manifesting as symptoms such as hemodynamic lability, excessive diaphoresis, tachycardia or bradycardia, and erythematous skin lesions.

There is no treatment for this disease, and the morbidity and mortality remain high. There is a 50% survival probability of reaching 40 years of age. The focus of treatment for preventing mortality in these patients has been symptomatic and supportive. It is important to provide adequate nutrition with supplemental gastrostomy feedings, and fundoplication is often required to decrease the risk of recurrent aspiration. Orthostatic hypotension can be treated with adequate hydration and mineralocorticoids such as fludrocortisone. Procedures for treatment of severe orthopedic problems can help with quality of life.

Management of Anesthesia

Anesthetic management of patients with familial dysautonomia can be challenging. Attempting to keep the patient calm in the perioperative setting is important to avoid dysautonomic crises. Preoperative midazolam can be used as an anxiolytic. Patients with familial dysautonomia have a decrease in norepinephrine production, which explains increased cardiovascular instability. In addition, patients are often dehydrated, which may contribute to hemodynamic instability during induction of anesthesia. Proper hydration preoperatively can help decrease this lability. Preoperative treatment with mineralocorticoids such as fludrocortisone can minimize orthostatic hypotension.

A rapid sequence induction is preferred, as these patients often have gastroesophageal reflux. However, mask induction with sevoflurane is a possibility if placing an intravenous catheter may cause extreme distress for the patient. Placement of an arterial line should be considered for monitoring of intraoperative hemodynamics.

Many of these patients will have a prolonged QT interval and may be more susceptible to bradycardia and asystole; thus a preoperative electrocardiogram (ECG) is advised. Precautions should be taken in the perioperative setting to avoid agents that would cause further QT prolongation. Patients with familial dysautonomia can be excessively sensitive to the use of vasopressors intraoperatively, so care should be used when titrating.

Maintenance of normocapnia is also important for reducing hemodynamic instability, especially hypertension due to hypercapnia. Familial dysautonomia patients are also at a higher risk for corneal abrasions due to lacrimal secretory disorder, and proper eye protection should take place intraoperatively.

Anesthetic emergence should be carefully planned. Pain control should be optimized with proper titration of intravenous opioids or use of regional anesthesia. Due to the blunted respiratory response to hypoxia in these patients, periods of apnea and hypoxia can be anticipated. If a muscle relaxant was given, it should be adequately reversed to ensure good respiratory effects. Hypotonia in these patients often increases the risk of aspiration pneumonia, and those with severe scoliosis can also have restrictive lung disease. Optimizing pulmonary status prior to the procedure and using minimally invasive surgical approaches have been associated with fewer postoperative pulmonary complications. Profound postoperative nausea and vomiting have been reported and can be treated effectively with benzodiazepines and other antiemetics.

DISEASES OF THE PERIPHERAL NERVOUS SYSTEM

Idiopathic Facial Paralysis (Bell Palsy)

Idiopathic facial paralysis is characterized by the rapid onset of motor weakness of the muscles innervated by the facial nerve. Additional symptoms can include the loss of taste sensation over the anterior two-thirds of the tongue as well as hyperacusis and diminished salivation and lacrimation. There is no cutaneous sensory loss because the trigeminal nerve, not the facial nerve, supplies sensory innervation to the face. The cause of idiopathic facial paralysis is presumed to be inflammation and edema of the facial nerve, most often in the facial nerve canal within the temporal bone. A virus, perhaps herpes simplex virus, may be the cause. There is an increased incidence during pregnancy.

Spontaneous recovery usually occurs in approximately 12 weeks. If no recovery is seen in 16 to 20 weeks, the clinical signs and symptoms are probably not due to idiopathic facial paralysis. Corticosteroids can decrease the likelihood of complete denervation of the facial nerve. Surgical decompression of the facial nerve may be needed for persistent or severe cases of idiopathic facial paralysis or for facial paralysis secondary to trauma. The presence of idiopathic facial paralysis does not influence the choice of anesthetic technique. If blinking is not possible, the patient's affected eye should be covered to protect against corneal dehydration.

Uveoparotid fever (Heerfordt syndrome) is a rare manifestation of sarcoidosis and can also result in facial paralysis. It is characterized by bilateral anterior uveitis, parotitis, and low-grade fever with facial nerve paralysis occurring in 50% to 70% of patients.

Trigeminal Neuralgia (Tic Douloureux)

Trigeminal neuralgia is characterized by brief but intense episodes of unilateral facial pain. These events can either occur spontaneously or are triggered by local sensory stimuli to the affected side of the face. Patients report brief, stabbing pain in the face that is restricted to one or more divisions of the trigeminal nerve, most often the mandibular division (Fig 15.3). Trigeminal neuralgia most often develops in otherwise healthy individuals during late middle age. The appearance of this neuralgia at an earlier age should arouse suspicion of multiple sclerosis. The pathophysiology of the pain associated with trigeminal neuralgia is uncertain. However, compression of the nerve root by a blood vessel, most commonly by the superior cerebellar artery, is sometimes the cause. Antiepileptic drugs and baclofen are useful for treating trigeminal neuralgia. Surgical therapy (selective radiofrequency destruction of trigeminal nerve fibers, transection of the sensory root of the trigeminal nerve, microsurgical decompression of the trigeminal nerve root) is recommended for individuals who develop pain refractory to drug therapy.

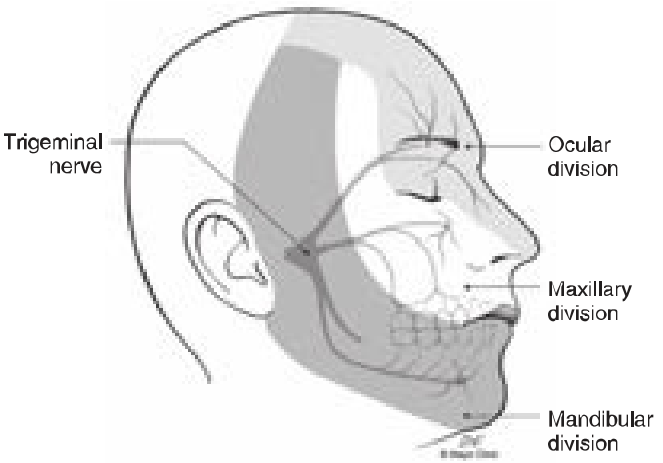

Fig. 15.3 Sensory innervation by the three branches of the trigeminal nerve. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Patients undergoing surgery may experience bradycardia caused by activation of the trigeminocardiac reflex. In patients having microsurgical decompression, placement of a retractor to gain access to the root of the trigeminal nerve can stretch the vestibulocochlear nerve (cranial nerve VIII) and potentially result in hearing loss. Therefore intraoperative monitoring of brainstem auditory evoked potentials may be used to assess the integrity of cranial nerve VIII. The potential enzyme-inducing effects of anticonvulsant drugs must be considered when predicting drug effects. Carbamazepine can also cause altered hepatic function and produce leukopenia and thrombocytopenia.

Glossopharyngeal Neuralgia

Glossopharyngeal neuralgia is characterized by episodes of intense pain in the throat, neck, tongue, and ear. Swallowing, chewing, coughing, or talking can trigger the pain. This neuralgia may also be associated with severe bradycardia and syncope due to activation of the glossopharyngeal reflex.

Glossopharyngeal neuralgia is usually idiopathic but has been described in patients with cerebellopontine angle pathology, vertebral and carotid artery occlusive disease, arachnoiditis, and extracranial tumors arising in the area of the pharynx,

larynx, and tonsils. The diagnosis of glossopharyngeal neuralgia is supported by pain in the distribution of the glossopharyngeal nerve and relief of this pain by topical anesthesia of the oropharynx at the tonsillar pillar.

In the absence of pain, cardiac symptoms associated with glossopharyngeal neuralgia may be confused with cardiac sick sinus syndrome or carotid sinus hyperactivity. Failure of carotid sinus massage to produce cardiac symptoms rules out carotid sinus hypersensitivity. Glossopharyngeal nerve block is useful for differentiating glossopharyngeal neuralgia from atypical trigeminal neuralgia or cardiac sick sinus syndrome. This nerve block does not, however, differentiate glossopharyngeal neuralgia from carotid sinus hyperactivity because afferent pathways of both syndromes are mediated by the glossopharyngeal nerve.

Glossopharyngeal neuralgia–associated cardiac symptoms should be aggressively treated pharmacologically, with a cardiac pacemaker, or a combination of these modalities. Pain associated with this syndrome is managed by administration of anticonvulsant drugs. Prevention of cardiovascular symptoms and predictable pain relief can be achieved by intracranial surgical transection of the glossopharyngeal nerve and the upper two roots of the vagus nerve. Although permanent pain relief is possible after repeated glossopharyngeal nerve block, this neuralgia is sufficiently life threatening to justify intracranial transection of the nerve in patients who do not respond to medical therapy.

Management of Anesthesia

Preoperative evaluation of patients with glossopharyngeal neuralgia is directed at assessing cardiac status and intravascular fluid volume. Hypovolemia may be present, since these patients avoid oral intake due to provocation of pain. A preoperative history of syncope or documented bradycardia concurrent with an episode of pain introduces the possible need for transcutaneous or transvenous cardiac pacing before induction of anesthesia. Continuous monitoring of ECG activity and of blood pressure via an intraarterial catheter is useful. Topical anesthesia of the oropharynx with lidocaine is helpful to prevent bradycardia and hypotension that may occur in response to direct laryngoscopy.

Cardiovascular changes should be expected in response to surgical manipulation during intracranial transection of the glossopharyngeal and vagus nerve roots. Bradycardia and hypotension are likely during manipulation of the vagus nerve. Anticholinergic drugs should be immediately available to treat these vagally mediated responses. Hypertension, tachycardia, and ventricular premature beats may occur after surgical transection of the glossopharyngeal nerve due to sudden loss of sensory input from the carotid sinus. Hypertension is usually transient but can persist into the postoperative period. In this setting, hydralazine may be useful. The possible development of vocal cord paralysis after vagal nerve transection may manifest as dyspnea, stridor, or possibly airway obstruction following tracheal extubation.

Charcot-Marie-Tooth Disease

The most common inherited cause of chronic motor and sensory peripheral neuropathy, Charcot-Marie-Tooth disease (CMT), has an estimated incidence of 1 in 2500 individuals. CMT is the clinical manifestation of a heterogenous group of genetic mutations that lead to alterations in peripheral nerve function as outlined in Table 15.1.

The more common forms of CMT, especially type 1A, manifest as distal skeletal muscle weakness, muscle wasting, and loss of tendon reflexes that become evident by the middle teenage years. Classically, this neuropathy is restricted to the lower one-third of the legs, producing foot deformities (high pedal arches and talipes) and peroneal muscle atrophy (stork leg–like appearance). The disease may slowly progress to include wasting of the quadriceps muscles as well as the muscles of the hands and forearms. Mild to moderate stocking-glove sensory loss occurs in many patients. Pregnancy may precipitate exacerbations of CMT.

Treatment of the milder forms of CMT is limited to supportive measures, including splinting, tendon transfers, and various arthrodeses. Severe forms of CMT, especially those that present earlier in life, are associated with significant disability and a reduced life span.

Management of Anesthesia

Management of anesthesia in patients with CMT should focus on the response to neuromuscular blocking drugs and the possibility of postoperative respiratory failure resulting from weakness of the respiratory muscles. Cardiac manifestations attributed to this neuropathy, including conduction disturbances, atrial flutter, and cardiomyopathy, occur occasionally. Drugs known to trigger malignant hyperthermia have been used safely in patients with CMT. The response to neuromuscular blocking drugs seems to be normal in patients with mild forms of CMT. It may be reasonable to avoid succinylcholine because of theoretical concerns about exaggerated potassium release in individuals with neuromuscular diseases. However, succinylcholine has been used safely in some patients having more mild forms of CMT without producing hyperkalemia or triggering malignant hyperthermia. It should be noted that the safe use of succinylcholine may not have been described in patients with rarer forms of CMT and should be used with caution or avoided. Use of neuraxial anesthesia for labor and delivery has been described.

Brachial Plexus Neuropathy

Primary brachial plexus neuropathy, otherwise known as idiopathic brachial neuritis, Parsonage-Turner syndrome, or shoulder girdle syndrome, is characterized by the acute onset of severe pain in the upper arm. The pathophysiology of primary brachial plexus neuropathy is currently unknown. The pain is typically most severe at the onset of the neuropathy. As the pain diminishes, paresis of muscles innervated by branches of the brachial plexus occurs. Skeletal muscle wasting, particularly involving the shoulder girdle and arm, is common. Secondary causes of brachial plexus neuropathy include trauma to the neck or upper limb. In neonates, shoulder dystocia during delivery is another cause of brachial plexus neuropathy.

Electrophysiologic studies are valuable in diagnosing brachial plexus neuropathy and demonstrating the multifocal pattern of

TABLE 15.1 Characteristics of the More Common Genotypes of Charcot-Marie-Tooth Disease

Type	Subtype	Inheritance Pattern	Chromosome	Mutation	Clinical Comments
1					All type 1 variant of CMT are predominately demyelinating
	1A	AD	11	Duplication of peripheral myelin protein-22 gene	Most common form of CMT
	1B	AD	1	Myelin protein-0 gene	Phenotype typical to CMT-1A with varying wide range of severity
	1C	AD	16	Lipopolysaccharide TNF-α factor gene	
	1D	AD	10	Early growth response protein gene	Usually severe phenotype 1 EAD 17 point
	1E	AD	17	Point mutation of peripheral myelin protein-22 gene	Earlier onset and more severe phenotype than type 1A
	1F	AD	8	Neurofilament light chain protein gene	
	1X	XL	X	Gap junction β-protein gene	Second most common form of CMT
2					All type 2 variants of CMT predominantly characterized by axonal dysfunction
	2A	AD	1	Mitofusin-2 gene	Fusion of mitochondria is a notable finding
	2B	AD	3	Ras-related protein-7A gene	Predominantly a sensory neuropathy
	2C	AD	12	Unknown gene	Diaphragm and vocal cord paresis on characteristic
	2D	AD	7	Glycyl RNA synthase gene	Can be a sensory/motor or purely motor neuropathy
	2E	AD	8	Neurofilament light gene	
3					
	Dejerine-Sottas syndrome	AD or AR	Multiple	Multiple possible mutations can lead to Dejerine-Sottas syndrome	Final common pathway of a group of mutations; severe symptoms before age 3 and poor prognosis
4					
	4A	AR	8	Ganglioside-induced differentiation association protein-1 gene	Primarily demyelinating; vocal cord paresis can be present
	4B1	AR	11	Myotubularin-related protein-2 gene	
	4B2	AR	11	Myotubularin-related protein-13 gene	Onset in infancy; notable for both proximal and distal neurologic deficits
	4B3	AR	22	Myotubularin-related protein-5 gene	
	4C	AR	5	Defect in SH3 domain and tetratricopeptides repeats-2 gene	Most common autosomal recessive form of CMT
	4D	AR	8	Unknown gene	Deafness is characteristic of CMT-4D
	4E	AR	1 or 10	Defect in myelin protein-0 gene or early growth response protein-2 gene	Also known as congenital hypomyelination syndrome
	4F	AR	19	Periaxin gene	
	4G	AR	10	Unknown gene	
	4H	AR	12	Actin filament-binding protein frabin gene	
	4J	AR	6	Factor induced-4 gene	

AD, Autosomal dominant; *AR*, autosomal recessive; *CMT*, Charcot-Marie-Tooth disease; *RNA*, ribonucleic acid; *TNF-α*, tumor necrosis factor α; *XL*, X-linked.

denervation. The diaphragm may also be affected. Sensory disturbances occur in most patients but tend to be minimal and generally disappear over time.

Nerve biopsy findings in individuals with hereditary brachial plexus neuropathy and Parsonage-Turner syndrome suggest an inflammatory-immune pathogenesis. Autoimmune neuropathies may also occur during the postoperative period independent of the site of surgery. It is possible that the stress of surgery activates an unidentified dormant virus in the nerve roots, a circumstance that would be similar to the onset of herpes zoster after surgery. In addition, strenuous exercise or pregnancy may be inciting events for brachial plexus neuropathy. Succinylcholine should be avoided in patients with significant muscle denervation.

Guillain-Barré Syndrome (Acute Idiopathic Polyneuritis)

Guillain-Barré syndrome is characterized by sudden onset of skeletal muscle weakness or paralysis that typically begins in the legs and spreads cephalad over the ensuing days, to possibly involve the arms, trunk, and face. It is an autoimmune disorder that causes multifocal inflammatory demyelination. With the virtual elimination of poliomyelitis, this syndrome has become the most common cause of acute generalized paralysis, with an annual incidence of one to two cases per 100,000 people. Intercostal weakness can impair ventilation, and pharyngeal muscle involvement can cause difficulty swallowing and impaired ability to protect the airway in severe cases. Because of lower motor neuron involvement, paralysis is flaccid, and corresponding tendon reflexes are diminished. Sensory disturbances (e.g., paresthesia) generally precede the onset of paralysis and are most prominent in the distal extremities. Pain is often present.

Autonomic nervous system dysfunction is a prominent finding in patients with Guillain-Barré syndrome and is usually manifested as fluctuations in blood pressure, sudden profuse diaphoresis, peripheral vasoconstriction, resting tachycardia, and cardiac conduction abnormalities. Orthostatic hypotension may be so severe that elevating the patient's head onto a pillow may lead to syncope. Thromboembolism may occur due to immobility. Sudden death associated with this disease is most likely caused by autonomic nervous system dysfunction.

Complete recovery from acute idiopathic polyneuritis can occur within a few weeks but may be delayed and incomplete if axonal degeneration occurs. The mortality rate associated with Guillain-Barré syndrome is 3% to 8%, and death is most often a result of sepsis, acute respiratory failure, pulmonary embolism, or cardiac arrest.

The diagnosis of Guillain-Barré syndrome is based on clinical signs and symptoms (Table 15.2), supported by findings of an increased protein concentration in the cerebrospinal fluid. In approximately 50% of patients, this syndrome develops after respiratory or gastrointestinal infection, which suggests that the cause may be related to either a viral or mycoplasma infection.

Treatment of Guillain-Barré syndrome is symptomatic. Impaired respiratory function may require mechanical ventilation. Pharyngeal muscle weakness may require insertion of a cuffed endotracheal tube or tracheostomy to prevent aspiration. Autonomic nervous system dysfunction may require treatment of hypertension or hypotension. Corticosteroids are not useful. Plasma exchange or infusion of γ globulin may benefit some patients but do not impact overall outcome.

TABLE 15.2 Diagnostic Criteria for Guillain-Barre Syndrome

Features Required for Diagnosis
- Progressive bilateral weakness in at least arms and legs
- Areflexia

Features Strongly Supporting the Diagnosis
- Progression of symptoms over 2–4 weeks
- Symmetry of symptoms
- Mild sensory symptoms or signs
- Cranial nerve involvement (especially bilateral facial weakness)
- Spontaneous recovery starting 2–4 weeks after progression halts
- Autonomic nervous system dysfunction
- No fever at onset
- Elevated concentrations of protein in CSF with a cell count <10/mm^3
- Decreased nerve conduction velocity

Features Making the Diagnosis Unlikely
- Definite sensory level
- Marked, persistent asymmetry of weakness
- Severe and persistent bowel and bladder dysfunction
- >50 white cells/mm^3 in CSF

CSF, Cerebrospinal fluid.

Management of Anesthesia

Abnormal autonomic nervous system function and the presence of lower motor neuron lesions are the major factors to consider in developing an anesthetic plan for patients with Guillain-Barré syndrome. Compensatory cardiovascular responses may be absent, so that profound hypotension occurs in response to changes in posture, blood loss, or positive airway pressure. Conversely, noxious stimulation, such as direct laryngoscopy, can cause exaggerated increases in blood pressure. Because of these unpredictable changes in blood pressure, it may be prudent to monitor blood pressure continuously with an intraarterial catheter. Patients may also exhibit exaggerated responses to indirect-acting vasopressors probably as a result of upregulation of postsynaptic receptors.

Succinylcholine should not be administered because there is a risk of excessive potassium release from denervated skeletal muscles. A nondepolarizing muscle relaxant with minimal circulatory effects, such as vecuronium or cisatracurium, may be used if needed. Even if a patient is breathing spontaneously before surgery, mechanical ventilation may be required during the postoperative period.

Entrapment Neuropathies

Entrapment neuropathies occur at anatomic sites where peripheral nerves pass through narrow passages. This includes the median nerve and carpal tunnel at the wrist and the ulnar nerve and cubital tunnel at the elbow. Peripheral nerves are probably more sensitive to compressive injury in patients who also have generalized polyneuropathies such as those with diabetes mellitus or hereditary peripheral neuropathies. A peripheral nerve may be more susceptible to compression if the same fibers have been partially damaged proximally (double crush hypothesis). Peripheral nerve damage resulting from compression depends on the severity of the compression and the anatomy of the nerve as outermost neurons are more susceptible to injury than neurons deeper in the nerve. Focal demyelination of nerve fibers impairs nerve conduction through the damaged area. Electromyographic and nerve conduction studies can show patterns characteristic of denervation and subsequent reinnervation of muscle fibers.

Carpal Tunnel Syndrome

Carpal tunnel syndrome is the most common entrapment neuropathy. It results from compression of the median nerve

between the transverse carpal ligament and the carpal bones at the wrist. This compression neuropathy most often occurs in otherwise healthy women (three times more frequently than in men) and is often bilateral, although the dominant hand is typically involved first. Patients describe repeated episodes of pain and paresthesia in the wrist and hand following the distribution of the median nerve (thumb, index, and middle fingers). Nerve conduction studies are the definitive method for confirming the diagnosis and demonstrate reduced conduction velocity in the median nerve at the wrist. Edema, as may occur postoperatively or during pregnancy, can be a secondary cause of carpel tunnel syndrome. Treatments include splinting, corticosteroid injections, and transection of the transverse carpal ligament.

Ulnar Neuropathy

Compression of the ulnar nerve after it passes through the condylar groove and enters the cubital tunnel results in clinical symptoms considered typical of ulnar nerve neuropathy. Signs and symptoms often include numbness and tingling in the ring and little fingers. It may be difficult to differentiate clinical symptoms of ulnar nerve neuropathy caused by compression in the condylar groove from symptoms related to entrapment in the cubital tunnel. Surgical treatment of cubital tunnel entrapment syndrome (by tunnel decompression and transposition of the nerve) may be helpful in relieving symptoms, but may also make symptoms worse, perhaps by interfering with the nerve's blood supply.

Meralgia Paresthetica

The lateral femoral cutaneous nerve, a pure sensory nerve, can become entrapped as it crosses under the inguinal ligament near the attachment of the ligament to the anterior superior iliac spine. Patients complain of burning pain down the lateral thigh, but they may also experience sensory loss in that region and possibly point tenderness at the site of entrapment. Treatment is usually conservative since meralgia paresthetica tends to regress spontaneously. Refractory cases may require local anesthetic and corticosteroid injections at the site of entrapment and possible surgical decompression.

Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy or causalgia, is a disorder that may occur following an injury or surgery most frequently in a limb. However, CRPS can also develop in the absence of an identifiable inciting injury. CRPS is more common in women, especially postmenopausal women. Although the exact etiology of CRPS is unknown, inappropriate activation of the inflammatory cascade, dysregulation of pain-mediating neuropeptides (i.e., substance P, neuropeptide Y, calcitonin gene-related peptide), central nervous system sensitization to pain stimuli, dysregulation of the sympathetic nervous system, and a possible genetic predisposition may all play a role. Symptoms include pain, swelling, decreased hair growth, skin changes, and bone demineralization. Pain is often the most debilitating symptom of CRPS, and the distribution is usually not consistent with the anatomic distribution of known nervous system structures. Patients may also have motor and autonomic dysfunction with the latter manifesting as changes in skin temperature, color, and sweat production. In the past, CRPS was considered to evolve through three stages, although that notion has widely been abandoned by most clinicians. However, as these stages may still be encountered in clinical practice, they are worth mentioning:

Stage 1: Throbbing and burning pain that does not correspond to an anatomic distribution develops in a limb (allodynia and vasomotor disturbances can occur.)

Stage 2: Development of soft tissue edema, muscle atrophy, and skin changes lasting 3 to 6 months

Stage 3: Limitation in range or motion, contractures, skin atrophy and fragility, nail changes, lack of hair growth, and bone demineralization

The diagnosis of CRPS is based on the Budapest criteria (Table 15.3). Other tests such as bone scintigraphy, autonomic testing, and magnetic resonance imaging can help support a diagnosis of CRPS.

Management of CRPS should start with prevention. There is some evidence that vitamin C supplementation in the setting of an injury may reduce the risk for CRPS. Management should be multidisciplinary and include pain control combined with physical therapy, psychological support, and patient education. Pain management may involve the use of NSAIDs, antiepileptic drugs (i.e., gabapentin, pregabalin), tricyclic antidepressants, bisphosphonates, ketamine, opioids, and topical lidocaine or capsaicin. For refractory pain, a pain management specialist may consider trigger point injections, sympathetic nerve blocks, spinal cord stimulation, or epidural clonidine. The prognosis of CRPS is highly variable. However, 60% of patients still have symptoms 6 years after onset.

Management of Anesthesia

Elective procedures on a limb with CRPS should be delayed, if possible, until pain and control of other symptoms are optimized. Vigilant attention should be given to positioning. Given limitations in range of motion and fragile skin in patients with CRPS, extra padding of pressure points should be utilized, and extremities should not be positioned in a manner that would exceed tolerable range of motion by the patient if awake. Increased analgesic requirements may occur following surgery, even if the procedure was not performed on the affected limb,

TABLE 15.3 Budapest Criteria for Diagnosis of Complex Regional Pain Syndrome

The patient must have the following:

- Continued and disproportionate pain
- At least one symptom in at least three of the following four categories:
  - Sensory: hyperesthesia or allodynia
  - Vasomotor: temperature asymmetry, skin color asymmetry, skin color changes
  - Sudomotor: edema, sweating changes, sweating asymmetry
  - Motor: decreased range of motion, weakness, tremor, dystonia, hair or nail changes
- No other diagnosis that better explains the signs and symptoms

as most patients with CRPS utilize chronic analgesics. One also should expect increased pain due to concomitant hyperalgesia if the procedure is performed on the affected limb. A multimodal approach to postoperative pain management should be considered. This can include parenteral and oral opioid and nonopioid analgesics, and adjuvant drugs such as gabapentin, pregabalin, and tricyclic antidepressants. Regional anesthesia should also be considered if possible. Consultation with a pain management specialist in the perioperative period can be beneficial.

Diseases Associated With Peripheral Neuropathies

Diabetes Mellitus

Diabetes mellitus is commonly associated with peripheral polyneuropathies. The incidence increases with the duration of the disease and decreases with better chronic glycemic control. The etiology of diabetic neuropathy is multifactorial and may include microvascular damage resulting in neuronal ischemia, formation of glycosylated intraneuronal proteins, activation of protein kinase C, and inhibition of glutathione, which increases reactive oxygen species.

Electrophysiologic studies show evidence of denervation and reduced nerve conduction velocity. The most common neuropathy is symmetric, predominantly sensory, and begins in the distal lower extremities and progresses cephalad. The principal manifestations are unpleasant tingling, numbness, burning, and aching in the lower extremities; skeletal muscle weakness; and distal sensory loss. Impotence, urinary retention, gastroparesis, resting tachycardia, and postural hypotension are common and reflect autonomic nervous system dysfunction. For reasons that are not understood, the peripheral nerves of patients with diabetes mellitus are more vulnerable to injury resulting from nerve compression or stretch.

Alcohol Abuse

Polyneuropathy of chronic alcoholism is nearly always associated with nutritional and vitamin deficiencies. Symptoms characteristically begin in the lower extremities, with pain and numbness in the feet. Weakness and tenderness of the intrinsic muscles of the feet, loss of the Achilles tendon reflex, and hyperalgesia in a stocking-glove distribution are early manifestations. Restoration of a proper diet, abstinence from alcohol, and multivitamin therapy promote slow but predictable resolution of the neuropathy.

Vitamin B_{12} Deficiency

The earliest neurologic symptoms of vitamin B_{12} deficiency resemble the neuropathy typically seen in patients who abuse alcohol. Paresthesia in the legs with sensory loss in a stocking distribution plus absent Achilles tendon reflexes are characteristic findings. Similar neurologic findings have been reported in dentists who experience long-term exposure to nitrous oxide and in individuals who habitually inhale nitrous oxide for nonmedical purposes. Nitrous oxide is known to inactivate certain vitamin B_{12}–dependent enzymes that, in turn, can lead to symptoms of neuropathy.

Uremia

Distal polyneuropathy with sensory and motor components often occurs in the extremities of patients with chronic renal failure. Symptoms tend to be more prominent in the legs than in the arms. Presumably, metabolic abnormalities are responsible for the axonal degeneration and segmental demyelination that accompany the neuropathy. Slowing of nerve conduction has been correlated with increased plasma concentrations of parathyroid hormone and myoinositol, a component of myelin. Improved nerve conduction velocity often occurs within a few days after renal transplantation. However, hemodialysis is ineffective in reversing this polyneuropathy.

Cancer

Peripheral sensory and motor neuropathies occur in patients with a variety of malignancies, especially those involving the lung, ovary, and breast. Polyneuropathy that develops in elderly patients should always arouse suspicion of undiagnosed cancer. Myasthenic (Eaton-Lambert) syndrome may be observed in patients with carcinoma of the lung due to abnormal production of an antibody against presynaptic calcium channels located on cholinergic neurons reducing neuronal release of acetylcholine. Myasthenic syndrome is associated with weakness and increased sensitivity to both depolarizing and nondepolarizing neuromuscular blocking drugs. Invasion of the lower trunks of the brachial plexus by tumors in the apex of the lungs (Pancoast syndrome) produces arm pain, paresthesia, and weakness of the hands and arms.

Collagen Vascular Diseases

Collagen vascular diseases are commonly associated with peripheral neuropathies. These occur most often in systemic lupus erythematosus, polyarteritis nodosa, rheumatoid arthritis, and scleroderma. Detection of multiple mononeuropathies suggests vasculitis of nerve trunks and should stimulate a search for the presence of a collagen vascular disease.

Sarcoidosis

Sarcoidosis is a disorder of unknown etiology in which noncaseating granulomas occur in multiple organ systems. Polyneuropathy resulting from the presence of granulomatous lesions in peripheral nerves is a frequent finding. Unilateral or bilateral facial nerve paralysis may result from sarcoid involvement of this nerve in the parotid gland(s) and is often one of the first manifestations of sarcoidosis.

Acquired Immunodeficiency Syndrome–Associated Neuropathy

Peripheral neuropathy is common in patients with acquired immunodeficiency syndrome (AIDS), but not in patients with human immunodeficiency virus infection without AIDS. AIDS-associated neuropathy is typically a distal symmetric polyneuropathy, and patients complain of numbness, tingling, and sometimes pain in the feet. There may be loss of vibratory and light touch sensation. Although the exact cause is unclear, infection with cytomegalovirus or *Mycobacterium avium-intracellulare,* lymphomatous invasion of

peripheral nerves, or adverse effects of antiretroviral medication may be responsible.

Perioperative Peripheral Neuropathies

Perioperative neuropathies have been described following a variety of surgical procedures and affecting different nerves. Although such neuropathies were originally thought to be primarily the result of errors in patient positioning during surgery, epidemiologic data suggest that in most circumstances preexisting aberrations of patient anatomy and physiology predispose the patient to this kind of injury. These include obesity, bony abnormalities, edema formation, metabolic derangements, and preexisting nerve abnormalities manifested as conduction delays. The failure of sedated, pain-free patients to frequently reposition themselves in bed postoperatively (and hence a failure to relieve pressure on individual nerves) may also be involved.

Ulnar neuropathy is the most common perioperative neuropathy, typically affecting obese males who undergo abdominal or pelvic surgical procedures. Symptoms of ulnar neuropathy do not typically present until at least 48 hours after surgery, and patients are often found to have contralateral nerve conduction dysfunction, which indicates a predisposition to this injury.

Postoperative brachial plexus neuropathy may initially be mistaken for ulnar neuropathy, and it appears to be associated with brachial plexus stretch resulting from sternal retraction during median sternotomy, placement in steep Trendelenburg position, and prone positioning with shoulder abduction and contralateral head rotation. Lower extremity neuropathies are associated with procedures performed in the lithotomy position and usually affect the common peroneal nerve. It is theorized that risk of common peroneal nerve damage is increased if the nerve becomes compressed by leg-holder hardware as the nerve crosses over the fibular head. Sciatic and femoral neuropathy may also be associated with lithotomy positioning, but these are seen much less often than peroneal neuropathy.

Management of patients who develop perioperative peripheral neuropathies begins with (1) taking a history and performing a physical examination, which should focus on identifying risk factors for or a history of neuropathy; (2) determining whether the deficit is sensory, motor, or mixed; and (3) documenting the distribution of the deficit. Most sensory deficits resolve within 5 days, so if the deficit is purely sensory, then expectant management is suggested. Since motor fibers tend to be located deeper within nerves, the presence of a motor deficit suggests a more extensive injury. In this situation, a neurology consultation is warranted.

KEY POINTS

- When caring for patients with diseases affecting the autonomic nervous system, one must carefully monitor for and be prepared to treat significant changes in heart rate and blood pressure.
- In the setting of autonomic disorders, changes in catecholamine release and adrenergic receptor density may occur. Therefore one should titrate the dosage of direct-acting adrenergic agonists and avoid the use of indirect-acting adrenergic agonists.
- Succinylcholine should be used with caution in patients with neurologic diseases affecting the peripheral nervous system because of the risk of hyperkalemia resulting from upregulation of acetylcholine receptors at the neuromuscular junction.
- Some diseases affecting the peripheral nervous system may be associated with significant neuropathic pain. Both opioid and nonopioid pain management options should be considered.

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16

Diseases of the Liver and Biliary Tract

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OUTLINE

EPIDEMIOLOGY

Nearly 4.5 million people in the United States are living with chronic liver disease, while more than 40,000 deaths annually are attributed to chronic liver disease. Liver dysfunction affects multiple organ systems and increases the risk of perioperative morbidity and mortality. While the prevalence of chronic viral infections has decreased due to improvements in medical treatments, the prevalence of alcohol-associated liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) continues to rise. Regardless of etiology, patients with liver dysfunction are undergoing nonhepatic surgeries, presenting unique challenges to the anesthesiologist.

FUNCTIONS OF THE LIVER

The liver plays an essential role in numerous metabolic and physiologic processes (Table 16.1). Nearly every organ system has the potential to be negatively impacted by liver dysfunction, given the liver's central role in metabolism of nutrients and drugs. Patients with liver disease are at higher risk of perioperative morbidity and mortality due to failure of one or more of these essential functions, hypoperfusion, tissue ischemia, and further activation of the systemic inflammatory response, leading to multiorgan failure.

One of the liver's major functions is to filter and transform substances from the blood. Nutrients and other substances from the digestive system enter the liver via the portal vein before undergoing metabolism. This process not only allows for blood to be cleared of harmful chemicals and bacteria but also allows for breakdown of drugs via oxidation and reduction processes. When portal hypertension is present, portosystemic shunts arise that allow blood to bypass the metabolic and detoxification process, leading to hepatic encephalopathy, increased risk for sepsis, and alterations in drug biotransformation.

Hemostasis in liver dysfunction is complex and unique given the concurrent risk for bleeding and thrombosis. The liver synthesizes most coagulation factors and proteins involved in

TABLE 16.1 Functions of the Liver

Function	Description
Synthesis of glucose and glycogen	Regulates blood glucose by producing, storing, and releasing glucose when needed
Synthesis of cholesterol and proteins	Provides support and aids in biosynthesis of hormones and vitamins
Metabolism of fats, proteins, and carbohydrates	Generates energy for homeostatic processes to occur
Metabolism of drugs	Cytochrome P450 enzymes in the liver deactivate or bioactivate drugs to a form that can be used by the body
Detoxification of blood	Clears harmful substances in the blood such as bacteria and toxins
Digestion of food	Produces bile to break down fats, vitamins, and minerals
Synthesis of acute phase reactants for immune support	Help to surmount and stimulate an immune response
Processes hemoglobin and stores iron	Regulates blood iron concentrations by increasing and decreasing the storage of iron as needed
Synthesis of coagulation factors and plasma proteins	Helps to regulate hemostasis
Assistance with volume control by blood reservoir function	Reservoir function allows release of blood during hypovolemia or acute blood loss

fibrinolysis, along with the hormone thrombopoietin. Although patients may have laboratory tests suggestive of a hypocoagulable state, they are often in a state of hemostatic balance due to changes in both the procoagulant and anticoagulant pathways. This state is often unstable, making the patient at risk for both bleeding and thrombosis.

Liver Anatomy

The liver receives the highest proportion of cardiac output of all the organs in the body: approximately 25% via the portal vein and hepatic artery. The portal vein, which is formed by the confluence of the splenic and superior mesenteric veins, provides 75% of blood flow to the liver. However, it accounts for only 50% of oxygen delivery given the portal venous blood's deoxygenated state after perfusing organs such as the stomach, intestines, spleen, and pancreas. The hepatic artery provides the remaining 25% of liver blood flow and 50% of oxygen delivery due to its higher oxygen content. Fig. 16.1 describes the pressure gradient of blood flow to the liver. Anatomically, the liver is divided into eight segments (Fig. 16.2).

Blood flow to the liver is regulated by intrinsic and extrinsic mediators. Hepatic arterial flow has an inverse relationship with changes in portal venous flow. Mediated by adenosine, hepatic artery dilation occurs as portal venous flow decreases. This helps maintain blood flow and oxygen content in the liver. This autoregulation is a one-way mechanism as the portal vein cannot dilate in response to decreased hepatic artery flow. Extrinsic factors, such as sympathetic innervation, regulate blood flow through the portal vein indirectly by modulating arterial tone in the splanchnic vessels. Portal venous pressure therefore reflects both splanchnic arterial tone and intrahepatic resistance to flow. When portal venous pressure is elevated, portosystemic shunts are formed from tributaries that allow portal venous blood to bypass the liver and flow directly to the systemic circulation,

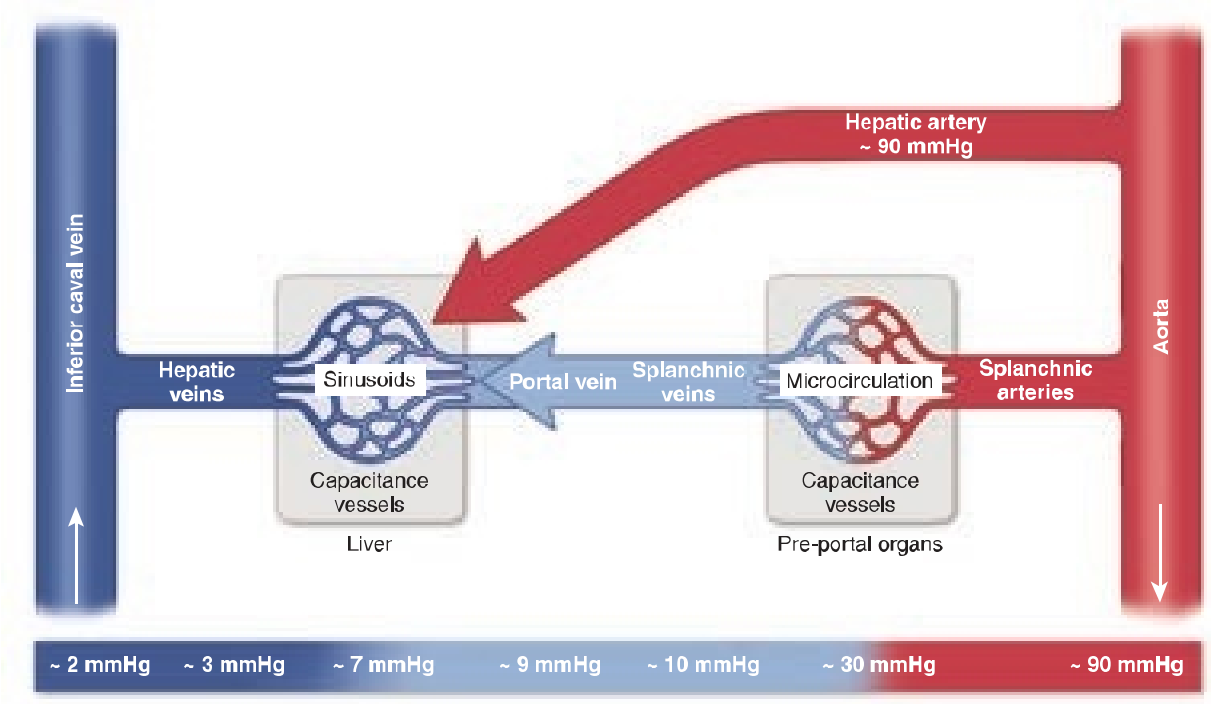


Fig. 16.1 Hepatic blood flow. The high-pressure hepatic arterial blood mixes with the low-pressure portal venous blood as the two vascular systems merge in the low-pressure hepatic sinusoids. This pressure gradient allows forward flow of blood through the liver. (Adapted from Gelman S, Mushlin PS, Weiskopf RB. Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. *Anesthesiology.* 2004;100:434-439 [figure 2].)

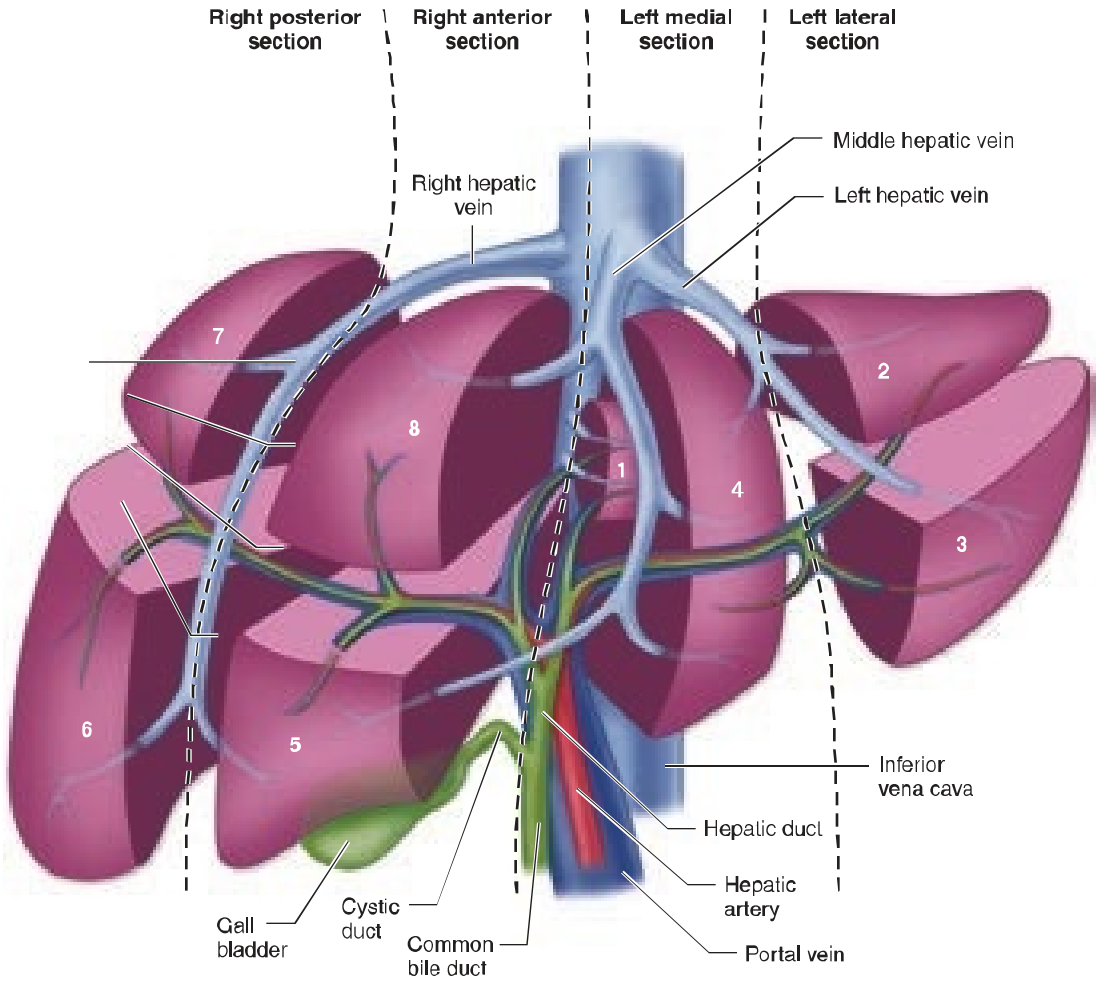


Fig. 16.2 Anatomic segments of the liver. Couinaud's classification system divides the liver into eight segments, each with their own vascular inflow, outflow, and biliary drainage. The three hepatic veins divide the liver into four vertical sectors: right posterior, right anterior, left medial, and left lateral. (From Siriwardena AK, et al. Management of colorectal cancer presenting with synchronous liver metastases. *Nat Rev Clin Oncol.* 2014;11:446-459 [figure 1].)

leading to the development of esophageal and gastric varices. Portal hypertension is considered present when the hepatic venous pressure gradient (HVPG [difference between wedged hepatic venous pressure and free hepatic venous pressure]) exceeds 10 mm Hg. HVPG is commonly used to predict the risk and severity of portal hypertension (Fig. 16.3).

Assessment of Liver Function

Evaluation of liver function should be guided by a careful history that considers risk factors for liver disease, severity of clinical findings, and presence of comorbidities. Risk factors for liver disease include family history, heavy alcohol usage, lifestyle, diabetes, obesity, intravenous drug use, tattoos, prior

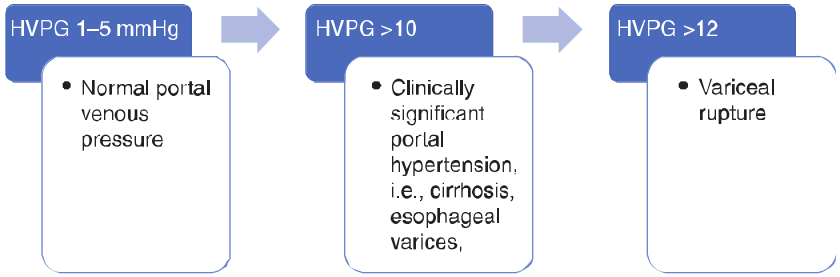


Fig. 16.3 Hepatic venous pressure gradient (HVPG) is commonly used as a surrogate for portal venous pressure measurement. HVPG is used to predict the risk and severity of portal hypertension.

transfusion, and use of medications that can cause hepatotoxicity. Specific questions regarding chronic fatigue, pruritis, easy bleeding/bruising, volume overload, changes in weight, and dark urine should be asked. The physical exam findings may reveal jaundice, ascites, asterixis, hepatomegaly, splenomegaly, or spider nevi. Patients may present without any physical exam findings.

When liver dysfunction is suspected, laboratory workup begins with a liver chemistry panel, complete blood count, and prothrombin time (PT)/international normalized ratio (INR). These tests help confirm clinical suspicion and include biomarkers of hepatobiliary disease that can be divided into three different groups: markers of hepatocellular injury or inflammation, cholestasis, and synthetic function. Table 16.2 lists common causes of hepatic dysfunction and correlating test results.

Hepatocellular injury and inflammation are reflected by increased serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), found in high concentrations in hepatocytes. Since AST and ALT are also present in skeletal and cardiac muscle, correlation with creatine kinase can be useful for discriminating extrahepatic causes. Liver disease processes can have distinctive patterns of enzyme elevations. Acute liver failure (ALF) secondary to medication use often results in AST and ALT levels more than 25 times greater than normal. ALD will usually have an AST:ALT ratio of at least 2:1, while nonalcoholic steatohepatitis will often have an AST:ALT ratio of 1:1. Although liver chemistry elevations can be suggestive of certain disease processes, they are not always specific.

Alkaline phosphatase, γ-glutamyltransferase (GGT), and bilirubin are used to assess for cholestasis. Alkaline phosphatase is an enzyme found in the biliary system and within bone, intestines, and the placenta. Elevation can indicate issues with the bile duct, pregnancy, or bone disease, thus clinical correlation is needed to assist with the appropriate diagnosis. GGT is an enzyme highly concentrated in the liver that is more specific for biliary disease compared to alkaline phosphatase. The level of bilirubin, the end product of heme catabolism, is a function of uptake, conjugation, and excretion by the liver. Bilirubin that is bound to albumin in the blood is known as indirect bilirubin. It is transported to the liver where it is conjugated to a water-soluble form, known as direct bilirubin, before secretion into the small intestine as bile. Elevated indirect bilirubin can be caused by prehepatic disorders such as hemolysis, ineffective erythropoiesis, medications, and portosystemic shunts. Elevated direct bilirubin can be caused by biliary obstruction, cholestasis, hepatocellular injury, and disorders such as Dubin-Johnson syndrome.

Synthetic function of the liver is indicated by albumin and PT/INR. Albumin is a plasma protein synthesized in the liver that acts as a primary modulator of plasma oncotic pressure and as a transporter for drugs. Synthesis of albumin is reduced with liver disease. PT is a test that evaluates the extrinsic and common pathway of the coagulation cascade to measure how long it takes for a thrombus to form. PT requires factors II, V, VII, and X, and therefore is prolonged with advanced liver disease due to any etiologic factor.

Liver imaging includes a variety of techniques. Imaging usually begins with ultrasound evaluation. Ultrasound can be used to assess liver size and nodularity, biliary tree anatomy, spleen size, and presence of hepatic masses. It can also detect ascites in its earliest stages (≥ 100 mL). Doppler ultrasound imaging can be used for assessment of portal venous patency and direction of portal flow. Computed tomography (CT) scan or magnetic resonance imaging (MRI) can be used for further evaluation of hepatobiliary anatomy and for exclusion of other intraabdominal processes.

DISEASES OF THE BILIARY TRACT

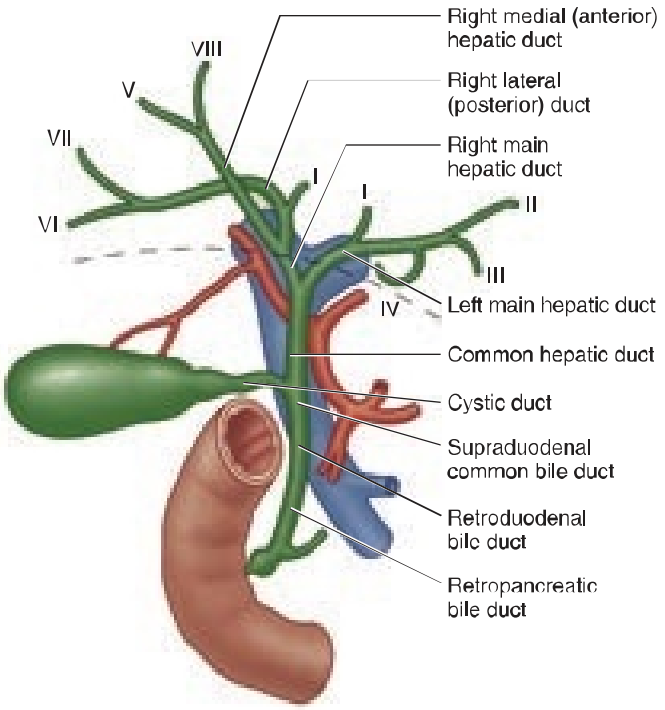
Biliary Tract Anatomy

The biliary system consists of the gallbladder, bile ducts, and structures involved in the production, storage, and transport of bile. Hepatocytes secrete bile (composed of water, bilirubin, bile salts, and cholesterol) into small ducts that form the common hepatic duct. Between meals, secreted bile is stored in the gallbladder. During a meal, the gallbladder contracts to secrete bile into the duodenum and aid in digestion of fats. Fig. 16.4 shows anatomy of the biliary tree.

TABLE 16.2 Causes of Hepatic Dysfunction Based on Liver Chemistry Test Results

Hepatic Dysfunction	Bilirubin	Aminotransferase Enzymes	Alkaline Phosphatase	Causes
Prehepatic	Increased unconjugated fraction	Normal	Normal	Hemolysis Hematoma resorption Bilirubin overload from blood transfusion
Intrahepatic (hepatocellular)	Increased conjugated fraction	Markedly increased	Normal to slightly increased	Viral infection Drugs Alcohol Sepsis Hypoxemia Cirrhosis
Posthepatic (cholestatic)	Increased conjugated fraction	Normal to slightly increased	Markedly increased	Biliary tract stones or tumors Sepsis

Schematic illustration of intrahepatic and extrahepatic biliary tract



The level of the porta hepatis is indicated by the dashed line.

Fig. 16.4 Anatomy of the biliary tract. Bile flows out of the liver via the right and left hepatic ducts, which drain into the common hepatic duct. The common hepatic duct then joins with the cystic duct from the gallbladder before entering the duodenum. Not all bile runs directly into the duodenum. Half of the bile produced by the liver is first stored in the gallbladder. (From Mahadevan V. Anatomy of the Gallbladder and Bile Ducts. *Surgery*. (Oxford). 2020;38(8):432-436 [figure 1].)

Cholelithiasis

Cholelithiasis occurs when substances in bile become hardened within the gallbladder. This can occur for several reasons: cholesterol oversecretion, excess bilirubin, or gallbladder hypomotility. Risk factors for gallstones include obesity, hyperlipidemia, diabetes, pregnancy, family history, and female gender. Nearly 80% of patients with cholelithiasis are asymptomatic. Symptomatic patients may have right upper quadrant pain or referred pain to the shoulders, nausea, vomiting, and indigestion. Acute cholecystitis occurs when a gallstone obstructs the cystic duct causing the gallbladder to become distended and inflamed. The patient may present with fever, pain in the right upper quadrant, and tenderness over the gallbladder. Management of these patients initially includes intravenous (IV) fluids, antibiotics, and pain management. Laparoscopic cholecystectomy is performed once the patient is medically optimized and stable. If the patient develops septic shock, a percutaneous cholecystostomy may be warranted, given the tenuous preoperative status. Anesthetic considerations should include the risk of opioid use and resultant sphincter of Oddi spasm. The risk of opioid-induced sphincter of Oddi spasm is low and can be antagonized using drugs such as glucagon, naloxone, or nitrate drugs.

Choledocholithiasis

Choledocholithiasis is a complication of cholelithiasis in which a gallstone obstructs the common bile duct impeding the flow of bile from the liver to the duodenum. Patients often present with symptoms of biliary colic suggested by intermittent episodes of nausea, vomiting, and crampy right upper quadrant pain. Common bile duct obstruction can lead to cholangitis, which is associated with fever, rigors, and jaundice in addition to the abovementioned symptoms. Treatment involves surgical or endoscopic removal of the obstruction. The most common method is preoperative endoscopic retrograde cholangiopancreatography (ERCP) to identify the stone followed by endoscopic sphincterotomy to remove it. Laparoscopic exploration of the common bile duct may also be performed concurrently with cholecystectomy.

HYPERBILIRUBINEMIA

Hyperbilirubinemia can be divided into two categories based on whether it is conjugated. Unconjugated (indirect) hyperbilirubinemia results from an imbalance between synthesis and catabolism of bilirubin. Conjugated (direct) hyperbilirubinemia results from reflux of direct or conjugated bilirubin into the blood following biliary obstruction. Table 16.3 lists causes of hyperbilirubinemia.

Gilbert Syndrome

Gilbert syndrome is a benign, autosomal dominant inherited disorder that results in unconjugated hyperbilirubinemia. Activity of the enzyme, uridine diphosphoglucuronate glucuronosyltransferase (UGT1A1), is decreased, resulting in mildly elevated indirect bilirubin levels. Patients may report jaundice, fatigue, or abdominal discomfort that is precipitated by dehydration, exercise, fasting, or stress. Symptoms typically

TABLE 16.3 Causes of Hyperbilirubinemia

Unconjugated (Indirect)
Physiologic jaundice of newborn
Jaundice of prematurity
Hemoglobin disorders (i.e., sickle cell anemia, thalassemia)
Hemolysis (i.e., immune mediated, hereditary)
Hereditary defects in conjugation (i.e., Gilbert syndrome, Crigler-Najjar syndrome)
Red blood cell enzyme disorders (i.e., glucose-6-phosphate dehydrogenase deficiency)
Drug induced
Sepsis
Conjugated (Direct)
Intrahepatic cholestasis
Hepatocellular injury (hepatitis, cirrhosis, drugs)
Congenital infections
Benign postoperative jaundice
Dubin-Johnson syndrome
Rotor syndrome
Obstructive jaundice
Biliary atresia

resolve spontaneously. Plasma indirect bilirubin is only mildly elevated.

Crigler-Najjar Syndrome

Crigler-Najjar syndrome is one of the most severe, albeit rare, forms of inherited unconjugated hyperbilirubinemia. It is inherited in an autosomal recessive pattern and characterized by either no or very little expression of the enzyme UGT1A1. Shortly after birth, affected infants develop signs of severe jaundice, fever, and vomiting. If untreated, the hyperbilirubinemia can result in severe brain damage. Diagnosis is made by high serum concentrations of indirect bilirubin. Treatment includes daily exchange transfusions, 12 hours /day phototherapy, and heme oxygenase inhibitors. Oral calcium phosphate is often used to bind bilirubin in the gut. Phenobarbital can be used in specific forms of the syndrome. Curative treatment is liver transplantation before the onset of brain damage.

Benign Postoperative Intrahepatic Cholestasis

Benign postoperative intrahepatic cholestasis is postoperative jaundice in which there is no hepatic inflammation or cell necrosis. The cause is often multifactorial and associated with hypotension, significant blood loss, multiple transfusions, or hypoxemia. Bilirubin and alkaline phosphatase levels can increase two- to fourfold within the first 7 to 10 days following surgery. The diagnosis is made after excluding other causes. Although the jaundice may appear severe and dramatic, the condition is generally self-limited.

HEPATITIS

Viral Hepatitis

Viral hepatitis is most commonly caused by hepatitis A (HAV), B (HBV), C (HCV), D (HDV), and E (HEV) viruses. Each of these can cause acute infections with the potential for substantial morbidity. HBV and HCV are associated with significant chronic sequelae, while HAV lacks a chronic stage and contributes only to acute infection. Table 16.4 lists characteristic features of the various viral hepatitides. Of those, HAV and HEV rarely result in chronic liver disease and infrequently lead to liver transplantation. Both HBV and HCV remain a common reason for liver transplantation in developing countries, while HCV remains the most common viral hepatitis leading to liver transplantation in the United States. Advances in antiviral therapies over the last decade have revolutionized management of HCV disease. Current treatment regimens typically include two direct-acting antiviral drugs that target specific steps within the HCV replication cycle with or without interferon for a duration of 8 to 12 weeks. Antiviral drug choice and treatment duration are based on the genotype of HCV, stage of liver disease, presence of cirrhosis, and previous response to interferon. Genotype 1 is the most common, accounting for 70% to 75% of all HCV infections in the United States. One of the recommended medication regimens for genotype 1 is a 12-week course of sofosbuvir/velpatasvir, which has been found to provide a rate of infection clearance of 98% in genotype 1A and 99% in genotype 1B. Duration of drug therapy is heavily dependent on history of prior therapy and severity of liver disease.

COVID-19

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by a novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 was first identified in December 2019 and quickly evolved into a worldwide pandemic over the course of months. It primarily manifests as a lung infection, but liver injury is not uncommon (14–53% of patients). COVID-19 infection with acute liver injury is thought to be prognostic and associated with higher mortality

TABLE 16.4 Characteristic Features of Viral Hepatitis

Parameter	Type A	Type B	Type C	Type D	Type E
Mode of transmission	Fecal-oral, sewage-contaminated water or shellfish	Transfusions, percutaneous, sexual, perinatal	Transfusions, percutaneous, sexual, perinatal	Percutaneous	Fecal-oral, contaminated water
Incubation period	20–37 days	60–110 days	35–70 days	30–110 days	15–60 days
Results of serum antigen and antibody tests	IgM early, IgG appears during convalescence	HBsAg and anti-HBcAg early and persist in carriers	Anti-HCV in 6 wk to 9 mo	Anti-HDV late; may be short lived	IgM early, IgG appears shortly afterwards
Course	Acute, does not progress to chronic liver disease	Chronic liver disease develops in 1–5% of adults and 80–90% of children	Chronic liver disease develops in up to 75%	Coinfection with type B	Usually acute, may cause chronic liver disease in those with weakened immune systems
Prevention after exposure	Pooled γ-globulin, hepatitis A vaccine	Hepatitis B immunoglobulin, hepatitis B vaccine	Two protease inhibitors −/− interferon	Unknown	Ribavirin in immunocompromised
Mortality	0.3–0.6%	0.3–1.5%	Unknown	Acute icteric hepatitis: 2–20%	1%, 10–30% among pregnant women

HBcAg, Hepatitis B core antigen; *HBsAg*, hepatitis B surface antigen; *HCV*, hepatitis C virus; *HDV*, hepatitis D virus; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M.
Adapted from Koofo EB. Acute hepatitis. *Sci Am Med*. 1999:1–9.

compared to COVID-19 infection without hepatic involvement. Abnormal liver chemistries with elevated aminotransferases are commonly described, while alteration of GGT and alkaline phosphatase is found less frequently. Preliminary data suggest that preexisting liver disease is associated with higher risk for hospitalizations and mortality in patients with COVID-19.

The pathogenesis of COVID-19–induced liver damage is not yet understood. Besides direct viral-induced injury, other theorized causes of liver injury include cytokine storm, sepsis, and drug-induced injury. Current therapy for COVID-19 is mainly supportive management such as intensive care, ventilator support, continuous renal replacement therapy for cytokine storm syndrome, and maintaining effective hemodynamics to prevent and treat multiple organ failure, including liver damage. There is a paucity of data on transplantation for severe COVID-19–induced liver injury.

Alcohol-Associated Liver Disease

Alcohol consumption is an important risk factor for a wide array of illnesses that lead to significant morbidity and mortality. ALD is the top indication for liver transplantation in the United States and has a national prevalence of 2%. Worldwide, alcohol consumption varies geographically, with the highest rates of reported per capita occurring in northern and eastern European countries and Russia.

Clinically, patients often show no symptoms with early ALD or with compensated cirrhosis. Underreporting of alcohol consumption is common given the stigma of heavy alcohol use. Patients may present with clinical manifestations of alcohol abuse such as malnutrition, muscle wasting, or parotid gland hypertrophy. Physical examination in the case of advanced liver disease may show evidence of jaundice, ascites, hepatosplenomegaly, or pedal edema. Laboratory tests such as mean corpuscular volume, liver enzymes, GGT, or bilirubin can suggest alcohol use, but are inadequate alone to establish ALD. Alcohol-specific biomarkers such as ethyl glucuronide and ethyl sulfate, which are detected in the urine, blood, and hair, can be used to narrow the diagnosis. Treatment of ALD is centered around abstinence from alcohol and management of liver failure. Liver transplantation is the definitive cure for severe ALD.

Nonalcoholic Fatty Liver Disease

NAFLD is characterized by excessive fat accumulation in the liver without any clear cause such as alcohol use. It is associated with obesity, insulin resistance, type 2 diabetes mellitus, and metabolic syndrome. The hallmark feature of NAFLD is hepatic steatosis, which occurs when there is more than 5% fat in hepatocytes. Progression can ensue if these fatty hepatocytes are exposed to insults or stress, which can then cause cell death and inflammation, leading to nonalcoholic steatohepatitis (NASH). NASH has a potentially progressive course leading to liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). NAFLD and NASH have become two leading indications for liver transplantation in the United States.

Diagnosis of NAFLD requires exclusion of coexisting causes of liver disease, lack of significant alcohol consumption, and the presence of steatosis on imaging or histology. Liver biopsy is the gold standard in diagnosing and distinguishing NAFLD from other liver disease. Management of NAFLD includes treating the liver disease as well as the associated comorbidities. Lifestyle changes such as weight loss, diet control, and exercise are advocated. Despite the use of multiple medications, there is no effective pharmacologic treatment. Liver transplant is the treatment for advanced fibrosis, cirrhosis, and related complications.

Autoimmune Hepatitis

Autoimmune hepatitis (AH) is an inflammatory disease of the liver characterized by autoantibodies and hypergammaglobulinemia. AH affects both genders, but predominantly occurs in women. AH can present with minimal/no symptoms, as an acute disease, or chronic disease. Severe symptoms can occur, including fulminant hepatic failure. Since clinical features lack diagnostic specificity, other diseases such as viral hepatitis and cholestasis must be excluded. Laboratory findings include antibodies such as antinuclear antibody (ANA), anti-smooth muscle antibody, and anti-liver kidney microsomal antibodies. AST and ALT may exceed 10 to 20 times the upper limit of normal in acute presentations. The mainstay of therapy includes prednisone alone or in combination with azathioprine. All patients with active AH are candidates for treatment regardless of symptom status. Overall, 60% to 80% of patients achieve remission, although relapse is common. Refractory disease therapy includes immunosuppression with mycophenolate, cyclosporine A, or tacrolimus. Liver transplantation may be indicated if therapy fails or if the patient presents in fulminant hepatic failure.

Drug-Induced Liver Injury

Drug-induced liver injury is quite common and can be caused by several classes of drugs. Acetaminophen overdose (accidental or intentional) remains the most common cause of drug-induced liver injury (Table 16.5). Most cases are benign and improve after withdrawal of the inciting drug. Recognition and removal of the offending agent as quickly as possible can help prevent the progression to hepatitis or liver failure. Liver injury may be the result of direct toxicity from the administered drug or from an immune-mediated mechanism. Most patients have clinical symptoms that are identical to other liver diseases, although some patients present with symptoms of systemic hypersensitivity (rash, fever, eosinophilia). The diagnosis requires exclusion of other causes of liver injury and relies upon knowledge of the patient's medication list. Establishment of a temporal relationship between drug exposure and development of signs of liver disease is helpful in confirming the diagnosis. Management is centered around cessation of the inciting drug, supportive care, and evaluation for liver transplantation.

Inborn Errors of Metabolism

Inborn errors of metabolism are a group of rare genetic or inherited disorders resulting from an enzyme defect that affects the breakdown or storage of carbohydrates, fatty acids, and proteins. Many are inherited as autosomal recessive, but they can rarely be autosomal dominant or X-linked. Inborn errors of

TABLE 16.5 Common Drugs Associated With Liver Injury

Analgesic
Acetaminophen
Nonsteroidal antiinflammatory drugs

Cardiovascular
Statins
Amiodarone
Methyldopa
Angiotensin-converting enzyme inhibitors

Antimicrobial
Isoniazid
Rifampicin
Pyrazinamide
Tetracycline
Macrolides
Sulfonamides
Azole antifungals
Fluoroquinolones
β-lactams

Neurologic/Antiepileptic
Phenobarbital
Phenytoin
Carbamazepine
Lamotrigine
Felbamate
Valproate
Chlorpromazine
Tricyclic antidepressants
Selective serotonin reuptake inhibitors
Norepinephrine reuptake inhibitors

Recreational
Amphetamines
Cocaine
Ecstasy
Ethanol

Adapted from Marschall K. *Stoelting's Anesthesia & Coexisting Disease*. 7th ed. Elsevier; 2017:353 (table 17.4).

metabolism occur in 1 of 2500 births. The age of presentation can vary from infancy to adolescence, with the more severe forms appearing in the neonatal period accompanied by significant morbidity and mortality.

Wilson Disease

Wilson disease, also known as hepatolenticular degeneration, is an autosomal recessive disease characterized by impaired copper metabolism. Excess copper levels lead to increased oxidative stress in the cells of the liver, basal ganglia of the brain, and the cornea. Patients can be asymptomatic or present with fulminant hepatic failure, along with neurologic or psychiatric manifestations. Other clinical findings may include hemolytic anemia, thrombocytopenia, renal failure, cardiomyopathy, and hyperpigmentation. The workup for suspected Wilson disease involves laboratory tests such as serum ceruloplasmin, aminotransferases, and urine copper levels. Low serum ceruloplasmin levels along with elevated copper excretion support the diagnosis. Kayser-Fleischer rings found on ocular slit-lamp examination is highly suggestive of Wilson disease, although not specific. A liver biopsy with copper quantitation may be required if there are indeterminate results from laboratory workup. The mainstay of treatment is copper chelation therapy with penicillamine and trientine. Oral zinc can also be used to stimulate binding of copper in the gut, preventing absorption and transport of copper to the liver.

α1-antitrypsin Deficiency

α1-antitrypsin deficiency is a genetic disorder that results in defective production of α1-antitrypsin protein. This protein protects the liver and lungs from neutrophil elastase, an enzyme that can disrupt connective tissue leading to inflammation, cirrhosis, and HCC. In the lungs, patients with α1-antitrypsin deficiency can develop early-onset panlobular emphysema and symptoms of chronic obstructive pulmonary disease. The incidence of α1-antitrypsin deficiency is estimated to be 1:1600 to 1:3500, although it is likely underdiagnosed due to its nonspecific presentation. α1-antitrypsin deficiency is the leading genetic cause of liver disease and liver transplant among children. Patients are found to have elevated transaminase levels and may present with signs of liver dysfunction. Serum α1-antitrypsin levels can be tested but can result in a false-positive result, since it is also an acute-phase reactant and therefore elevated in the setting of inflammation. The diagnosis is confirmed with PI*ZZ α1-antitrypsin phenotyping. Treatment of α1-antitrypsin deficiency lung disease includes use of pooled human α1-antitrypsin protein as supportive therapy. However, pooled human α1-antitrypsin protein has no role in treatment of liver disease. Transplantation is the only curative therapy for α1-antitrypsin liver disease. Transplant recipients express the donor phenotype and do not experience recurrence of liver disease.

Hemochromatosis

Hemochromatosis is a disorder associated with excess iron in the body that can lead to multiorgan dysfunction. Hereditary hemochromatosis is an autosomal recessive disorder characterized by excessive intestinal absorption of dietary iron. Repeated blood transfusions or high doses of iron can also lead to hemochromatosis. Excess iron accumulates in organs and leads to tissue injury. Patients may present with cirrhosis, heart failure, diabetes, adrenal insufficiency, or polyarthropathy. They may also present with generalized symptoms of fatigue and malaise, and on routine workup are found to have elevated serum liver enzymes or elevated transferrin saturation. Screening for hemochromatosis includes serum transferrin, transferrin saturation, and ferritin levels. Ferritin levels above 300 μg/L in men and 200 μg/L in women or transferrin saturation of more than 50% in men or 40% in women should lead to further testing. Genetic testing for the HFE mutation or other common mutations will confirm the diagnosis. Echocardiography and MRI can be used to identify cardiomyopathy and assess liver abnormalities. Liver biopsy can be used to quantify iron in the liver and assess liver damage. Liver transplantation may be required.

TABLE 16.5 Common Drugs Associated With Liver Injury

Analgesic
Acetaminophen
Nonsteroidal antiinflammatory drugs

Cardiovascular
Statins
Amiodarone
Methyldopa
Angiotensin-converting enzyme inhibitors

Antimicrobial
Isoniazid
Rifampicin
Pyrazinamide
Tetracycline
Macrolides
Sulfonamides
Azole antifungals
Fluoroquinolones
β-lactams

Neurologic/Antiepileptic
Phenobarbital
Phenytoin
Carbamazepine
Lamotrigine
Felbamate
Valproate
Chlorpromazine
Tricyclic antidepressants
Selective serotonin reuptake inhibitors
Norepinephrine reuptake inhibitors

Recreational
Amphetamines
Cocaine
Ecstasy
Ethanol

Adapted from Marschall K. *Stoelting's Anesthesia & Coexisting Disease*. 7th ed. Elsevier; 2017:353 (table 17.4).

metabolism occur in 1 of 2500 births. The age of presentation can vary from infancy to adolescence, with the more severe forms appearing in the neonatal period accompanied by significant morbidity and mortality.

Wilson Disease

Wilson disease, also known as hepatolenticular degeneration, is an autosomal recessive disease characterized by impaired copper metabolism. Excess copper levels lead to increased oxidative stress in the cells of the liver, basal ganglia of the brain, and the cornea. Patients can be asymptomatic or present with fulminant hepatic failure, along with neurologic or psychiatric manifestations. Other clinical findings may include hemolytic anemia, thrombocytopenia, renal failure, cardiomyopathy, and hyperpigmentation. The workup for suspected Wilson disease involves laboratory tests such as serum ceruloplasmin, aminotransferases, and urine copper levels. Low serum ceruloplasmin levels along with elevated copper excretion support the diagnosis. Kayser-Fleischer rings found on ocular slit-lamp examination is highly suggestive of Wilson disease, although not specific. A liver biopsy with copper quantitation may be required if there are indeterminate results from laboratory workup. The mainstay of treatment is copper chelation therapy with penicillamine and trientine. Oral zinc can also be used to stimulate binding of copper in the gut, preventing absorption and transport of copper to the liver.

α1-antitrypsin Deficiency

α1-antitrypsin deficiency is a genetic disorder that results in defective production of α1-antitrypsin protein. This protein protects the liver and lungs from neutrophil elastase, an enzyme that can disrupt connective tissue leading to inflammation, cirrhosis, and HCC. In the lungs, patients with α1-antitrypsin deficiency can develop early-onset panlobular emphysema and symptoms of chronic obstructive pulmonary disease. The incidence of α1-antitrypsin deficiency is estimated to be 1:1600 to 1:3500, although it is likely underdiagnosed due to its nonspecific presentation. α1-antitrypsin deficiency is the leading genetic cause of liver disease and liver transplant among children. Patients are found to have elevated transaminase levels and may present with signs of liver dysfunction. Serum α1-antitrypsin levels can be tested but can result in a false-positive result, since it is also an acute-phase reactant and therefore elevated in the setting of inflammation. The diagnosis is confirmed with PI*ZZ α1-antitrypsin phenotyping. Treatment of α1-antitrypsin deficiency lung disease includes use of pooled human α1-antitrypsin protein as supportive therapy. However, pooled human α1-antitrypsin protein has no role in treatment of liver disease. Transplantation is the only curative therapy for α1-antitrypsin liver disease. Transplant recipients express the donor phenotype and do not experience recurrence of liver disease.

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Early diagnosis is essential, as the late effects of iron accumulation can be prevented by periodic phlebotomies. Phlebotomy can be performed at weekly intervals until ferritin levels are less than 50 μg/L. Deferoxamine, an iron-chelating drug, can be administered long term to reduce iron levels.

Primary Biliary Cholangitis

Primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis, is an autoimmune disorder that leads to progressive destruction of intrahepatic bile ducts, in addition to periportal inflammation and cholestasis. Progressive damage can lead to scarring, fibrosis, and eventually cirrhosis. PBC is thought to be triggered by environmental factors, such as cigarette smoking, toxic wastes, and hair dye, in genetically susceptible individuals. Patients present with jaundice, fatigue, and itching, but many have asymptomatic presentations, often being referred due to elevated cholestasis enzymes (alkaline phosphatase and GGT). Antimitochondrial antibodies found on serology are diagnostic features of PBC. The presence of other autoantibodies, such as antinuclear antibody and anti-glycoprotein-210 antibodies, are common but not diagnostic. Abdominal ultrasound, CT scan, or magnetic resonance cholangiopancreatography (MRCP) can usually be performed to rule out obstruction of the bile ducts. Liver biopsy reveals evidence of interlobular bile ducts destruction with a predominance of lymphocytic infiltration. The goal of medical therapy is to prevent disease progression and manage symptoms related to chronic cholestasis. Ursodeoxycholic acid, a bile acid, is one of the main treatments for PBC. It has been shown to slow progression and improve liver transplant-free survival. Bile acid sequestrants such as cholestyramine are used to reduce itching. Liver transplant is the curative therapy for patients with advanced liver disease due to PBC.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is another chronic inflammatory autoimmune disease affecting the bile ducts. Unlike PBC, PSC primarily affects the large ducts. Progressive fibrosis leads to strictures of the biliary tree, which can culminate in liver cirrhosis and end-stage liver disease. PSC is more likely to affect males and has a median age of presentation of 40 years old. Most patients have a subtle presentation of fatigue or pruritus. The diagnosis of PSC is made after findings of elevated serum markers of cholestasis (alkaline phosphatase and GGT) in combination with MRCP or ERCP demonstrating characteristic multifocal strictures and dilation of intrahepatic and/or extrahepatic bile ducts. Autoantibodies such as antinuclear, anti-smooth muscle, and anticardiolipin may be present but are not specific for diagnosis. Liver biopsy can reinforce a diagnosis of PSC but is rarely used given the patchy nature of PSC.

Treatment goals are centered around slowing or reversing the progression of scarring while managing the symptoms. No pharmacologic agents have proven to alter the natural history of the disease. Liver transplant is the only proven long-term treatment. Given the autoimmune pathophysiology of PSC, some patients will experience disease recurrence after transplantation.

Cardiac Causes of Liver Disease

Since the liver receives one-fourth of total cardiac output, it is extremely sensitive to hemodynamic compromise. Cardiac etiologies of liver failure lead to both ischemic hepatitis and congestive hepatopathy. Cardiogenic ischemic hepatitis, also known as shock liver, is caused by insufficient perfusion of the liver and can be secondary to cardiogenic shock. Persistent hypotension can overwhelm the compensatory hepatic dilatation response to reduced portal venous flow. Cardiogenic ischemic hepatitis can be asymptomatic or resemble acute viral hepatitis after a latency period of 2 to 24 hours. Congestive hepatopathy is caused by impaired hepatic venous outflow secondary to right-sided heart failure. Cardiac conditions such as cor pulmonale, ischemic cardiomyopathy, tricuspid regurgitation, mitral stenosis, and constrictive pericarditis can each lead to a state of passive hepatic congestion. The increase in venous pressure caused by the elevated right-sided heart pressures leads to perisinusoidal edema and impairment of the diffusion of oxygen and nutrients to the hepatocytes. Congestive hepatopathy is usually subclinical. When symptomatic, patients may have jaundice, malaise, early satiety, or intermittent right upper quadrant pain. Treating the underlying cardiac disease will lead to improvement of congestion and preclude further liver injury.

ACUTE LIVER FAILURE (FORMERLY FULMINANT HEPATIC FAILURE)

ALF is a life-threatening critical illness characterized by severe hepatocyte injury that occurs in less than 26 weeks and can occur in days. ALF presents with rapid-onset elevation of aminotransferases, altered mental status, and coagulation abnormalities. The pathophysiology involves massive hepatocyte necrosis causing cellular swelling and membrane disruption. The two most common etiologies are drug-induced and viral hepatitis. Drug-induced hepatitis accounts for almost half of all cases of ALF in the United States; acetaminophen is the most common culprit. Due to successful public health measures, viral etiologies are less common in the United States. Of the viral infections that can lead to ALF, HAV, HBV, and HVE are the most common. Other causes of ALF include hypoxia-induced liver injury, acute Budd-Chiari syndrome, venoocclusive disease, mushroom ingestion, AH, acute fatty liver of pregnancy, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, heat stroke, and malignant infiltration.

Patients with ALF may present with jaundice, nausea, or right upper quadrant discomfort. Encephalopathy and cerebral edema may develop, along with multiorgan failure and death. Laboratory findings support significant liver dysfunction and, frequently, acute renal injury. Management of ALF entails treating the etiology, supportive care, management of complications, and determination of prognosis. Early management should include consideration for transfer to a transplant center for potential transplantation. While extracorporeal liver-assist devices have been used in clinical trials in patients with ALF with the goal of detoxification and restoration of synthetic functions, safety and efficacy of these devices have not been demonstrated in controlled, randomized clinical trials.

CIRRHOSIS

Liver cirrhosis is the final stage of chronic liver disease. The pathologic hallmark of cirrhosis is the replacement of normal hepatic parenchyma with scar tissue. Patients are often asymptomatic in early cirrhosis, but as it progresses, symptoms of liver dysfunction start to arise, such as jaundice, ascites, easy bruising, hepatic encephalopathy, and variceal hemorrhage. The most common causes of cirrhosis are alcohol-associated, nonalcoholic fatty liver, HCV, and HBV. Findings on evaluation usually include elevated aminotransferases, bilirubin, alkaline phosphatase, and PT/INR along with thrombocytopenia. A small, nodular-appearing liver is often found on ultrasound imaging. The gold standard for diagnosis is a liver biopsy. Liver transplantation is the only curative option for cirrhosis. Steps should be taken to treat the underlying etiology and prevent the progression of fibrosis, especially in earlier stages of the disease.

Portal Hypertension

Portal hypertension is caused by an increase in vascular resistance within the portal venous system. In cirrhosis, the increased resistance is caused by fibrosis and regenerative nodules within the liver. Even with the diversion of portal blood flow through collaterals, portal hypertension persists due to splanchnic vasodilation. HVPG over 5 mm Hg constitutes portal hypertension. HVPG of 10 mm Hg or greater is clinically significant and predicts the development of varices, decompensated cirrhosis, and HCC. HVPG greater than 12 mm Hg predicts the potential for variceal rupture.

Ascites and Spontaneous Bacterial Peritonitis

Ascites is the most common complication of cirrhosis. In decompensated cirrhosis, portal hypertension results in increased blood volume and transudative accumulation of fluid within the peritoneal cavity. Patients will often complain of increased abdominal girth, abdominal discomfort, increased weight, and shortness of breath. Management of ascites involves a low-salt diet, diuretics, paracentesis, and albumin replacement. A transjugular intrahepatic portosystemic shunt (TIPS) may be placed to reduce the portal hypertension and manage refractory ascites.

Spontaneous bacterial peritonitis is the most common infection in patients with cirrhosis. The diagnosis of spontaneous bacterial peritonitis requires the presence of an absolute polymorphonuclear leukocyte count of 250 cells/mm^3 or more in the ascitic fluid and the absence of another cause for the findings. Patients with high suspicion for spontaneous bacterial peritonitis should be started on empirical antibiotics until cultures return. Antibiotics such as fluoroquinolones are commonly used for prevention in high-risk patients.

Varices

Gastroesophageal varices are present in about half of patients with cirrhosis. Variceal hemorrhage is the most lethal complication of cirrhosis. Factors predictive of variceal rupture include large vessel diameter (indicating high wall tension) and HVPG greater than 12 mm Hg. Patients with known varices should receive treatment such as nonselective blockers, which reduce the risk of bleeding. If there are medical contraindications to blockers, then treatment with prophylactic endoscopic variceal ligation is often performed. Endoscopic variceal ligation can also be used to prevent rebleeding in patients who have recovered from an episode of variceal bleeding. Once a variceal hemorrhage has occurred, volume resuscitation should be performed promptly with the goal of hemodynamic stability, followed by therapeutic endoscopy for variceal ligation or sclerotherapy. In cases of refractory bleeding, balloon tamponade or a TIPS may be necessary.

Hepatic Encephalopathy

Hepatic encephalopathy presents as a spectrum of neuropsychiatric symptoms ranging from subtle fluctuating cognitive impairment to coma. The pathogenesis is linked to the buildup of nitrogenous waste due to poor liver detoxification, resulting in neurotoxic effects. Triggers of hepatic encephalopathy include infection, electrolyte or metabolic disturbance, or medications such as benzodiazepines and antipsychotics. Evaluation of a patient with signs of hepatic encephalopathy begins with a search for alternative causes of altered mental status (e.g., stroke, medications) and assessment of precipitating factors. Hyperammonemia alone is not diagnostic. Serum ammonia levels are elevated in 90% of people with liver disease but not always associated with encephalopathy. Treatment of hepatic encephalopathy depends on the suspected underlying cause. Given that pneumonia and spontaneous bacterial peritonitis may be precipitating factors for encephalopathy, antibiotics can be administered empirically in high-risk patients. The two main therapies to treat elevated ammonia levels are nonabsorbable disaccharides (lactulose) and nonabsorbable antibiotics (rifaximin). Both reduce the number of ammonia-producing bacteria in the gut.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is a complication of severe liver disease characterized by decreased renal blood flow and a poor prognosis. It is caused by significant circulatory dysfunction secondary to locally acting vasodilators such as nitric oxide and prostaglandins. These vasodilators produce splanchnic arterial vasodilation, decreased mean arterial pressure (MAP), relative renal hypoperfusion, and activation of vasoconstrictor systems such as the renin-angiotensin-aldosterone system and vasopressin. The splanchnic vascular bed is refractory to the action of these vasoconstrictor systems, and ascites and hyponatremia result. HRS can develop in the setting of infection such as spontaneous bacterial peritonitis, or after large volume paracentesis. The diagnosis requires the presence of cirrhosis and acute renal failure, and exclusion of other causes of renal failure. Midodrine, octreotide, and albumin for volume expansion is a widely used treatment for HRS. Hemodialysis is employed in those patients who have no renal response to medical treatment and are awaiting liver transplant.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome is defined by a clinical triad of chronic liver disease, hypoxemia, and the presence of

intrapulmonary vascular dilation. Platypnea, the worsening of dyspnea in the upright position, is pathognomonic for hepatopulmonary syndrome. This phenomenon is associated with orthodeoxia (hypoxemia) when the patient changes from the lying to the upright position. The pathophysiology is thought to be secondary to increased perfusion at the base of the lungs when the patient stands up leading to increased shunt effect. Diagnosis is confirmed by detection of an intrapulmonary right-to-left shunt by bubble study on echocardiography. Bubbles appearing on the left side of the heart three to four beats after injection is diagnostic of an intrapulmonary shunt. Liver transplantation is the only effective treatment and often leads to reversal of hypoxemia.

Portopulmonary Hypertension

Portopulmonary hypertension is characterized by pulmonary arterial hypertension in the setting of portal hypertension with or without liver disease. The pathology arises from systemic vasodilation with local pulmonary production of vasoconstrictors. A mean pulmonary artery pressure greater than 25 mm Hg at rest is considered diagnostic. The curative treatment of portopulmonary hypertension is liver transplantation. A mean pulmonary artery pressure greater than 45 mm Hg is considered a contraindication to transplantation. Pulmonary vasodilators such as phosphodiesterase inhibitors, nitric oxide, prostacyclin analogs, and endothelin receptor antagonists are commonly used as a bridge to transplant.

TABLE 16.6 Child-Turcotte-Pugh Score and Survival of Chronic Liver Disease

Points	Class	1-Year Survival	2-Year Survival
5–6	A	100%	85%
7–9	B	81%	57%
10–15	C	45%	35%

The Child-Turcotte-Pugh score was developed in 1964 to estimate the risk of operative mortality in patients with bleeding esophageal varices. It has since been modified and has become a widely used tool to assess the prognosis of chronic liver disease and cirrhosis.

TABLE 16.7 3-Month Survival Based on Model for End-Stage Liver Disease (MELD) Score

MELD Score	Observed Mortality
9	1.9–3.7%
10–19	6–20%
20–29	19.6–45.5%
30–39	52.6–74.5%
≥40	71.3–100%

MELD score assesses severity of chronic liver disease using factors such as serum bilirubin, serum creatinine, and international normalized ratio. MELD score also has proven utility in assessing 3-month survival in patients with liver cirrhosis.

ANESTHESIA FOR PATIENTS WITH LIVER DISEASE

Patients with liver disease have a unique pathophysiology that necessitates a specialized evaluation before undergoing surgery given the greater risk for surgical and anesthesia-related complications. There are certain settings in which the risk of mortality is unacceptably high and makes elective surgery contraindicated, such as acute hepatitis, ALF, and severe chronic hepatitis. With less severe liver disease, surgical risk assessment, urgency of the surgery, and known medical comorbidities should be considered. The two most commonly used scores to stratify the severity of liver disease are the Child-Turcotte-Pugh (CTP) and Model for End Stage Liver Disease (MELD) scores (Tables 16.6 and 16.7) The CTP score is a point-based system that emphasizes the complications of portal hypertension using factors such as total bilirubin, albumin, prothrombin time, hepatic encephalopathy, and ascites. The MELD score uses components such as serum bilirubin, INR, creatinine, and sodium to calculate a score that also predicts liver disease prognosis. Fig. 16.5 shows an approach to preoperative risk assessment.

All liver patients should be evaluated with preoperative complete blood count, metabolic panel, and PT/INR. In addition to standard anesthesia monitors, a low threshold can be considered for placement of invasive monitoring, such as an arterial catheter to allow continuous blood pressure monitoring and facilitate blood sampling. The usefulness of central venous pressure (CVP) monitoring is more controversial and should be reserved for indications such as vasopressor administration or for venous access in patients with difficult IV access.

Patients with liver disease are at increased risk for aspiration, hypotension, and hypoxemia during induction of anesthesia. Patients may have enhanced sedation and prolonged duration of action from induction agents and sedatives. Succinylcholine and cisatracurium do not require hepatic metabolism, and thus are ideal muscle relaxants in this patient population. Maintenance of anesthesia can be achieved with volatile anesthetics. Intraoperative hemodynamic management should focus on maintaining the patient's baseline blood pressure, with the addition of vasopressors if needed, utilizing lung protective ventilation strategies and coagulation management if significant bleeding is present.

ABNORMAL LIVER CHEMISTRY IN THE SURGICAL PATIENT

Potential benefits of preoperative testing are detection of previously undiagnosed conditions that could affect a patient in the perioperative setting. Many societies and guidelines argue for selective use of preoperative tests that will change the outcome or alter management based on a patient's clinical history, comorbidities, and physical exam. Given the very low incidence of abnormalities that influence management, routine testing of aminotransferases or alkaline phosphatase is not recommended before surgery. If routine testing is performed and returns with an abnormal value, the tests should be repeated for confirmation. A careful history and laboratory workup that evaluates risk factors for liver disease is essential to identify a cause for the

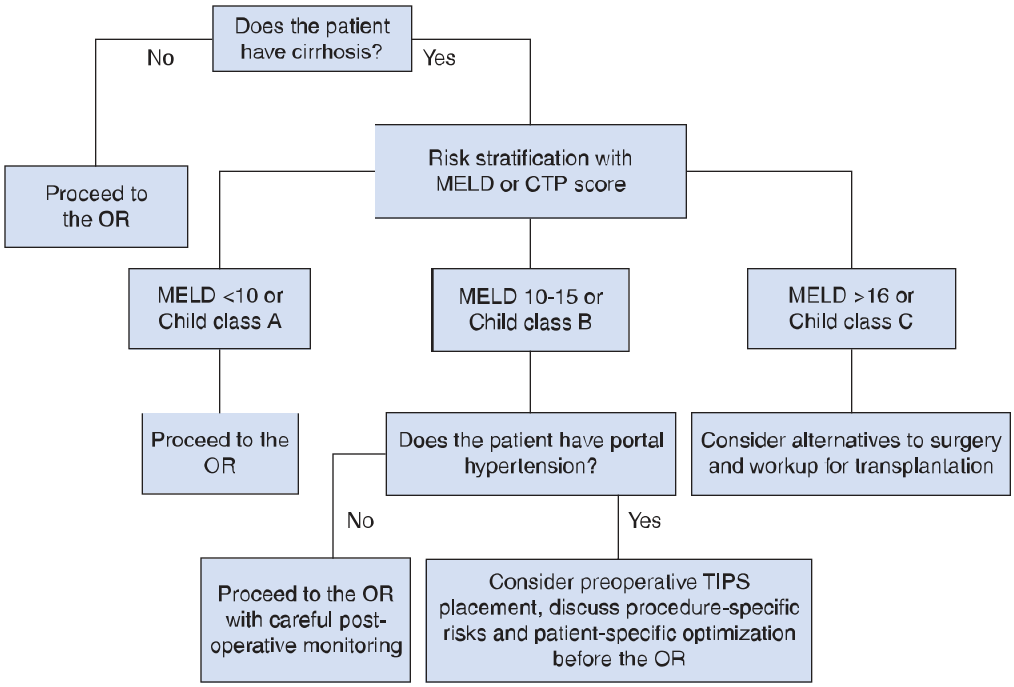

Fig. 16.5 Recommended approach for preoperative risk assessment of patients with liver disease undergoing elective surgery. (Adapted from Prenner S, Ganger D. Risk stratification and preoperative evaluation of the patient with known or suspected liver disease. *Clin Liver Dis.* 2016;7(5):104 [figure 1].)

elevation. Patients presenting with signs of acute hepatitis (coagulopathic or encephalopathic) should be immediately referred to a hepatologist.

PROCEDURES AND OPERATIONS FOR LIVER DISEASE

Transjugular Intrahepatic Portosystemic Shunt

TIPS is a procedure to manage portal hypertension by creating a direct communication between the portal vein and the hepatic vein, resulting in the shunting of portal venous flow to the systemic circulation. TIPS reduces the portosystemic pressure gradient, helping to alleviate bleeding and ascites. The major clinical indications for the procedure are refractory variceal hemorrhage and refractory ascites. Absolute contraindications for TIPS include heart failure, severe tricuspid regurgitation, and severe pulmonary hypertension. Risk-benefit discussions are important, as there can be worsening of hepatic encephalopathy, along with severe complications such as catastrophic bleeding, direct liver injury, or hepatic ischemia.

Partial Hepatectomy

A partial hepatectomy is the surgical resection of part of the liver to remove hepatic neoplasms. Preoperative evaluation requires assessment of anatomic difficulty, severity of liver dysfunction, tumor size, and comorbidities. The surgeon must leave adequate hepatic tissue for regeneration after the surgery. The amount of liver resection that can be tolerated is dependent on preexisting liver disease and dysfunction. Removal of up to 75% of the liver is tolerated in patients with normal liver function, whereas patients with liver dysfunction will require a relatively higher residual liver volume.

Anesthetic considerations include appropriate invasive monitoring with an arterial catheter and management of potentially high blood loss with availability of blood products. Adequate vascular access for delivering blood or vasopressors is required. Surgical techniques often involve clamping of the inferior vena cava or the hepatic artery to control blood loss and can result in tenuous intraoperative hemodynamics. Standard practice for fluid management is to maintain a low CVP by fluid restriction, as allowed, prior to resection to reduce intraoperative blood loss.

Patients often require patient-controlled analgesia for postoperative pain management. Due to the risk of epidural hematoma in patients with liver disease, epidural analgesia use must be carefully considered. Liver resection is known to cause postoperative coagulation disturbances.

Liver Transplantation

Liver transplantation is the definitive treatment for end-stage liver disease and ALF. In 2019, there were 8900 liver transplants performed in the United States, up by nearly 8% from the prior year. The 5-year graft survival rate for liver transplantation is greater than 75%. More than 12,000 people are actively waiting on the liver transplant list. The most common indication for liver transplantation is ALD. This reflects a decline in HCV infection due to novel treatments. Other leading indications are NAFLD and HCC.

Donor organs come from two broad categories: living or deceased donors. With living donors, the health of the organ is well known, and the ischemia time of the organ is minimal, as the

TABLE 16.8 Special Considerations in Liver Transplantation

Surgical Phase	Surgical Considerations	Anesthetic Considerations
Preoperative	Transplantation evaluation (including psychological evaluation, MELD score, UNOS listing)	Preoperative evaluation, vascular access, blood product availability
Dissection	Surgical incision, mobilization of liver and vascular structures, isolation of bile duct	Hemodynamic compromise from loss of ascites, hemorrhage during dissection, decreased venous return
Anhepatic	Clamping of hepatic artery and portal vein, removal of diseased liver, anastomosis of IVC and portal vein of donor liver	Hemodynamic compromise from full or partial IVC clamping, metabolic (lactic) acidosis, hypocalcemia from citrate intoxication, hyperkalemia, hypothermia, hypoglycemia
Reperfusion	Anastomosis of hepatic artery and biliary system, reperfusion of transplanted liver	Hemodynamic instability, dysrhythmias, hyperkalemia, acidosis, pulmonary emboli, cardiac arrest
Posttransplantation	Hemostasis, evaluation of graft function, ultrasound for vascular patency	ICU admission, early or late extubation, hemodynamic management

Marschall K. *Stoelting's Anesthesia & Coexisting Disease*. 7th ed. Elsevier; 2017:357 (table 17.8).
MELD, Model for end-stage liver disease; *UNOS*, united network for organ sharing; *IVC*, inferior vena cava.

donor and recipient surgeries are timed together. Organs from deceased donors are further classified as being procured after brain death or cardiac death. Brain-dead donors are declared legally dead and are kept hemodynamically stable to maintain perfusion of organs. Donors after cardiac death (DCD) are donors that have suffered controlled or uncontrolled cardiac arrest.

Liver allocation requires extensive matching based on blood type, body size, and other medical factors. The matching system then sets the order of transplant candidates based on medical urgency, MELD score plus any exceptions, distance from the donor hospital, blood type compatibility, age of both the donor and recipient, and length of time on the wait list.

Intraoperative care during liver transplantation focuses on providing a safe anesthetic, controlling coagulation with blood management, and maintaining hemodynamics with vasopressors or inotropes as needed. Given the tenuous hemodynamic status during liver transplantation, cardiac monitoring with an arterial catheter, central venous catheter, and potentially a pulmonary artery catheter and/or transesophageal echocardiography will be necessary. The surgical procedure involves an abdominal dissection, removal of the native liver, placement of the liver graft, reperfusion, reconstruction of the biliary duct, and then closure. Table 16.8 describes the stages of liver transplantation.

KEY POINTS

- The overall prevalence of liver disease continues to rise due to increased alcohol-associated liver disease and nonalcoholic fatty liver disease.
- The liver plays a central role in metabolism, hemostasis, detoxification, and immunity. Liver dysfunction can potentially lead to multiorgan failure.
- Blood supply to the liver accounts for 25% of cardiac output and is delivered through the portal vein and hepatic artery. The portal vein provides 75% of blood flow and 50% of oxygen content to the liver. The hepatic artery provides the remaining 25% of blood flow and 50% of oxygen content.
- Assessment of hepatic function is based on careful history that considers risk factors for liver disease, physical examination, and laboratory workup. Biomarkers of hepatobiliary disease include markers of hepatocellular injury, cholestasis, and synthetic function.
- Bilirubin is the end product of heme catabolism. Elevations in indirect bilirubin can be secondary to hemolysis, ineffective erythropoiesis, medications, and portosystemic shunts. Elevations in direct bilirubin can be secondary to cholestasis, hepatocellular injury, sepsis, and Dubin-Johnson syndrome.
- Hepatitis C is the most common viral indication for liver transplantation. The evolution of highly effective direct-acting antiviral HCV therapy has dramatically improved outcomes of patients with hepatitis C. Alcohol-associated liver disease (ALD) is the number one indication for liver transplant in the United States.
- Nonalcoholic fatty liver disease (NAFLD) is the accumulation of fat in the liver in the absence of significant alcohol use. Obesity and metabolic syndrome are major risk factors.
- Acute liver failure (ALF) is severe hepatocyte injury that results in loss of liver function over the course of days or weeks in a patient without preexisting liver disease or stable chronic liver disease. It is associated with hepatic encephalopathy and coagulation abnormalities.
- Cirrhosis is a late stage of chronic liver disease characterized by irreversible scarring of the hepatic parenchyma. Fibrosis of the parenchyma leads to obstruction of portal blood flow and results in portal hypertension and other sequelae.
- Portal hypertension is high pressure within the portal vein that leads to esophageal varices, ascites, and ultimately hepatorenal syndrome. HVPG greater than 5 mm Hg indicates

portal hypertension, while greater than 12 mm Hg predicts variceal rupture.
- Hepatic encephalopathy presents as a spectrum of symptoms reflecting brain function decline as a result of nitrogenous waste due to severe liver disease.
- Hepatorenal syndrome (HRS) is a progressive form of renal failure due to severe liver disease. Splanchnic vasodilation due to portal hypertension leads to renal hypoperfusion and activation of multiple vasoconstrictor systems that continue a negative feedback loop of renal injury.
- Hepatopulmonary syndrome (HPS) is hypoxemia and dyspnea secondary to intrapulmonary vascular dilations in the presence of advanced liver disease. Platypnea, the worsening of dyspnea in the upright position, is a hallmark of HPS.
- The two most commonly used scoring systems to stratify the severity of liver disease are the Child-Turcotte-Pugh (CTP) score and the Model for End Stage Liver Disease (MELD) score.
- Patients with acute hepatitis, acute liver failure, and severe chronic hepatitis are at high risk for perioperative complications. The decision for elective surgery in patients with less severe liver disease should be based on surgical risk assessment that considers the severity of liver disease, medical comorbidities, and urgency of surgery.
- Routine preoperative testing of aminotransferases or alkaline phosphatase in patients with no liver disease is not recommended, given the low incidence of abnormalities that influence management.
- A transjugular intrahepatic portosystemic shunt (TIPS) procedure is used to treat refractory variceal hemorrhage and refractory ascites. A shunt is created between the portal vein and the hepatic vein to reduce the portosystemic pressure gradient.

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Diseases of the Gastrointestinal System

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OUTLINE

The principal function of the gastrointestinal (GI) tract is to provide the body with a supply of water, nutrients, and electrolytes. Each division of the GI tract—esophagus, stomach, small and large intestines—is adapted for specific functions such as passage, storage, digestion, and absorption of food. Impairment of any part of the GI tract may have significant effects on a patient coming for surgery.

PROCEDURES TO EVALUATE AND TREAT DISEASES OF THE GASTROINTESTINAL SYSTEM

Upper Gastrointestinal Endoscopy

Upper GI endoscopy, or esophagogastroduodenoscopy (EGD), can be done for diagnostic and/or therapeutic purposes and is usually performed in the left lateral decubitus position. It involves placement of an endoscope into the esophagus and through the stomach and pylorus and into the duodenum. EGD is a relatively safe procedure with a mortality rate ranging from 0.01 to 0.4 per 1000 persons and an overall complication range of 0.6 to 5.4 per 1000 persons. Most complications are cardiopulmonary in nature. EGD may be performed with or without sedation/anesthesia. If deep sedation/general anesthesia is chosen, the anesthesiologist shares the upper airway with the gastroenterologist, which introduces a unique challenge. In addition, these procedures are frequently performed outside of the main operating room suite, challenging anesthesiologists to provide a high level of patient safety with little or no immediate backup while simultaneously meeting the efficiency demands of the endoscopy center. Currently there is no consensus on which anesthetic medication(s) or technique is best for minimizing complications and maximizing efficiency.

Respiratory complications of EGD include desaturation, airway obstruction, laryngospasm, and aspiration. Studies suggest that the incidence of respiratory complications in nonintubated patients is higher than in intubated patients and that there is no decrement in efficiency because of endotracheal intubation.

Because there is no consensus for the best anesthetic technique for upper GI endoscopy, and because the expectations vary between gastroenterologists and anesthesiologists, the anesthesiologist must have a thorough understanding of both diagnostic and therapeutic EGD procedures and patient comorbidities to formulate an appropriate anesthetic plan. Many patients for diagnostic endoscopy can be managed without the assistance of an anesthesiologist. Typically, an anesthesia team is involved if a patient is not a good candidate for mild to moderate sedation or there are other comorbid conditions that pose challenges to nonanesthesiologists, such as the need for endotracheal intubation. Patients with a difficult airway or at risk of airway obstruction (e.g., patients with sleep apnea) require an endotracheal tube, especially if prone positioning will be used. Patients at risk for aspiration, such as those with a full stomach, gastroparesis, achalasia, and morbid obesity, may also require endotracheal intubation.

Endoscopic procedures that may be technically challenging or unusually stimulating (e.g., bile or pancreatic stent changes, dilations, per oral endoscopic myotomy) usually require general anesthesia to ensure control of noxious stimuli. Patients with complex medical conditions should have their procedures done in an operating room suite or in a hospital setting with ready access to appropriate extra equipment and personnel and to have a higher level of postoperative care.

Colonoscopy

Like EGD, colonoscopy can be done for diagnostic or therapeutic purposes and with or without deep sedation/anesthesia. There is no consensus on the anesthetic technique that best maximizes safety and efficiency.

A major concern prior to colonoscopy is bowel preparation, with its high risk of dehydration and the required period of fasting necessary to provide a safe anesthetic. Most bowel preps are completed the evening prior to the procedure, and a traditional 6- to 8-hour nothing-by-mouth (NPO) period is requested by the anesthesiologist to decrease the risk of pulmonary aspiration of gastric contents. Recent prep protocols may call for some of the bowel prep to be done the day before the colonoscopy and some on the morning of the procedure. This method, known as the split-dose bowel prep, may provide a superior prep and has greater patient tolerance. It has been shown that gastric residual volume is the same after a split-prep with 2 hours of fasting in the morning as when there is an overnight fast with the traditional prep. This suggests that the risk of aspiration may be similar for these two preps. However, a consensus has not yet been reached in this regard.

Other Diagnostic Tools

High-resolution manometry (HRM) should be done if a motility disorder is suspected. HRM uses a catheter that can detect pressures at 1-cm or smaller intervals along the length and circumference of the catheter. Thus it allows pressure readings to be made simultaneously along the entire length of the esophagus, including at the upper and lower esophageal sphincters. The patient is given small aliquots of fluid to swallow after the catheter has been placed through the esophagus and into the proximal stomach. The catheter passes through the gastroesophageal (GE) junction. Measurements are made in a three-dimensional display of time, distance down the esophagus, and pressure at all points along the esophagus. This creates a test result called esophageal pressure topography.

A barium contrast study is a noninvasive study that remains useful, especially for patients who are poor candidates for endoscopy. It can demonstrate esophageal reflux, hiatal hernias, ulcerations, erosions, and strictures.

Reflux testing can be done via ambulatory esophageal pH recordings over a 24- to 48-hour period using a transmitter anchored to the esophageal mucosa or a transnasal wire electrode.

DISEASES OF THE ESOPHAGUS

Symptoms of Esophageal Disease

To evaluate esophageal symptoms, a thorough clinical history can provide some clues and help focus the evaluation. The most common symptoms of esophageal disease are dysphagia, heartburn, and regurgitation. Others include chest pain, odynophagia, and globus sensation.

Dysphagia is a symptom referring to difficulty swallowing. Patients typically describe a sensation of food getting stuck in the chest or throat. Dysphagia can be classified based on its anatomic origin (i.e., oropharyngeal or esophageal). Oropharyngeal dysphagia is commonly seen after head and neck surgery and with certain neurologic conditions such as stroke and Parkinson disease. Esophageal dysphagia is classified based on its physiology (i.e., mechanical or due to dysmotility) (Table 17.1). The clinical history of the dysphagia—better or worse with solids or liquids, episodic or constant, or progressive in character—helps guide the diagnostic workup. Dysphagia only for solid food usually indicates a structural disorder, and dysphagia for both liquids and solids suggests a motility disorder.

Heartburn is a symptom described as burning or discomfort behind the sternum, possibly radiating to the neck. The association between heartburn and gastroesophageal reflux disease (GERD) is so strong that current management of heartburn includes empirical treatment for GERD, realizing that in a few patients the "heartburn" could have a cardiac cause. Regurgitation refers to the effortless return of gastric contents into the pharynx without the nausea or retching that would be experienced with vomiting.

Chest pain caused by esophageal disease is often difficult to distinguish from chest pain due to a cardiac origin. The description of heartburn in addition to the pain may be helpful to clarify that the discomfort is caused by gastroesophageal reflux. Odynophagia is pain with swallowing. This symptom is often described with esophagitis of infectious origin and with esophageal ulcers. Globus sensation is the feeling of "a lump in the

TABLE 17.1 Etiologies of Dysphagia

Mechanical Disorders

Benign Strictures

- Peptic stricture
- Schatzki ring
- Esophageal webs
- Anastomotic stricture
- Eosinophilic esophagitis
- Post fundoplication
- Radiation-induced strictures
- Post endoscopic mucosal resection
- Extrinsic compression from vascular structures
- Extrinsic compression from benign lymph nodes or an enlarged left atrium

Malignant Strictures

- Esophageal adenocarcinoma
- Squamous cell cancer
- Extrinsic compression from malignant lymph nodes

Motility Disorders

- Achalasia
- Hypotensive peristalsis
- Hypertensive peristalsis
- Nutcracker esophagus
- Distal/diffuse esophageal spasm
- Functional obstruction
- Gastrointestinal reflux disease (GERD)
- Other diseases: pseudoachalasic, Chagas disease, scleroderma

throat." Patients with this sensation are often referred for a dysphagia evaluation.

EGD permits direct visualization of esophageal abnormalities as well as collection of biopsy and cytology specimens. It is the best form of evaluation when mechanical causes of dysphagia are suspected. This modality can also detect mucosal lesions and the presence of Barrett esophagus. It allows for dilation of strictures during the examination.

Esophageal Motility Disorders

Esophageal motility disorders frequently present with dysphagia, heartburn, or chest pain. The most common disorders are achalasia, diffuse esophageal spasm, and GERD.

The Chicago Classification

Using HRM, the Chicago Classification of esophageal motility assesses 10 swallows and can classify patients as having (1) normal esophageal motility, (2) abnormal GE junction relaxation, (3) a major motility disorder with normal GE junction relaxation, or (4) borderline peristalsis.

Achalasia

Achalasia is a neuromuscular disorder of the esophagus with an incidence of 1 per 100,000 persons per year. It consists of esophageal outflow obstruction caused by inadequate relaxation of the lower esophageal sphincter (LES) and a dilated hypomotile esophagus. It is theorized that there is loss of ganglion cells in the myenteric plexus in the esophageal wall as a result of either a degenerative neuronal disease or an infection. This is followed by absence of the inhibitory neurotransmitters nitric oxide and vasoactive intestinal polypeptide on the LES. Thus there is unopposed cholinergic stimulation of the LES, and it consequently fails to relax. The end result is hypertension of the LES, reduced peristalsis, and esophageal dilatation with impaired emptying of food into the stomach and thus food stasis in the esophagus.

Symptoms include dysphagia with both liquids and solids (95%), regurgitation (60%), heartburn (40%), and chest pain (40%). In the long term, this disease is associated with an increased risk of esophageal cancer. Pulmonary aspiration is common, with resultant pneumonia, lung abscess, and/or bronchiectasis. The diagnosis of achalasia can be made by esophagram, which reveals the classic "bird's beak" appearance. EGD can exclude other structural issues, but esophageal manometry is the standard for definitive diagnosis. With HRM and the Chicago Classification, achalasia can be classified into three distinct patterns. Type I (classic) involves minimal esophageal pressurization and has a better outcome, with myotomy as the initial treatment rather than dilation or botulinum toxin injection. Type II shows pressurization of the entire esophagus and has the best outcome regardless of the initial treatment. Type III involves esophageal spasm with premature contractions and has the worst outcome.

Treatment. All treatments for achalasia are palliative. They can relieve the obstruction caused by the LES but cannot correct the peristaltic deficiency of the esophagus. Medications, including nitrates and calcium channel blockers, can be used to try to relax the LES. Invasive measures include endoscopic botulinum toxin injection, pneumatic dilation, laparoscopic Heller myotomy, and per oral endoscopic myotomy (POEM). The POEM procedure involves endoscopically dividing the circular muscular layer of the LES but leaving the longitudinal muscular layer intact. Therefore it may offer the efficacy of surgery with the morbidity of an endoscopic procedure. However, the procedure is not without risk. Up to 40% of patients will develop a pneumothorax or pneumoperitoneum, and half of these will require a chest tube or peritoneal drain. Dilation is the most effective nonsurgical treatment, and laparoscopic Heller myotomy remains the best surgical treatment of achalasia. Esophagectomy can be considered in very advanced disease and would eliminate the risk of esophageal cancer as well as mitigate symptoms.

Anesthetic concerns. Patients with achalasia are at high risk of perioperative aspiration and must be treated using full-stomach precautions. The dilated esophagus may retain food for many days after ingestion, so the duration of fasting is misleading in terms of aspiration risk. A large-bore nasogastric tube can be inserted to decompress and empty the esophagus prior to induction, or a large-channel endoscope can be passed to evacuate most of the esophageal contents. Rapid-sequence induction/endotracheal intubation or awake intubation is required in all patients.

Patients presenting for repair via POEM require general anesthesia and mechanical ventilation. Prior to the procedure, patients may fast for up to 48 hours. The procedure is performed in the supine position, and the esophagus is insufflated

with carbon dioxide. During insufflation, patients may have an increase in end-tidal carbon dioxide ($ETCO_2$) that can be managed with controlled mechanical ventilation.

Distal Esophageal Spasm

Distal esophageal spasm (DES) is now the preferred term for describing diffuse esophageal spasm because it is typically the distal portion of the esophagus that is spastic. DES typically occurs in elderly patients and is most likely due to autonomic nervous system dysfunction. An esophagram may show a "corkscrew esophagus" or a "rosary bead esophagus." Pain produced by esophageal spasm may mimic angina pectoris; it frequently responds favorably to treatment with nitroglycerin, which can confuse the clinical picture. The antidepressants trazodone and imipramine can decrease chest pain due to distal esophageal spasm. The phosphodiesterase inhibitor sildenafil can also reduce this pain.

Esophageal Structural Disorders

Esophageal Diverticula

Esophageal diverticula are outpouchings of the wall of the esophagus. The most common locations for these are pharyngoesophageal (Zenker diverticulum), midesophageal, and epiphrenic (supradiaphragmatic diverticulum).

Zenker diverticulum (Fig. 17.1) appears in a natural zone of weakness in the posterior hypopharyngeal wall (Killian triangle) and can cause significant bad breath from retention of food particles consumed up to several days previously. A midesophageal diverticulum may be caused by traction from old adhesions or inflamed lymph nodes or by propulsion associated with esophageal motility abnormalities. An epiphrenic diverticulum may be associated with achalasia. Large symptomatic esophageal diverticula are removed surgically.

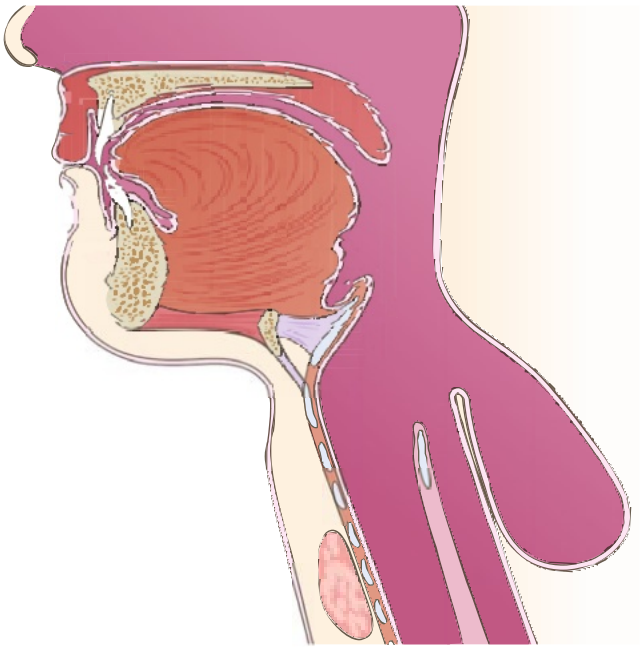

Fig. 17.1 Lateral view of neck showing the location of a Zenker diverticulum in relationship to the cricoid cartilage. Note that it is directly behind the cricoid cartilage. (From Law R, Katzka DA, Baron TH. Zenker's diverticulum. *Clin Gastroenterol Hepatol.* 2014;12:1773–1782, with permission.)

Small or midsize Zenker diverticula are usually asymptomatic. If they become large and filled with food, they can compress the esophagus and cause dysphagia. Regurgitation of food contents and the risk of aspiration of this material from a diverticulum can occur at any time during anesthesia—during induction, during endotracheal intubation, after intubation, or with surgical manipulation—and there can be leakage around the endotracheal tube cuff. Various anesthetic regimens are acceptable during surgical repair of a Zenker diverticulum, with a top priority given to efforts to prevent aspiration. The effectiveness of cricoid pressure in reducing the risk of aspiration during rapid-sequence induction/intubation is doubtful in this situation. A preoperative barium swallow analyzed by an expert in this technique could help determine whether cricoid pressure will be useful or not. If the diverticular sac is immediately behind the cricoid cartilage, cricoid pressure might force the contents of the sac into the pharynx rather than protect the patient from regurgitation. Most often, general anesthesia is induced in the head-up position without cricoid pressure.

Regardless of anesthetic technique, the pouch may be emptied prior to anesthetic induction by the patient exerting external pressure. Insertion of a nasogastric tube should be avoided because it can perforate the diverticulum. For transesophageal echocardiography the probe needs to be inserted very carefully to prevent perforation of the diverticulum.

Hiatal Hernia

A hiatal hernia is a herniation of part of the stomach into the thoracic cavity through the esophageal hiatus in the diaphragm. A sliding hiatal hernia is one in which the GE junction and fundus of the stomach slide upward. This type of hernia is seen in about 30% of patients having upper GI tract radiographic examinations. Many of these patients are asymptomatic (i.e., no symptoms of reflux). This hernia may result from weakening of the anchors of the GE junction to the diaphragm, from longitudinal contraction/shortening of the esophagus, or from increased intraabdominal pressure. A paraesophageal hernia is one in which the GE junction stays in its normal location, and a pouch of stomach is herniated next to the GE junction through the esophageal hiatus. Hiatal hernias are very infrequently repaired. The fact that most patients with hiatal hernias do not have symptoms of reflux esophagitis emphasizes the importance of the integrity of the LES.

Esophageal Tumors

Esophageal cancer occurs in 4 to 5 per 100,000 people in the United States. It usually presents with progressive dysphagia to solid food and weight loss. Esophageal cancer has a poor survival rate because abundant esophageal lymphatics lead to early lymph node metastases. Esophageal cancer can be a squamous cell cancer or an adenocarcinoma. Formerly, most esophageal cancers were of the squamous cell type and situated about midesophagus. Today most esophageal cancers are adenocarcinomas and are located at the lower end of the esophagus. It is postulated that adenocarcinomas are linked to the dramatic increase in GERD, Barrett esophagus, and obesity.

Esophagectomy. Esophagectomy can be a curative or palliative option for malignant esophageal lesions. It can also be considered when benign obstructive conditions are not responsive to conservative management. There are several surgical approaches to esophagectomy, including transthoracic, transhiatal, and minimally invasive. Minimally invasive esophagectomy combines a laparoscopic resection of the GE junction and the proximal stomach with a thoracoscopic resection of the esophagus. Survival rates at 5 years with any of these surgical approaches ranges from 12% to 60%.

Morbidity and mortality. The morbidity and mortality of esophagectomy are quite high. Morbidity rates can be as high as 50% in specialized high-volume centers, and mortality rates approach 5%. Most major postoperative complications are cardiovascular, and these contribute to poor outcomes. Acute lung injury (ALI) and/or acute respiratory distress syndrome (ARDS) has been reported as high as 25% to 38% of esophagectomies; more recent evidence of ALI is less than 10%. However, if ARDS develops, mortality approaches 50%.

The cause of ARDS in the setting of esophagectomy is not completely understood, but it may be that inflammatory mediators, pulmonary cytokines, and gut-related endotoxins trigger the pulmonary dysfunction. Another contributing factor may be the use of prolonged one-lung ventilation. The current practice of protective lung ventilation (limiting the tidal volume during mechanical ventilation to 6 mL/kg plus positive end-expiratory pressure [PEEP]) likely decreases ventilator-associated trauma. A history of smoking, low body mass index, long duration of surgery, cardiopulmonary instability, and the occurrence of a postoperative anastomotic leak also increase the risk of ARDS.

Other common postoperative complications include anastomotic leaks, dumping syndrome, and esophageal stricture.

Anesthetic implications. Patients are often malnourished (protein-calorie malnutrition) before esophagectomy and for many months afterward. Fortunately, over the past decade, regular surveillance of patients with Barrett esophagus has led to the diagnosis of some esophageal cancers in very early stages, so these patients typically arrive for surgery in good nutritional balance. Some patients presenting for esophagectomy have had chemotherapy and/or radiation therapy, so pancytopenia, dehydration, and lung injury can be present.

In the postoperative period, patients may need to return to the operating room for correction of an anastomotic leak. They may have acute lung injury, sepsis, or shock. *There is a very significant risk of aspiration in all patients who have had an esophagectomy, a risk that persists for life.*

Recurrent laryngeal nerve injury has been described in patients after esophagectomy, likely related to the cervical portion of the surgery. A vocal cord palsy can lead to airway compromise during extubation and clearly increases the risk of aspiration. Spontaneous resolution of recurrent laryngeal nerve palsy has been described in about 40% of patients.

Thoracic epidural analgesia for perioperative pain management has been shown to reduce the incidence of pulmonary complications and promote earlier return of bowel function. The latter facilitates expeditious resumption of enteric feeding. The best analgesic drugs for thoracic epidural analgesia are uncertain. Local anesthetics, local anesthetics combined with opioids, and opioids alone can be used. Hemodynamic variables and fluid management will be affected by the choice of the epidural analgesic medication(s).

Gastroesophageal Reflux Disease

GERD is defined as gastroesophageal reflux that causes bothersome symptoms, mucosal injury in the esophagus or at extraesophageal sites, or a combination of both. It is a common problem, with approximately 15% of adults in the United States being affected based on self-reporting of chronic heartburn. The most common symptoms are heartburn and regurgitation. Dysphagia and chest pain are less commonly noted.

Pathophysiology of GERD

Natural antireflux mechanisms consist of the LES, the crural diaphragm, and the anatomic location of the GE junction below the diaphragmatic hiatus. The LES opens with swallowing and closes afterward to prevent gastric acid in the stomach from refluxing into the esophagus. At rest, the LES exerts a pressure high enough to prevent gastric contents from entering the esophagus.

With GE junction incompetence, gastric contents can reenter the esophagus, causing symptoms and/or mucosal damage. Three common mechanisms of incompetence are (1) transient LES relaxation (elicited by gastric distention), (2) LES hypotension (average resting tone, 13 mm Hg in patients with GERD vs. 29 mm Hg in patients without GERD), and (3) anatomic distortion of the GE junction such as with a hiatal hernia. The reflux contents may include hydrochloric acid, pepsin, pancreatic enzymes, and bile. Bile is a cofactor in the development of Barrett metaplasia and adenocarcinoma.

Complications of GERD

Chronic peptic esophagitis is caused by reflux of acidic gastric fluid into the esophagus, producing retrosternal discomfort (i.e., heartburn). Local complications include esophagitis, strictures, ulcers, Barrett metaplasia, and its associated risk of adenocarcinoma. With the laryngopharyngeal reflux variant of GERD, gastric contents reflux into the pharynx, larynx, and tracheobronchial tree, resulting in chronic cough, bronchoconstriction, pharyngitis, laryngitis, bronchitis, or pneumonia. Recurrent pulmonary aspiration can lead to progressive pulmonary fibrosis or chronic asthma. It is notable that up to 50% of patients with asthma have either endoscopic evidence of esophagitis or an increased esophageal acid exposure on 24-hour ambulatory pH monitoring.

Treatment

Therapy for GERD includes lifestyle modification, including avoidance of foods that reduce LES tone (e.g., fatty and fried foods, alcohol, peppermint, chocolate) and avoidance of acidic foods (e.g., citrus and tomato products). Pharmacologic measures aim to inhibit gastric acid secretion, with proton pump inhibitors being more effective than histamine (H_2) receptor antagonists. These drugs do not prevent reflux but increase the

pH of the reflux, which allows esophagitis to heal. Surgical options for severe symptoms include laparoscopic Nissen fundoplication, in which an antireflux barrier is created by wrapping the proximal stomach around the distal esophagus.

Perioperative Management and Anesthetic Considerations

Depending on the planned surgery and anesthetic, medications to treat GERD may be given preoperatively. Cimetidine and ranitidine decrease gastric acid secretion and increase gastric pH. Cimetidine's effect begins in 1 to 1.5 hours and lasts for about 3 hours. Ranitidine is four to six times more potent than cimetidine and has fewer side effects. Famotidine and nizatidine can be given intravenously and are similar in effect to ranitidine but have a longer duration of action. Proton pump inhibitors are generally given orally the night before surgery and again on the morning of surgery.

Sodium citrate is an oral nonparticulate antacid that increases gastric pH. It can be given with a gastrokinetic agent (e.g., metoclopramide) shortly prior to induction of anesthesia. It is generally used in those who are diabetic, morbidly obese, or pregnant.

In terms of anesthetic management, GERD represents an aspiration risk. For pulmonary aspiration to occur, gastric contents must flow to the esophagus (GE reflux), contents must reach the pharynx (esophagopharyngeal reflux), and laryngeal reflexes must be obtunded (as with sedation or general anesthesia). For this aspirated material to cause an aspiration pneumonitis, it is believed there must be a volume of at least 0.4 mL/kg (≈ 30 mL in a 70-kg person) of gastric contents aspirated, and the pH of the gastric contents must be below 2.5.

Other factors that contribute to the likelihood of intraoperative aspiration of gastric contents include urgent or emergent surgery, a full stomach, a difficult airway, inadequate anesthetic depth, use of the lithotomy position, autonomic neuropathy, insulin-dependent diabetes mellitus, gastroparesis, pregnancy, increased intraabdominal pressure, severe illness, and morbid obesity.

Patients with GERD may have certain complications of their GERD that can affect anesthetic management. Mucosal complications (e.g., esophagitis, esophageal stricture) can result in esophageal dilatation and compound the risk for aspiration. Extraesophageal or respiratory complications (e.g., laryngitis, bronchitis, bronchospasm, recurrent pneumonia, progressive pulmonary fibrosis) can also have anesthetic implications.

Rapid-sequence induction with immediate endotracheal intubation is typically used in patients with uncontrolled symptoms of GERD. Cricoid pressure has recently become more controversial as part of a rapid-sequence induction. Cricoid pressure has been utilized to compress the lumen of the pharynx between the cricoid cartilage and the cervical vertebrae. The force applied to the cricoid cartilage should be sufficient to prevent aspiration but not so great as to cause possible airway obstruction or to permit esophageal rupture in the event of vomiting. However, there have been some studies to show that cricoid pressure can worsen the Cormack-Lehane grade during laryngoscopy, prolonging intubation time and increasing one's risk for aspiration.

There are very few randomized trials evaluating cricoid pressure for rapid-sequence induction. A recent prospective randomized multicenter trial of almost 3500 patients did not show an increased aspiration risk with or without cricoid pressure. Succinylcholine increases LES pressure and intragastric pressure, but the barrier pressure (LES pressure minus intragastric pressure) is unchanged.

Endotracheal intubation is essential for protecting the airway in anesthetized patients when aspiration is considered a risk. The endotracheal tube is superior to all other airway devices in reducing the risk of aspiration.

PEPTIC ULCER DISEASE

Burning epigastric pain exacerbated by fasting and improved with meal consumption is the typical symptom complex associated with peptic ulcer disease (i.e., ulcers in the mucosal lining of the stomach or duodenum). The lifetime prevalence of peptic ulcer disease in the United States is about 12% in men and 10% in women. Interestingly, an estimated 15,000 deaths per year occur as a consequence of complicated peptic ulcer disease. Bleeding, peritonitis, dehydration, perforation, and sepsis, especially in elderly debilitated or malnourished patients, are risk factors for death caused by peptic ulcer disease.

Helicobacter pylori

Barry Marshall and Robin Warren received the Nobel Prize for their work in establishing the link between *Helicobacter pylori* and peptic ulcer disease, one of the great advances in medicine in the past 50 years. *H. pylori* infection is virtually always associated with chronic active gastritis, but only 10% to 15% of infected individuals actually develop a peptic ulceration. Ironically the earliest stages of *H. pylori* infection are accompanied by a marked decrease in gastric acid secretion. Then this organism induces increased acid secretion through both direct and indirect actions of the organism and proinflammatory cytokines. These actions affect the function of G, D, and parietal cells in the stomach and reduce duodenal mucosal bicarbonate production.

Complications

Bleeding

Peptic ulcer disease is the most common cause of nonvariceal upper GI bleeding, and hemorrhage is the leading cause of death associated with peptic ulcer disease. The lifetime risk of hemorrhage in patients with a duodenal ulcer who have not had surgery and do not receive maintenance drug therapy is approximately 35%. The current risk of mortality from bleeding is between 10% and 20%. Significant risk factors for rebleeding or in-hospital mortality include a systolic blood pressure below 100 mm Hg; heart rate above 100 beats per minute; the presence of melena, syncope, or altered mentation; concomitant renal, liver, or cardiac disease; and the findings at endoscopy.

Perforation

The lifetime risk of perforation in patients with duodenal ulceration who do not receive treatment is approximately 10%.

Perforation is usually accompanied by sudden and severe epigastric pain caused by spillage of highly acidic gastric secretions into the peritoneum. The mortality of emergency ulcer surgery is correlated with the presence of preoperative shock, significant coexisting medical illnesses, and perforation longer than 48 hours before surgery.

Obstruction

Gastric outlet obstruction can occur acutely or slowly. These patients should be considered to have a full stomach when they come for surgery. Acute obstruction is caused by edema and inflammation in the pyloric channel and the first portion of the duodenum. Pyloric obstruction is suggested by recurrent vomiting, dehydration, and hypochloremic alkalosis resulting from loss of acidic gastric secretions. Treatment consists of nasogastric suction, hydration, and intravenous administration of antisecretory drugs (i.e., proton pump inhibitors). In most instances, acute obstruction resolves within 72 hours with these supportive measures. However, repeated episodes of ulceration and healing can lead to pyloric scarring and a subsequent fixed stenosis and chronic gastric outlet obstruction.

Gastric Ulcer

Benign gastric ulcers are a form of peptic ulcer disease occurring with one-third the frequency of benign duodenal ulcers. There are five types of gastric ulcers (Table 17.2). Use of nonsteroidal antiinflammatory drugs (NSAIDs) is the other common cause of gastroduodenal ulcer disease. If *H. pylori* is also present, the risk of NSAID-induced ulcers is significantly increased.

Stress Gastritis

Major trauma accompanied by shock, sepsis, respiratory failure, burns, hemorrhage, massive transfusion, or head injury is often associated with the development of acute stress gastritis. Acute stress gastritis is particularly prevalent after central nervous system injury, intracranial hypertension, and thermal injury involving more than 35% of body surface area. The major complication of stress gastritis is gastric hemorrhage. The incidence of gastric bleeding is significantly associated with a coagulopathy, thrombocytopenia, an international normalized ratio (INR) higher than 1.5, and an activated partial thromboplastin time (aPTT) greater than twice normal.

TABLE 17.2 Classification of Gastric Ulcers

Type of Gastric Ulcer	Location
Type I	Along the lesser curvature close to incisura; no acid hypersecretion
Type II	Two ulcers, first on gastric body, second duodenal; usually acid hypersecretion
Type III	Prepyloric with acid hypersecretion
Type IV	At lesser curvature near gastroesophageal junction; no acid hypersecretion
Type V	Anywhere in stomach, usually seen with nonsteroidal antiinflammatory drug (NSAID) use

Treatment

Antacids

Antacids are rarely used by clinicians as a primary therapy for gastritis. However, patients often use them for symptomatic relief of dyspepsia. The most commonly used antacids are aluminum hydroxide and magnesium hydroxide, and many over-the-counter brands (e.g., Maalox, Mylanta) contain a combination of both aluminum and magnesium hydroxide to avoid the side effects of constipation or diarrhea. Neither magnesium nor aluminum-containing preparations should be used in patients with chronic renal failure. The former can cause hypermagnesemia, and the latter can cause neurotoxicity. Other potent antacids include calcium carbonate (Tums) and sodium bicarbonate. Long-term use of calcium carbonate can lead to milk-alkali syndrome (hypercalcemia and hyperphosphatemia) with possible development of renal stones and progression to renal insufficiency. Sodium bicarbonate use may induce metabolic alkalosis.

H_2-Receptor Antagonists

Four H_2-receptor antagonists—cimetidine, ranitidine, famotidine, and nizatidine—are currently available, and their structures share homology with histamine. All will significantly inhibit basal and stimulated gastric acid secretion. This class of drugs is effective for the treatment of active ulcer disease (4–6 weeks of treatment) and as adjuvant therapy (with antibiotics) for the management of *H. pylori* infection. Cimetidine was the first H_2-receptor antagonist used for the treatment of acid peptic disorders, with healing rates approaching 80% at 1 month. Ranitidine, famotidine, and nizatidine are all more potent H_2-receptor antagonists than cimetidine. Cimetidine and ranitidine, but not famotidine and nizatidine, bind to hepatic cytochrome P450. Therefore careful monitoring of treatment with drugs such as warfarin, phenytoin, and theophylline that also use cytochrome P450 for metabolism is indicated.

Proton Pump Inhibitors

Omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole are substituted benzimidazole derivatives that covalently bind and irreversibly inhibit hydrogen-potassium–adenosine triphosphatase (H^+,K^+-ATPase). These are the most potent acid-inhibitory drugs available. Proton pump inhibitors inhibit all phases of gastric acid secretion. Onset of action is rapid, with a maximum effect achieved within 2 to 6 hours and a duration of action of up to 72 hours. As with any drug that leads to a significant reduction in gastric hydrochloric acid production, proton pump inhibitors may interfere with absorption of drugs such as ketoconazole, ampicillin, iron, digoxin, and diazepam. Their absorption may be either increased or decreased depending on the characteristics of the particular drug. Hepatic cytochrome P450 may also be inhibited by some proton pump inhibitors (omeprazole, lansoprazole).

Prostaglandin Analogues

Because of their central role in maintaining mucosal integrity and repair, prostaglandin analogues were developed for the treatment of peptic ulcer disease. At present the prostaglandin

E_1 derivative misoprostol is the only drug in this class approved by the US Food and Drug Administration for clinical use in the prevention of gastroduodenal mucosal injury induced by NSAIDs. Prostaglandin analogues enhance mucosal bicarbonate secretion, stimulate mucosal blood flow, and decrease mucosal cell turnover. The most common side effect is diarrhea. Other toxicities include uterine contractions and uterine bleeding; thus misoprostol is contraindicated in women who may be pregnant.

Cytoprotective Agents

Sucralfate is a complex sucrose salt in which the hydroxyl groups have been substituted by aluminum hydroxide and sulfate. It can act by several mechanisms. In the gastric environment, aluminum hydroxide dissociates from the sulfate anion, which can then bind to positively charged tissue proteins found within the ulcer bed. This process provides a physicochemical barrier, impeding further tissue injury by either acid or pepsin. Sucralfate may also induce a trophic effect by binding growth factors (e.g., endothelial growth factor), enhance prostaglandin synthesis, stimulate mucous and bicarbonate secretions, and enhance mucosal defense and repair. Toxicity from sucralfate is rare, and constipation is the most common side effect. Sucralfate should be avoided in patients with chronic renal insufficiency to prevent aluminum-induced neurotoxicity.

Colloidal bismuth subcitrate and bismuth subsalicylate (Pepto-Bismol) are the most widely used bismuth-containing antacids and antiulcer drugs. The mechanism by which these agents induce ulcer healing is unclear. Potential mechanisms include ulcer coating, prevention of further pepsin and hydrochloric acid–induced damage, binding of pepsin, and stimulation of prostaglandins, bicarbonate, and mucous secretion. Long-term use of high dosages, especially of colloidal bismuth subcitrate, could lead to neurotoxicity.

Miscellaneous Drugs

Anticholinergic drugs designed to inhibit activation of the muscarinic receptor in parietal cells have limited success in ulcer healing because of their relatively weak acid-inhibiting effect and significant side effects (dry eyes, dry mouth, urinary retention).

Treatment of *Helicobacter pylori* Infection

The National Institutes of Health, American Digestive Health Foundation, and European Maastricht and Asia Pacific consensus conferences recommend that *H. pylori* be eradicated in patients with peptic ulcer disease. Eradication of this organism is associated with a dramatic decrease in ulcer recurrence. However, no single drug is effective in eradicating *H. pylori*. Combination triple therapy for 14 days provides the greatest efficacy and consists of a proton pump inhibitor (at about double the usual dose) and two antibiotics. The antibiotics used with the greatest frequency are amoxicillin, metronidazole, tetracycline, and clarithromycin, but an increase in antimicrobial resistance can cause changes in antibiotic therapy.

Surgical Treatment

Operative intervention is reserved for the treatment of complicated ulcer disease. The most common complications requiring surgery are hemorrhage, perforation, and obstruction, as well as failure of a recurrent ulcer to respond to medical therapy and/or the inability to exclude malignant disease. The first goal of any surgical treatment should be removal of the source of the ulcer so that ulcer healing can be achieved and the risk of recurrence minimized. The second goal is treatment of coexisting anatomic complications such as pyloric stenosis or perforation. The third major goal should be prevention of undesirable long-term side effects from the surgery.

Three procedures—truncal vagotomy and drainage, truncal vagotomy and antrectomy, and proximal gastric vagotomy—have traditionally been used for surgical treatment of peptic ulcer disease. Surgical treatment now, however, is often directed exclusively at correcting the immediate problem (e.g., closure of a duodenal perforation without gastric denervation). Division of both vagal trunks at the esophageal hiatus (truncal vagotomy) denervates the acid-producing fundal mucosa as well as the remainder of the viscera supplied by the vagus nerve. Because denervation results in impairment of gastric emptying, truncal vagotomy must be combined with a procedure to eliminate pyloric sphincter dysfunction, usually a pyloroplasty.

ZOLLINGER-ELLISON SYNDROME

In 1955, Zollinger and Ellison described two patients with gastroduodenal and intestinal ulceration together with gastrin hypersecretion and a non–L islet cell tumor of the pancreas (gastrinoma). The incidence of Zollinger-Ellison syndrome varies from 0.1% to 1% of individuals with peptic ulcer disease. Men are affected more often than women, and in the majority of cases the disorder is identified in patients between the ages of 30 and 50.

Pathophysiology

Gastrin stimulates acid secretion through gastrin receptors on parietal cells and via histamine release. It also exerts a trophic effect on gastric epithelial cells. Long-standing hypergastrinemia causes markedly increased gastric acid secretion by both parietal cell stimulation and increased parietal cell mass. This increased gastric acid output leads to peptic ulcer disease, erosive esophagitis, and diarrhea.

Abdominal pain and peptic ulceration are seen in up to 90% of patients with Zollinger-Ellison syndrome; diarrhea is seen in 50%, and 10% have diarrhea as their only symptom. Gastroesophageal reflux is seen in about half of patients. Initial presentation and ulcer location in the duodenal bulb may be indistinguishable from that in ordinary peptic ulcer disease. Ulcers in unusual locations (second part of the duodenum and beyond), ulcers refractory to standard medical therapy, and ulcer recurrence after acid-reducing surgery or ulcers presenting with complications (bleeding, obstruction, and perforation) should create suspicion of a gastrinoma. Gastrinomas can develop in the presence of multiple endocrine neoplasia (MEN) type I, a disorder involving primarily three organ sites: the parathyroid

TABLE 17.3 Causes of Increased Fasting Serum Gastrin Level

Hypochlorhydria and achlorhydria (IJ pernicious anemia)	Retained gastric antrum
G-cell hyperplasia	Gastric outlet obstruction
Renal insufficiency	Massive small bowel obstruction
Rheumatoid arthritis	Vitiligo
Pheochromocytomas	Diabetes mellitus
Helicobacter pylori infection	Use of antisecretory drugs

glands, pancreas, and pituitary gland. In view of the stimulatory effect of calcium on gastric secretion, the hyperparathyroidism and hypercalcemia seen in MEN I patients may have a direct effect on ulcer disease. Resolution of hypercalcemia by parathyroidectomy will reduce gastrin and gastric acid output in gastrinoma patients.

Treatment

The first step in the evaluation of a patient with suspected Zollinger-Ellison syndrome is obtaining a fasting gastrin level (Table 17.3). Gastric acid induces feedback inhibition of gastrin release. Such feedback is absent in Zollinger-Ellison syndrome. Unfortunately up to 50% of patients with gastrinomas have metastatic disease at the time of diagnosis.

Patients with duodenal ulcers as part of Zollinger-Ellison syndrome are treated initially with proton pump inhibitors at doses higher than those used to treat GERD and peptic ulcer disease, and then the doses of these drugs are guided by gastric acid measurements. A potentially curative surgical resection of a gastrinoma is indicated in the absence of evidence of MEN I syndrome and the absence of an unresectable liver metastasis or coexisting significant medical disorders that are likely to limit life expectancy.

Management of Anesthesia

Management of anesthesia for gastrinoma excision must consider the presence of gastric hypersecretion as well as the likely presence of a large gastric fluid volume. Esophageal reflux is common in these patients despite the ability of gastrin to increase LES tone. Depletion of intravascular fluid volume and electrolyte imbalances (hypokalemia, metabolic alkalosis) may accompany profuse watery diarrhea. The associated endocrine abnormalities (MEN I syndrome) can also influence the management of anesthesia. Antacid prophylaxis with proton pump inhibitors and H_2-receptor antagonists is maintained up to the time of surgery. A preoperative coagulation screen and liver function tests are recommended since alterations in fat absorption can influence production of clotting factors. Administration of a proton pump inhibitor or ranitidine or octreotide is useful for preventing gastric acid hypersecretion during surgery.

POSTGASTRECTOMY SYNDROMES

A number of syndromes have been described following gastric operations performed for peptic ulcer disease or gastric neoplasm. The overall occurrence of severe postoperative symptoms is low, perhaps 1% to 3% of cases, but the symptoms can be rather disabling. The two most common postgastrectomy syndromes are dumping and alkaline reflux gastritis.

Dumping

Dumping syndrome consists of a series of vasomotor and GI symptoms and signs. There may be two phases to dumping: early and late. Dumping is caused by the entry of hyperosmolar gastric contents into the proximal small bowel, which results in a shift of fluid into the small bowel lumen, plasma volume contraction, and acute intestinal distention. Release of vasoactive GI hormones may also play a role. Early dumping symptoms occur 15 to 30 minutes after a meal and include nausea, epigastric discomfort, diaphoresis, crampy abdominal pain, diarrhea, tachycardia, palpitations, and in extreme cases dizziness or even syncope. The late phase of dumping follows a meal by 1 to 3 hours and can include vasomotor symptoms thought to be secondary to hypoglycemia, which occurs as a result of excessive insulin release. Dietary modifications—consumption of frequent small meals with a few simple sugars and a reduction in the amount of fluid ingested with a meal—can be very helpful.

Octreotide therapy has been reported to improve dumping symptoms in diet-refractory cases. The drug is administered subcutaneously before a meal or by depot injection monthly. Somatostatin analogues have beneficial effects on the vasomotor symptoms of dumping, probably as a result of the pressor effects of the somatostatin analogues on splanchnic blood vessels. In addition, somatostatin analogues inhibit the release of vasoactive peptides from the gut, decrease peak plasma insulin levels, and slow intestinal transit. Acarbose (an _-glucosidase inhibitor that delays the digestion of carbohydrates) is often beneficial in late dumping.

Alkaline Reflux Gastritis

Alkaline reflux gastritis is identified by the occurrence of the clinical triad of (1) postprandial epigastric pain often associated with nausea and vomiting, (2) evidence of reflux of bile into the stomach, and (3) histologic evidence of gastritis. There is no pharmacologic treatment for alkaline reflux gastritis. The only proven treatment is operative diversion of intestinal contents from contact with the gastric mucosa. The most common surgical procedure for this purpose is a Roux-en-Y gastrojejunostomy.

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel diseases are the second most common chronic inflammatory disorders (after rheumatoid arthritis). The diagnosis of ulcerative colitis and Crohn disease, and the differentiation between these disorders, is based on nonspecific clinical and histologic patterns that are often obscured by intercurrent infection, iatrogenic events, medication, or surgery. The incidence of inflammatory bowel disease in the United States is approximately 18 per 100,000 persons.

Ulcerative Colitis

Ulcerative colitis is a mucosal disease involving the rectum and extending proximally to involve part or all of the colon.

Approximately 40% to 50% of patients have disease limited to the rectum and rectosigmoid, 30% to 40% have disease extending beyond the sigmoid but not involving the entire colon, and 20% have a pancolitis. Proximal spread occurs in continuity without areas of spared mucosa. In severe disease the mucosa is hemorrhagic, edematous, and ulcerated. The major symptoms and signs of ulcerative colitis are diarrhea, rectal bleeding, tenesmus, passage of mucus, and crampy abdominal pain. Symptoms in moderate to severe disease may also include anorexia, nausea, vomiting, fever, and weight loss. Active disease can be associated with an increase in levels of acute-phase reactants, platelet count, and erythrocyte sedimentation rate and a decrease in hematocrit. In severely ill patients the serum albumin level is low, and leukocytosis may be present.

Complications

Catastrophic illness is an initial presentation in only 15% of patients with ulcerative colitis. In 1% of patients a severe episode may be accompanied by massive hemorrhage, which usually stops with treatment of the underlying disease. However, if the patient requires 6 to 8 units of blood within 24 to 48 hours, colectomy is frequently performed. Toxic megacolon is defined as a dilated transverse colon with loss of haustrations. It occurs in approximately 5% of episodes and can be triggered by electrolyte abnormalities or narcotics. Toxic megacolon will resolve about half of the time with medical therapy, but urgent colectomy may be required in those who do not experience improvement with conservative treatment. Perforation of the colon is the most dangerous complication of ulcerative colitis, and the physical signs of peritonitis may not be obvious, especially if the patient is receiving glucocorticoids. The mortality rate associated with perforation of the colon is approximately 15%. Some patients can develop toxic colitis and such severe ulcerations that the bowel may perforate without dilating. Obstruction caused by benign stricture formation occurs in 10% of patients.

Crohn Disease

Although Crohn disease usually presents as acute or chronic bowel inflammation, the inflammatory process typically evolves into one of two patterns of disease, a penetrating-fistulous pattern or an obstructing pattern, each with different treatments and prognoses.

The most common site of inflammation is the terminal ileum. Therefore the usual presentation is ileocolitis with a history of recurrent episodes of right lower quadrant pain and diarrhea. A spiking fever suggests intraabdominal abscess formation. Weight loss, often 10% to 20% of body weight, is common and a consequence of fear of eating, anorexia, and diarrhea. An inflammatory mass may be palpated in the right lower quadrant of the abdomen and mimic acute appendicitis. Local extension of the mass can cause obstruction of the right ureter or inflammation of the bladder, manifested as dysuria and fever. Bowel obstruction may take several forms. In the early stages, bowel wall edema and spasm produce intermittent obstruction and increasing postprandial pain. Over the course of years, persistent inflammation gradually progresses to fibrous narrowing and stricture formation. Diarrhea decreases and is replaced by chronic bowel obstruction. Severe inflammation of the ileocecal region may lead to localized wall thinning, with microperforation and formation of fistulas to the adjacent bowel, skin, urinary bladder, or mesentery.

Extensive inflammatory disease is associated with a loss of digestive and absorptive surfaces, which results in malabsorption and steatorrhea. Nutritional deficiencies can also result from poor intake and enteric losses of protein and other nutrients, causing hypoalbuminemia, hypocalcemia, hypomagnesemia, coagulopathy, and hyperoxaluria with nephrolithiasis. Vertebral fractures are caused by a combination of vitamin D deficiency, hypocalcemia, and prolonged glucocorticoid use. Pellagra from niacin deficiency can occur in extensive small bowel disease, and malabsorption of vitamin B_{12} can lead to a megaloblastic anemia and neurologic symptoms.

Diarrhea is a sign of active disease caused by bacterial overgrowth in obstructed areas, fistulization, bile acid malabsorption resulting from a diseased or resected terminal ileum, and intestinal inflammation with decreased water absorption and increased secretion of electrolytes.

Stricture formation can produce symptoms of bowel obstruction. Colonic disease may fistulize into the stomach or duodenum, causing feculent vomitus, or into the proximal or middle small bowel.

Up to one-third of patients with Crohn disease have at least one extraintestinal manifestation of the disease, such as arthritis, a dermatologic condition, uveitis, or renal calculi. Patients with perianal Crohn disease are at an even higher risk of developing extraintestinal manifestations (Table 17.4).

Treatment of Inflammatory Bowel Disease

Surgical Treatment

Crohn disease is a recurring disorder that cannot be cured by surgical resection. However, some of the complications of Crohn disease may require surgery. Patients with extensive colonic disease may require a total proctocolectomy and end ileostomy. The most common surgery is resection of an area of small intestine involved in a fistula or obstruction. Resection of

TABLE 17.4 Extraintestinal Manifestations of Inflammatory Bowel Disease

Dermatologic	Erythema nodosum, pyoderma gangrenosum
Rheumatologic	Peripheral arthritis
Ocular	Conjunctivitis, anterior uveitis/iritis, episcleritis
Hepatobiliary	Hepatomegaly, fatty liver, biliary cirrhosis, cholelithiasis, primary sclerosing cholangitis
Urologic	Renal calculi, ureteral obstruction
Coagulation disorders	Thromboembolic disease (pulmonary embolism, cerebrovascular accidents, arterial emboli) with increased levels of fibrinopeptide A, factor V, factor VIII and fibrinogen, accelerated thromboplastin generation, antithrombin III deficiency, protein S deficiency
Other	Endocarditis, myocarditis, and pleuropericarditis Interstitial lung disease Secondary/reactive amyloidosis

TABLE 17.5 Indications for Surgery in Inflammatory Bowel Disease

Ulcerative Colitis	
Massive hemorrhage, perforation, toxic megacolon, obstruction, intractable and fulminant disease, cancer	
Crohn Disease	
Stricture, obstruction, hemorrhage, abscess, fistulas, intractable and fulminant disease, cancer, unresponsive perianal disease	

half of the small bowel comes close to the upper limit of resection because removal of more than two-thirds of the small intestine results in short bowel syndrome and the need for parenteral nutrition.

Nearly half of patients with extensive chronic ulcerative colitis undergo surgery within the first 10 years of their illness; indications for surgery are listed in Table 17.5. The complication rate is approximately 20% in elective, 30% in urgent, and 40% in emergent proctocolectomy. The complications are primarily hemorrhage, sepsis, and neural injury. In contrast to Crohn disease, a total proctocolectomy can be a curative procedure in ulcerative colitis. Newer versions of this surgery can maintain continence while surgically removing the involved rectal mucosa.

Medical Treatment

5-acetylsalicylic acid (5-ASA) is the mainstay of therapy for mild to moderate inflammatory bowel disease. It was originally developed to deliver both antibacterial (sulfapyridine) and topical antiinflammatory (5-ASA) therapy into the lumen of the small intestine and colon. 5-ASA is effective in inducing remission in both ulcerative colitis and Crohn disease and in maintaining remission in ulcerative colitis. Adverse reactions to 5-ASA are uncommon. Sulfa-free aminosalicylate preparations such as mesalamine can deliver a larger amount of the pharmacologically active ingredient 5-ASA to the site of active bowel disease while limiting systemic toxicity. There are many preparations of mesalamine available. Different tablet coatings can deliver the drug to different areas of the intestines and/or prolong drug effect.

The majority of patients with moderate to severe ulcerative colitis benefit from oral or parenteral glucocorticoids. Prednisone is usually started at dosages of 40 mg/day for active ulcerative colitis that is unresponsive to 5-ASA therapy. Topically applied glucocorticoids are beneficial for distal colitis and may serve as an adjunct in those who have rectal involvement. These glucocorticoids are absorbed from the rectum in significant amounts and can lead to adrenal suppression after prolonged use.

Glucocorticoids are also effective for treatment of moderate to severe Crohn disease. Controlled-ileal-release budesonide is nearly equipotent to prednisone in treating ileocolonic Crohn disease and has fewer glucocorticoid side effects. Steroids play no role in maintenance therapy in either ulcerative colitis or Crohn disease. Once clinical remission has been induced, corticosteroids should be tapered and discontinued.

Antibiotics have no role in the treatment of active or quiescent ulcerative colitis. However, pouchitis, which occurs in approximately one-third of ulcerative colitis patients after colectomy, usually responds to treatment with metronidazole or ciprofloxacin. These two antibiotics should be used as first-line drugs in perianal and fistulous Crohn disease and as second-line therapy in active Crohn disease after 5-ASA drugs become ineffective.

Azathioprine and 6-mercaptopurine are purine analogues commonly used in the management of glucocorticoid-dependent inflammatory bowel syndromes. Azathioprine is readily absorbed and then converted to 6-mercaptopurine, which is then metabolized to an active end product. Efficacy is seen within 3 to 4 weeks. Pancreatitis occurs in 3% to 4% of patients, generally within the first few weeks of therapy, and is completely reversible when these immunomodulatory drugs are discontinued.

Methotrexate inhibits dihydrofolate reductase, which results in impaired DNA synthesis. Additional antiinflammatory properties may be related to a decrease in interleukin-1 (IL1) production.

Cyclosporine alters the immune response by acting as a potent inhibitor of T-cell–mediated responses. Although cyclosporine acts primarily via inhibition of IL2 production by helper T cells, it also decreases recruitment of cytotoxic T cells and blocks other cytokines, interferon-Γ, and tumor necrosis factor. It has a more rapid onset of action than 6-mercaptopurine and azathioprine. Renal function should be monitored frequently. An increase in creatinine requires a dosage reduction or discontinuation of the drug.

Tacrolimus is a macrolide antibiotic with immunomodulatory properties similar to cyclosporine. A particular advantage of its use in inflammatory bowel disease is its excellent absorption in the small bowel even if bile is not present or the mucosa is not intact. Thus it can be taken orally with good effect.

Other biologic therapies are being used with Crohn disease and ulcerative colitis. These include antitumor necrosis factor antibodies such as infliximab. Both diseases respond well to infliximab, but difficulties with this therapy include development of antibodies to infliximab and a significantly increased risk of development of certain forms of leukemia and lymphoma.

Natalizumab is an immunoglobulin antibody against Ⅎ integrin indicated for treatment of Crohn disease refractory to or intolerant of antitumor necrosis factor therapy. It causes remission in about 40% of patients with advanced Crohn disease. Its major adverse effect is the potential for development of progressive multifocal leukoencephalopathy (PML) associated with the Creutzfeldt-Jakob virus. The risk of developing PML with natalizumab therapy is about 1:1000.

CARCINOID TUMORS

Carcinoid tumors originate from the GI tract most of the time. They can occur in almost any GI tissue. Less than a quarter of carcinoid tumors are first found in the lung. These tumors typically secrete GI peptides and/or vasoactive substances (Table 17.6).

TABLE 17.6 Secretory Characteristics of Carcinoid Tumors in Various Sites

	Foregut	Midgut	Hindgut
Serotonin secretion	Low	High	Rare
Other substances secreted	ACTH, 5-HTP, GRF	Tachykinins; rarely 5-HTP, ACTH	Rarely 5-HTP, ACTH; other peptides
Carcinoid syndrome	Atypical	Typical	Rare

ACTH, Corticotropin; *GRF*, growth hormone–releasing factor; *5-HTP*, 5-hydroxytryptophan.

TABLE 17.7 Location and Presentation of Carcinoid Tumors

Carcinoid Location	Presentation
Small intestine	Abdominal pain (51%), intestinal obstruction (31%), tumor (17%), gastrointestinal bleeding (11%)
Rectum	Bleeding (39%), constipation (17%), diarrhea (17%)
Bronchus	Asymptomatic (31%)
Thymus	Anterior mediastinal mass
Ovary and testicle	Mass discovered on physical examination or ultrasonography
Metastases	In the liver; frequently presents as hepatomegaly

Carcinoid Tumors Without Carcinoid Syndrome

Carcinoid tumors (Table 17.7) are often found incidentally during surgery for suspected appendicitis. Symptoms are often vague, so the diagnosis is often delayed.

Carcinoid Tumors With Systemic Symptoms Due to Secreted Products

Carcinoid tumors can contain GI peptides such as gastrin, insulin, somatostatin, motilin, neurotensin, tachykinins (substance K, substance P, neuropeptide K), glucagon, gastrin-releasing peptide, vasoactive intestinal peptide, pancreatic peptide, other biologically active peptides (corticotropin, calcitonin, growth hormone), prostaglandins, and bioactive amines (serotonin). These substances may or may not be released by the tumor in sufficient amounts to cause symptoms. Midgut carcinoids are more likely to produce various peptides than foregut carcinoids. Only 25% of carcinoids are capable of producing mediators, carcinoids that do not often present as a mass and/or bowel obstruction.

Carcinoid Syndrome

Carcinoid syndrome occurs in approximately 10% of patients with carcinoid tumors and is a result of the large amounts of serotonin and vasoactive substances reaching the systemic circulation. The two most common signs are flushing and diarrhea (with the associated dehydration and electrolyte abnormalities). The characteristic flush is of sudden onset. Physically it appears as a deep red blush, especially in the neck and face, often associated with a feeling of warmth and occasionally associated with pruritus, tearing, diarrhea, or facial edema. Hypotension and hypertension can occur, as well as bronchoconstriction. Flushes may be precipitated by stress, alcohol, exercise, certain foods, and drugs such as catecholamines, pentagastrin, and serotonin reuptake inhibitors. Carcinoid tumors may have cardiac manifestations resulting from endocardial fibrosis, primarily on the chambers of the right side of the heart and on the tricuspid and pulmonic valves. Usually the left side of the heart is protected from this disease because of the ability of the lung to clear the vasoactive substances secreted by the carcinoid tumor. But left-sided lesions can occur if there is pulmonary involvement or via a right-to-left intracardiac shunt. Other clinical manifestations include wheezing and pellagra-like skin lesions. Retroperitoneal fibrosis can cause ureteral obstruction.

Most patients with carcinoid syndrome overproduce serotonin, which is responsible for the diarrhea through its effects on gut motility and intestinal secretion. Serotonin receptor antagonists relieve the diarrhea in most patients. Serotonin does not, however, appear to be involved in the flushing. In patients with gastric carcinoid tumors the red, patchy, pruritic flush is likely due to histamine release and can be prevented by H_1- and H_2-receptor blockers. Both histamine and serotonin may be responsible for bronchoconstriction.

A potentially life-threatening complication of carcinoid syndrome is development of a carcinoid crisis. Clinically this manifests as intense flushing, diarrhea, abdominal pain, and cardiovascular signs, including tachycardia, hypertension, or hypotension. If not adequately treated, it can be fatal. The crisis may occur spontaneously or be provoked by stress, chemotherapy, or biopsy. Anesthetic drugs that can precipitate a carcinoid crisis are noted in Table 17.8.

The diagnosis of carcinoid syndrome relies on measurement of urinary or plasma serotonin concentrations or measurement of serotonin metabolites in the urine. The measurement of 5-hydroxyindolecacetic acid (5-HIAA) is performed most frequently. False-positive test results may occur if the patient is eating serotonin-rich foods.

Treatment

Therapy for carcinoid tumors includes avoiding conditions that precipitate flushing, treating heart failure and/or wheezing, providing dietary supplementation with nicotinamide, and controlling diarrhea. If the patient continues to have symptoms, serotonin receptor antagonists or somatostatin analogues are useful. Many of these drugs have very short half-lives and must

TABLE 17.8 Drugs Associated With Carcinoid Crisis

Drugs That May Provoke Mediator Release

Succinylcholine, mivacurium, atracurium, tubocurarine

Epinephrine, norepinephrine, dopamine, isoproterenol, thiopental

Drugs Not Known to Release Mediators

Propofol, etomidate, vecuronium, cisatracurium, rocuronium, sufentanil, alfentanil, fentanyl, remifentanil

All inhalation agents; desflurane may be the better choice in patients with liver metastasis because of its low rate of metabolism.

be given as continuous infusions. The 5-hydroxytryptophan (5-HT_1 and 5-HT_2) receptor antagonists can control the diarrhea but usually do not decrease flushing. The 5-HT_3 receptor antagonists (e.g., ondansetron, tropisetron, alosetron) can control diarrhea and nausea in the majority of patients and even occasionally ameliorate the flushing. A combination of H_1- and H_2-receptor antagonists may be useful in controlling flushing.

Most neuroendocrine tumors have somatostatin receptors on their cells, so somatostatin can bind to these receptors and prevent symptoms, including flushing. Synthetic analogues of somatostatin such as octreotide control symptoms in more than 80% of patients with a carcinoid tumor. Lanreotide is the most widely used drug in this class. It is given in a depot form by subcutaneous injection every 4 weeks. Somatostatin analogues are effective in both relieving symptoms and decreasing urinary 5-HIAA levels. They can also prevent development of a carcinoid crisis during known precipitating events such as surgery, anesthesia, chemotherapy, and stress. Octreotide should be administered 24 to 48 hours before surgery and then continued throughout the procedure.

The bronchoconstriction of carcinoid tumors is typically resistant to treatment, and β agonists may exacerbate the problem owing to mediator release. Octreotide and histamine blockers combined with ipratropium have been used with good results.

Transarterial chemoembolization (TACE) with or without chemotherapy can reduce tumor size in most patients, but surgery is the only potentially curative therapy for nonmetastatic carcinoid tumors.

Management of Anesthesia

General anesthesia is required for carcinoid tumor resection surgery. No single anesthetic medication has been associated with worse outcomes during this kind of surgery, but it is suggested to avoid histamine-releasing medications. Invasive arterial blood pressure monitoring is necessary for intraoperative management because of the potential for rapid changes in hemodynamic variables. Administration of octreotide preoperatively and before manipulation of the tumor will attenuate most adverse hemodynamic responses. Ondansetron, a serotonin antagonist, is a good antiemetic for these patients. Delayed awakening in this patient population has been described, and patients may need to be admitted to the intensive care unit for postoperative monitoring. Symptoms may persist postoperatively if the surgery was palliative, there is known metastatic disease, or there are undiagnosed metastases.

Use of epidural analgesia in patients who have been adequately treated with octreotide is a safe technique, provided the local anesthetic is administered in a gradual manner accompanied by careful hemodynamic monitoring.

ACUTE PANCREATITIS

Acute pancreatitis is an acute inflammatory disorder of the pancreas. The incidence has increased 10-fold since the 1960s, which could reflect increased alcohol use and/or improved diagnostic techniques.

Pathogenesis

The pancreas contains numerous digestive enzymes (proteases). Autodigestion of the pancreas is normally prevented by packaging of the proteases in precursor form, synthesis of protease inhibitors, and the low intrapancreatic concentration of calcium, which decreases trypsin activity. Loss of any of these protective mechanisms leads to enzyme activation, autodigestion, and acute pancreatitis.

Gallstones and alcohol abuse are the most common causative factors in 60% to 80% of patients with acute pancreatitis. Gallstones are believed to cause pancreatitis by transiently obstructing the ampulla of Vater, which causes pancreatic ductal hypertension. Acute pancreatitis is also common in patients with acquired immunodeficiency syndrome and those with hyperparathyroidism and its associated hypercalcemia. Trauma-induced acute pancreatitis is generally associated with blunt trauma rather than penetrating injury. Blunt trauma may compress the pancreas against the spine. Postoperative pancreatitis can occur after abdominal and other noncardiac surgery and after cardiac surgery, especially procedures that require cardiopulmonary bypass. Clinical pancreatitis develops in 1% to 2% of patients following endoscopic retrograde cholangiopancreatography (ERCP).

Excruciating, unrelenting midepigastric pain that radiates to the back occurs in almost every patient with acute pancreatitis. Sitting and leaning forward may decrease the pain. Nausea and vomiting can occur at the peak of the pain. Abdominal distention with ileus often develops. Dyspnea may reflect the presence of pleural effusions or ascites. Low-grade fever, tachycardia, and hypotension are fairly common. Shock may occur as a result of (1) hypovolemia from exudation of blood and plasma into the retroperitoneal space, (2) release of kinins that cause vasodilation and increase capillary permeability, and (3) systemic effects of pancreatic enzymes released into the general circulation.

Obtundation and psychosis may reflect alcohol withdrawal. Tetany may occur as a result of hypocalcemia since, in this situation, calcium binds to free fatty acids and forms soaps.

The hallmark of acute pancreatitis is an increase in serum amylase and lipase concentration. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) are the best noninvasive tests for documenting the morphologic changes or local complications associated with acute pancreatitis. ERCP can be useful for evaluating and treating certain forms of pancreatitis such as traumatic pancreatitis (localization of injury) and severe gallstone pancreatitis (papillotomy, stone removal, and drainage).

The differential diagnosis of acute pancreatitis includes a perforated duodenal ulcer, acute cholecystitis, mesenteric ischemia, and bowel obstruction. Acute myocardial infarction may cause severe abdominal pain, but the serum amylase concentration is not increased. Patients with pneumonia may also have significant epigastric pain and fever.

Multiple scoring systems have been devised to help identify illness severity. The Ranson criteria/scoring system is one of the older systems utilized to assess severity of illness. This has been generally replaced with either the BISAP, Glasgow,

or even now the SOFA score. Despite different systems, the cumbersome nature and the general requirement of needing to wait for investigational data to return have limited its widespread utilization.

For example, the criteria in the modified Glasgow scale can be remembered by the acronym PANCREAS (Po_2 ≤ 60 mm Hg, age ≥ 55, neutrophil [white blood cell] count ≥ 15,000, calcium ≤ 8 mg/dL, renal [urea] ≥ 45 mg/dL, enzymes [AST ≥ 200, lactate dehydrogenase (LDH) > 600], albumin < 3.2 mg/dL, sugar < 200 mg/dL). A score of 3 or more within 48 hours is indicative of severe disease.

Complications

About 25% of patients who develop acute pancreatitis experience significant complications. Shock can develop early in the course and is a major risk factor for death. Sequestration of large volumes of fluid in the peripancreatic space, hemorrhage, and systemic vasodilation contribute to hypotension. Arterial hypoxemia is often present early in the course of the disease. ARDS is seen in 20% of patients. Renal failure occurs in 25% of patients and is associated with a poor prognosis. GI hemorrhage and coagulation defects from disseminated intravascular coagulation may occur. Infection of necrotic pancreatic material or abscess formation is a serious complication associated with a mortality rate higher than 50%.

Treatment

Aggressive intravenous fluid administration is necessary to treat the significant hypovolemia that occurs in all patients, even those with mild pancreatitis. Traditionally, oral intake is stopped to "rest" the pancreas and prevent aggravation of the accompanying ileus. There is increasing data to suggest that early oral feeding in patients with mild disease decreases hospital stay and decreased infectious complications. In more severe disease, enteral feeding (orogastric, postpyloric, or surgically placed feeding tube) may also be helpful, especially in patients who are intubated and mechanically ventilated. Recently a systematic review found that feeding the stomach was safe and well tolerated in patients with severe disease. There is some evidence of slightly increased aspiration in patients fed gastrically, which is minimized with aspiration precautions. Current guidelines recommend against the use of parenteral feeding. Total parenteral nutrition (TPN) has been associated with increased infectious complications. TPN is indicated, however, in patients who do not tolerate enteral feeding. Nasogastric suction may be needed to treat persistent vomiting or ileus. Opioids are administered to manage the severe pain. Endoscopic removal of obstructing gallstones is indicated early after the onset of symptoms to decrease the risk of cholangitis. Drainage of intraabdominal collections of fluids or necrotic material can now be accomplished without surgery.

ERCP is a fluoroscopic examination of the biliary or pancreatic ducts by endoscopically guided injection of contrast through the duodenal papilla. Interventions via ERCP include drainage through tubes of various sizes that can be changed (upsized) if needed. Other interventions include stent placement, sphincterotomy, stone extraction, and hemostasis.

Chronic Pancreatitis

The incidence of chronic pancreatitis is difficult to determine since the disease may be asymptomatic or abdominal pain may be attributed to other causes. The persistent inflammation characteristic of chronic pancreatitis leads to irreversible damage to the pancreas. There is loss of both exocrine and endocrine function.

Chronic pancreatitis is most often due to chronic alcohol abuse. Alcohol may have a direct toxic effect on the pancreas. Diets high in protein seem to predispose alcoholic patients to the development of chronic pancreatitis. Up to 25% of adults in the United States with chronic pancreatitis are diagnosed with idiopathic chronic pancreatitis; it has been suggested that a significant number of these cases could be related to genetic defects. Chronic pancreatitis also occurs in association with cystic fibrosis and hyperparathyroidism.

Chronic pancreatitis is often characterized as epigastric pain that radiates to the back and is frequently postprandial. However, up to one-third of patients have painless chronic pancreatitis. Steatorrhea is present when at least 90% of pancreatic exocrine function is lost. Diabetes mellitus is the end result of loss of endocrine function. Pancreatic calcifications develop in most patients with alcohol-induced chronic pancreatitis.

The diagnosis of chronic pancreatitis may be based on a history of chronic alcohol abuse and demonstration of pancreatic calcifications. Patients who have chronic pancreatitis are often thin or even emaciated. This is due to maldigestion of proteins and fats because the amount of pancreatic enzymes entering the duodenum is reduced to less than 20% of normal. Serum amylase concentrations are usually normal. Ultrasonography is useful for documenting the presence of an enlarged pancreas or identifying a pseudocyst. CT in patients with chronic pancreatitis demonstrates dilated pancreatic ducts and changes in the size of the pancreas. ERCP is the most sensitive imaging test for detecting early changes in the pancreatic ducts caused by chronic pancreatitis.

Treatment of chronic pancreatitis includes management of pain, malabsorption, and diabetes mellitus. Opioids are often required for adequate pain control, and in some patients celiac plexus blockade may be considered. An internal surgical drainage procedure (pancreaticojejunostomy) or endoscopic placement of stents and/or extraction of stones may be helpful in patients whose pain is resistant to medical management. Enzyme supplements are administered to facilitate fat and protein absorption. Insulin is administered as needed.

GASTROINTESTINAL BLEEDING

GI bleeding (Table 17.9) most often originates in the upper GI tract (from peptic ulcer disease). Bleeding in the lower GI tract from diverticulosis or tumor accounts for about 10% to 20% of cases of GI bleeding and commonly affects older patients.

Upper Gastrointestinal Tract Bleeding

Patients with acute upper GI tract bleeding may experience hypotension and tachycardia if blood loss exceeds 25% of total blood volume. Patients with orthostatic hypotension usually have

TABLE 17.9 Common Causes of Upper and Lower Gastrointestinal Tract Bleeding

Upper Gastrointestinal Tract Bleeding
Peptic Ulcer Disease
Varices
Mallory-Weiss tear
Erosive/hemorrhagic gastropathy
Tumor
Esophageal ulcer
Portal hypertensive gastropathy
Dieulafoy lesion
Cameron lesion
Post-sphincterotomy bleeding
Anastomatic ulcer
Hemobilia
Undifferentiated
Lower Gastrointestinal Tract Bleeding
Diverticulosis
Angiodysplasia
Hemorrhoids
NSAID-induced LGIB
Ischemic colitis
Inflammatory bowel disease
Postpolypectomy bleeding
Infectious colitis
Radiation colitis
Neoplasms
Stercoral ulcers
Undifferentiated

Adapted from Kim JJ, Sheibani S, Park S, et al. Causes of bleeding and outcomes in patients hospitalized with upper gastrointestinal bleeding. *J Clin Gastroenterol.* 2014;48(2):113–118; Bounds BC, Friedman LS. Lower gastrointestinal bleeding. *Gastroenterol Clin N Am.* 2003;32:1107–1125.

a hematocrit below 30%. The hematocrit may be normal early in the course of acute hemorrhage because there has been insufficient time for equilibration of plasma volume. After fluid resuscitation, anemia becomes more overt. Melena indicates that bleeding has occurred at a site above the cecum. Blood urea nitrogen levels are typically above 40 mg/dL because of absorbed nitrogen from the blood in the small intestine. Elderly individuals, those with esophageal variceal bleeding, those with malignancy, and those who develop bleeding during hospitalization for other medical conditions have a mortality rate exceeding 30%. Multiple organ system failure rather than hemorrhage is the usual cause of death in such patients. Upper endoscopy after hemodynamic stabilization is the diagnostic/therapeutic procedure of choice in patients with acute upper GI bleeding.

For patients with bleeding peptic ulcers, endoscopic coagulation (thermotherapy or injection with epinephrine or a sclerosing material) is indicated when active bleeding is visible. Even patients receiving anticoagulants can be safely treated with endoscopic coagulation of a peptic ulcer. Perforation occurs in approximately 0.5% of patients undergoing endoscopic coagulation. With bleeding esophageal varices, endoscopic ligation of the bleeding varices is as effective as sclerotherapy. A transjugular intrahepatic portosystemic shunt (TIPS) may be used in patients with esophageal variceal bleeding resistant to control by endoscopic coagulation or sclerotherapy. However, insertion of such a shunt can lead to worsening encephalopathy. Mechanical balloon tamponade of bleeding varices can be accomplished with a Sengstaken-Blakemore tube. However, such a device is rarely used now that endoscopic therapy for bleeding varices is so successful. Surgical treatment of nonvariceal upper GI tract bleeding may be undertaken to oversew an ulcer or perform gastrectomy for diffuse hemorrhagic gastritis in patients who continue to bleed despite optimal supportive therapy and in whom endoscopic coagulation is unsuccessful.

EGD is overall quite safe for evaluation of upper GI bleeding. However, cardiopulmonary complications remain a concern because of the potential for aspiration of blood and/or gastric contents and the presence of other medical conditions. Endotracheal intubation is the preferred method for airway protection for upper GI bleeding severe enough to require endoscopy.

Lower Gastrointestinal Tract Bleeding

Lower GI tract (colonic) bleeding usually occurs in older patients and typically presents as abrupt passage of bright red blood and clots via the rectum. Causes include diverticulosis, tumors, ischemic colitis, and certain forms of infectious colitis. Sigmoidoscopy to exclude anorectal lesions is indicated as soon as a patient is hemodynamically stable. Colonoscopy can be performed after the bowel has been cleansed. If bleeding is persistent and brisk, angiography and embolic therapy may be attempted. Up to 15% of patients with lower GI tract bleeding require surgical intervention to control it.

ADYNAMIC ILEUS

Adynamic ileus, formerly known as acute colonic pseudoobstruction, is a form of colonic ileus characterized by massive dilatation of the colon in the absence of a mechanical obstruction. The disorder is characterized by loss of effective colonic peristalsis and subsequent distention of the colon. This syndrome generally develops in seriously ill patients hospitalized for major medical problems. These patients have electrolyte disorders, are immobile, or have received narcotic or anticholinergic medications. The disorder can also be observed in surgical patients after a variety of non-GI operations. If left untreated, the colonic dilatation could result in ischemia of the right colon and cecum and, if the ileocecal valve is competent, in perforation. One hypothesis as to the etiology of colonic pseudoobstruction invokes an imbalance in neural input to the colon distal to the splenic flexure. It suggests an excess of sympathetic stimulation and a paucity of parasympathetic input. This can result in spastic contraction of the distal colon and functional obstruction. Plain radiographs of the abdomen reveal dilatation of the proximal colon and a decompressed distal colon, with some air in the rectosigmoid region. Patients in whom the cecal diameter is less than 12 cm (risk of perforation is much greater if cecal diameter exceeds 12 cm) can undergo an initial trial of conservative therapy. This would include correction of

electrolyte abnormalities, avoidance of narcotic and anticholinergic drugs, hydration, mobilization, tap water enemas, and nasogastric suction. The majority of patients who will have resolution of this problem with conservative therapy will have this happen within 2 days. This suggests that a 48-hour trial of conservative management is warranted in patients in stable condition. Patients for whom conservative therapy fails should be considered for an active intervention. This could include repetitive colonoscopy or administration of neostigmine. Intravenous neostigmine at a dose of 2 to 2.5 mg given over 3 to 5 minutes results in immediate colonic decompression in 80% to 90% of patients, presumably by improving parasympathetic tone in the bowel. Because symptomatic bradycardia is an expected side effect of neostigmine administration, all patients undergoing this treatment require cardiac monitoring. Placement of a cecostomy is another active intervention that may be needed.

KEY POINTS

- Natural antireflux mechanisms consist of the lower esophageal sphincter, the crural diaphragm, and the anatomic location of the gastroesophageal junction below the diaphragmatic hiatus.
- Factors that contribute to the likelihood of aspiration during anesthesia and surgery include the urgency of surgery, the presence of a difficult airway, inadequate anesthetic depth, lithotomy position, increased intraabdominal pressure, insulin-dependent diabetes mellitus, autonomic neuropathy, pregnancy, severe illness, and obesity.
- Patients with silent aspiration may present with symptoms and signs of bronchial asthma.
- All patients who have undergone esophagectomy have a lifelong very high risk of aspiration.
- Major trauma accompanied by shock, sepsis, respiratory failure, hemorrhage, massive transfusion, burns, head injury, or multiorgan injury is often associated with development of acute stress gastritis.
- Following gastric surgery for peptic ulcer disease or gastric neoplasm, patients may develop dumping syndrome or alkaline reflux gastritis.
- Inflammatory bowel diseases are the second most common chronic inflammatory diseases (after rheumatoid arthritis). Ulcerative colitis and Crohn disease are associated with abdominal pain, fluid and electrolyte disturbances, bleeding, bowel perforation, peritonitis, fistula formation, GI tract obstruction, cancer, and numerous extraintestinal manifestations of the diseases.
- Carcinoid tumors may be associated with carcinoid syndrome due to release of large amounts of serotonin and other vasoactive substances into the systemic circulation, causing flushing, diarrhea, tachycardia, hypertension, or hypotension.
- Gallstones and alcohol abuse cause the majority of cases of acute pancreatitis. Chronic pancreatitis is usually caused by chronic alcohol abuse, but up to 25% of cases are labeled as idiopathic in origin.
- Gastrointestinal bleeding most often originates in the upper GI tract and is often due to peptic ulcer disease. About 20% of GI bleeding originates in the lower GI tract and can be due to diverticulosis, tumors, ischemic colitis, or certain forms of infectious colitis.

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18

Inborn Errors of Metabolism

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OUTLINE

Inborn errors of metabolism manifest as a variety of metabolic defects that may complicate the management of anesthesia (Table 18.1). In some instances, these defects are clinically asymptomatic and become manifest only in response to specific triggering events, such as ingestion of certain foods or administration of certain drugs, including some anesthetic drugs.

PORPHYRIA

Porphyria is a group of metabolic disorders, each of which results from a specific enzyme deficiency in the heme synthetic pathway that leads to the accumulation of the preceding form of porphyrin. Physiologically, heme is the most important porphyrin and is bound to proteins to form hemoproteins such as hemoglobin and cytochrome P450 isoenzymes. Production of heme is regulated by the activity of aminolevulinic acid (ALA) synthase present in mitochondria. ALA synthase formation is controlled by endogenous concentrations of heme in a feedback loop that ensures the level of heme production parallels heme requirement. ALA synthase is readily inducible, and therefore its supply can respond rapidly to increase in heme requirements. However, in porphyria, any increase in heme requirements results in accumulation of pathway intermediates (Fig. 18.1).

TABLE 18.1 Selected Inborn Errors of Metabolism

Porphyria
Purine metabolism disorders
Carbohydrate metabolism disorders
Hemochromatosis
Wilson disease

Classification

Porphyria is classified as either hepatic or erythropoietic depending on the primary site of overproduction or accumulation of the precursor porphyrin (Table 18.2). However, for anesthesiologists, the more functional classification of acute versus nonacute porphyria may be more important since only acute forms of porphyria are relevant to the management of anesthesia (Table 18.3). They are the only forms of porphyria that can result in life-threatening reactions in response to drugs often used in the perioperative period.

Acute Porphyria

Acute porphyria is a group of inherited autosomal dominant disorders with variable expression. The enzyme defects in these forms of porphyria are deficiencies rather than absolute deficits of heme pathway enzymes. Although there is no direct influence of gender on the pattern of inheritance, attacks occur more frequently in women and are most frequent during the third and fourth decades of life. Furthermore, attacks are rare before puberty or following the onset of menopause. In the presence of deficient enzymes in the heme synthesis pathway, any event that induces ALA synthase activity will precipitate porphyrinogen buildup that eventually leads to porphyria attacks. Drugs, fasting (e.g., before elective surgery), dehydration, stress (e.g., associated with anesthesia and surgery), infection, and hormonal fluctuations such as those during menstruation can all trigger acute attacks. Pregnancy in patients with acute porphyria is often associated with spontaneous abortion, systemic hypertension, and an increased incidence of low-birthweight infants.

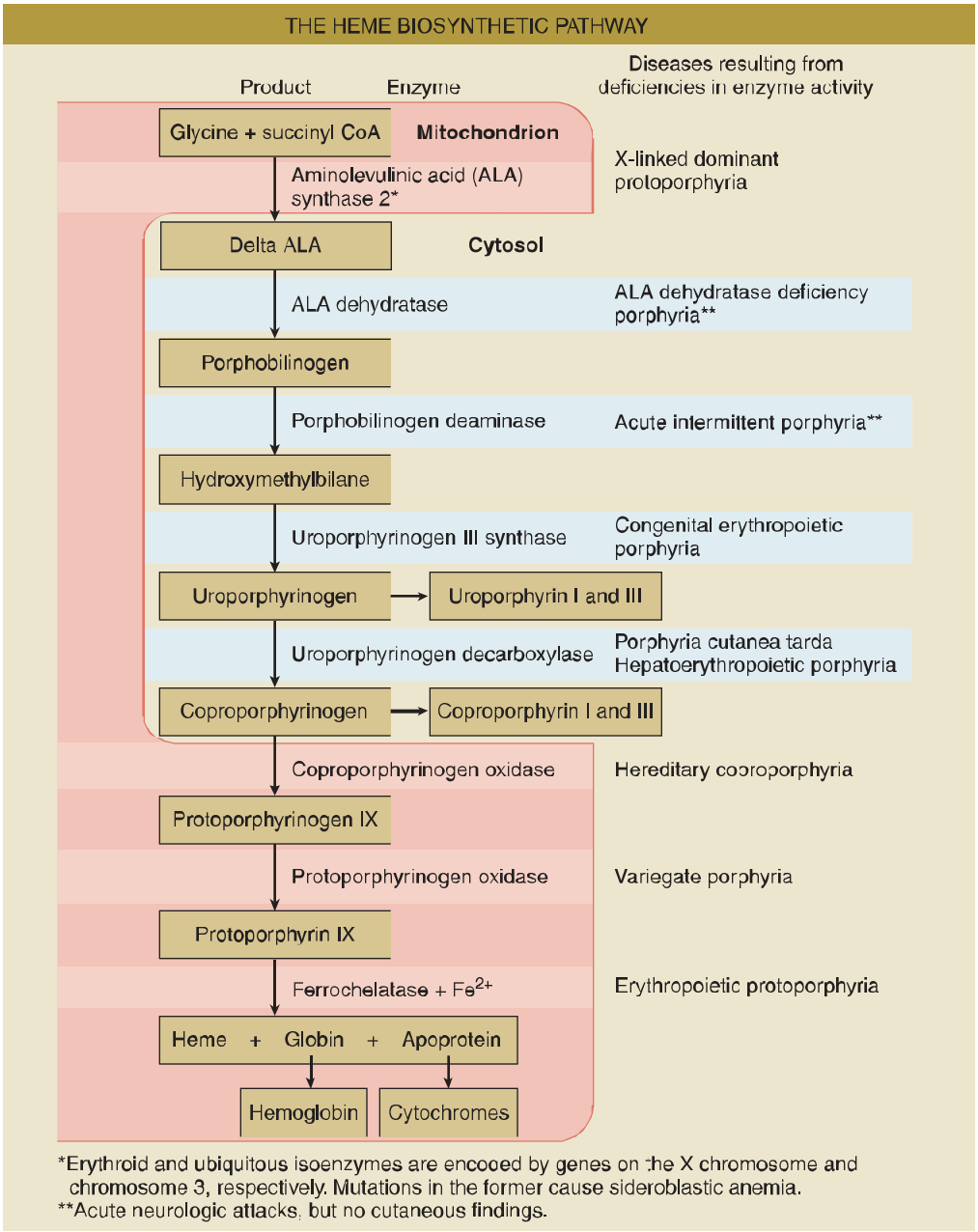

Fig. 18.1 The heme biosynthetic pathway. Type of porphyria is determined by the specific enzyme deficiency related to heme development. Symptoms and toxicities occur as a result of accumulation of intermediates produced in the pathway. The anesthesiologist should be aware of acute types of porphyria as they can have life-threatening reactions with common perioperative drugs.

TABLE 18.2 Traditional Classification of Porphyrias

Hepatic
Acute intermittent porphyria
Variegate porphyria
Hereditary coproporphyria
Aminolevulinic acid dehydratase porphyria
Porphyria cutanea tarda

Erythropoietic
Congenital erythropoietic protoporphyria
Erythropoietic protoporphyria
X-linked protoporphyria

TABLE 18.3 Acute and Nonacute Porphyrias

Acute Porphyrias
Acute intermittent porphyria
Variegate porphyria
Hereditary coproporphyria
Aminolevulinic acid dehydratase porphyria

Nonacute Porphyrias
Porphyria cutanea tarda
Congenital erythropoietic protoporphyria
Erythropoietic protoporphyria
X-linked protoporphyria

Acute Intermittent Porphyria

Of all the acute porphyria, acute intermittent porphyria is the most common subtype and the one most likely to be life threatening. Acute intermittent porphyria mainly affects the gastrointestinal and nervous systems. The defective enzyme is porphobilinogen deaminase, and the gene encoding this enzyme is located on chromosome 11. Since the enzyme deficiency occurs early in the heme synthetic pathway, an excess of these heme precursors does not cause skin disease.

Variegate Porphyria

Variegate porphyria is characterized by neurotoxicity and cutaneous photosensitivity. Skin lesions are usually bullous eruptions and occur on exposure to sunlight. This photosensitivity can be attributed to increases in light-absorbing porphyrin intermediates and their metabolites. The enzyme defect is late in the heme synthetic pathway at the level of protoporphyrinogen oxidase. The gene encoding this enzyme is on chromosome 1.

Hereditary Coproporphyria

Hereditary coproporphyria is a rare form of acute porphyria. Patients with coproporphyria typically experience neurotoxicity and cutaneous hypersensitivity, although these signs tend to be less severe than is seen in variegate porphyria. The defective enzyme is coproporphyrinogen oxidase, encoded on chromosome 9.

ALA Dehydratase Porphyria

ALA dehydratase (ALAD) porphyria is a rare autosomal recessive disorder. The gene encoding ALAD is on chromosome 9.

Nonacute Porphyrias

Porphyria Cutanea Tarda

Porphyria cutanea tarda is an autosomal dominant disorder caused by decreased hepatic activity of uroporphyrinogen decarboxylase. ALA synthase activity is unimportant in this form of porphyria, and drugs capable of precipitating attacks in other forms of porphyria do not provoke acute attacks in this porphyria. Likewise, neurotoxicity does not accompany porphyria cutanea tarda. Signs and symptoms appear as photosensitivity reactions, especially in men older than 35 years. Porphyrin accumulation in the liver can also be associated with hepatocellular necrosis. Anesthetic drugs are not hazardous in affected patients, although the choice of drugs should take into consideration the possibility of liver disease.

Congenital Erythropoietic Protoporphyria

Erythropoietic porphyria is a form of porphyria that, in contrast to porphyrins synthesized in the liver, is synthesized in the red blood cells (RBCs). Congenital erythropoietic protoporphyria (CEP) is a rare form of porphyria and is transmitted as an autosomal recessive trait. Hemolytic anemia, bone marrow hyperplasia, and splenomegaly are often present in this form of porphyria. Infections are common and photosensitivity can be severe. Neurotoxicity and abdominal pain do not occur in erythropoietic porphyria, and administration of barbiturates does not adversely affect this disease. Death often occurs during childhood.

Erythropoietic Protoporphyria

Erythropoietic protoporphyria (EPP) is a much more common and less debilitating form of erythropoietic porphyria. Signs and symptoms include photosensitivity, vesicular cutaneous eruptions, and edema. In occasional patients, cholelithiasis develops secondary to increased excretion of protoporphyrin. Administration of barbiturates does not adversely affect the course of the disease. Survival to adulthood is common.

X-Linked Protoporphyria

This form of erythropoietic porphyria has only recently been identified. Its clinical manifestation is very similar to that of EPP except for its mode of inheritance and the degree of zinc binding to RBC protoporphyrins.

Acute Attacks of Porphyria

Acute attacks of porphyria are characterized by severe abdominal pain, autonomic nervous system instability, electrolyte disturbances, and neuropsychiatric manifestations ranging from mild to life-threatening events. Skeletal muscle weakness progressing to quadriparesis and respiratory failure is a potentially lethal neurologic manifestation of an acute attack of porphyria. Central nervous system involvement is likely the result of increased concentrations of ALA in the brain. This chemical appears to be toxic to the brain. Central nervous system manifestations of acute porphyria include upper motor neuron lesions and cranial nerve palsies, with abnormalities of the cerebellum and basal ganglia seen less frequently. These neurologic lesions in combination with autonomic neuropathy and hypovolemia can cause significant cardiovascular instability. Seizures may occur during an attack of acute porphyria. Psychiatric disturbances may develop, but despite classic tales of so-called werewolf behavior and other bizarre psychiatric problems, mental disorders are not very common.

Gastrointestinal symptoms of acute porphyria include abdominal pain, vomiting, and diarrhea. However, despite severe abdominal pain that may mimic acute appendicitis, acute cholecystitis, or renal colic, clinical examination of the abdomen is typically normal. Abdominal pain is thought to be related to autonomic neuropathy. Dehydration and electrolyte disturbances involving sodium, potassium, and magnesium may be prominent. Tachycardia and hypertension or, less commonly, hypotension are manifestations of cardiovascular instability.

Complete and prolonged remissions are likely between episodes, and many individuals with the genetic defect of a porphyria never develop symptoms. It is important to note, however, that patients at known risk of porphyria but previously asymptomatic (silent or latent porphyria) may experience their first symptoms in response to administration of triggering drugs during the perioperative period. ALA synthase concentrations are increased during all acute attacks of porphyria.

Triggering Drugs

Drugs may trigger an acute attack of porphyria by inducing the activity of ALA synthase or interfering with the negative feedback control at the final common pathway of heme synthesis. It is not possible to predict which drugs will be porphyrinogenic,

although chemical groupings such as the allyl groups present on barbiturates and certain steroid structures have been incriminated in the induction of porphyria. Only the acute forms of porphyria are affected by drug-induced enzyme induction. It is not clear why the manifestations of nonacute porphyrias are apparently unaffected by enzyme-inducing drugs.

Labeling drugs as safe or unsafe for patients with porphyria is often based on anecdotal experience with the use of particular drugs in porphyric patients and reports of induction of acute attacks. Drugs may be tested in cell culture models for their ability to induce ALA synthase activity or for their effects on porphyrin synthesis. Alternatively, the action of drugs on the porphyrin synthetic pathway can be investigated in animal models. Both cell culture and animal models tend to overestimate the ability of drugs to induce excess porphyrin intermediates.

It is difficult to assess the porphyrinogenic potential of anesthetic drugs, since other factors such as sepsis or stress may also precipitate a porphyric crisis in the perioperative period. Any classification of anesthetic drugs with regard to their ability to precipitate a porphyric crisis is likely to be imperfect (Table 18.4). Particular care is needed when selecting drugs for patients with acute intermittent porphyria or clinically active forms of porphyria and when prescribing drugs in combination; exacerbation of porphyria is more likely under these circumstances.

Management of Anesthesia

The principles of safe anesthetic management of patients with the potential for an acute attack of porphyria include identification of susceptible individuals and determination of potentially porphyrinogenic drugs. Laboratory identification of porphyric individuals can be difficult, since biochemical abnormalities during an asymptomatic phase are usually absent. In the presence of a suggestive family history, determination of erythrocyte porphobilinogen activity is the most appropriate screening test for patients suspected of having acute intermittent porphyria. In addition, a thorough physical exam of any neuropathy and/or autonomic nervous system instability should be noted.

Preoperative starvation should be minimized, but if a prolonged fast is unavoidable, preoperative administration of a glucose-containing infusion is prudent, since caloric restriction has been linked to precipitation of attacks of acute porphyria.

Guidelines for drug selection should take into account the following: (1) There is evidence that a single exposure to a potent inducer might be well tolerated but not during an acute attack. (2) Exposure to multiple potential inducers is more dangerous

TABLE 18.4 Potential of Drugs to Provoke Acute Porphyria Attacks[a]

Anesthetic Medications	Recommendation
Inhalation Anesthetics	
Nitrous oxide, isoflurane, sevoflurane, desflurane	All OK
Intravenous Anesthetics	
Propofol, dexmedetomidine	OK
Thiopental, thiamylal, methohexital, etomidate, ketamine	All BAD
Narcotic Opioids for Intravenous Administration	
Morphine, meperidine, hydromorphone, methadone	All OK
Fentanyl, alfentanil, sufentanil	All OK
Remifentanil, tramadol	No Data
Narcotic Opioids for Oral Administration	
Codeine, hydrocodone, oxycodone	All OK
Nonnarcotic Analgesics	
Aspirin, acetaminophen, some NSAIDs	OK
Ketorolac	BAD
Neuromuscular Blockers	
Succinylcholine, pancuronium, vecuronium	All OK
Reversal Drugs for Neuromuscular Blockers	
Atropine, glycopyrrolate	OK
Edrophonium, neostigmine, pyridostigmine, physostigmine	All OK
Local Anesthetics	
Lidocaine, tetracaine, bupivacaine, mepivacaine, ropivacaine	All OK
Benzocaine	No data
Sedatives	
Midazolam, diazepam, lorazepam	All OK
Antiemetics	
Ondansetron, scopolamine, metoclopramide	All OK
Famotidine, ranitidine, cimetidine	All OK
Cardiovascular Medications	
Esmolol, propranolol, labetalol, metoprolol, atenolol	All OK
Epinephrine, dopamine, dobutamine	All OK
Adenosine	OK
Amiodarone	BAD
Calcium channel blockers	Many are BAD. *Check each calcium channel blocker before administration!*
Narcotic Antagonist	
Naloxone	OK

BAD, Probably unsafe or very likely to be unsafe for prolonged use; No data, insufficient data available to make a recommendation about its use; NSAIDs, nonsteroidal antiinflammatory drugs; OK, very likely or probably likely to be safe for prolonged use.
[a]Expert assessments.
Adapted from the American Porphyria Foundation Drug Database. www.porphyriafoundation.org.

than exposure to any single drug. (3) Lists of "safe" and "unsafe" anesthetic drugs and adjuncts may be based on animal or cell culture experiments, so the actual clinical effects of these agents may be unknown. Note that the American Porphyria Foundation maintains an up-to-date drug database of potential drugs that can provoke acute porphyria attacks (see Table 18.4).

If an acute exacerbation is suspected during the perioperative period, particular attention must be given to skeletal muscle strength and cranial nerve function, since these signs may predict impending respiratory failure and an increased risk of pulmonary aspiration. Postoperative mechanical ventilation may be required in these patients, although this is rare. Other clinical deviations include hypertension, tachycardia, hypovolemia, and electrolyte abnormalities. In addition, patients commonly experience severe abdominal pain, which can minimize a surgical abdomen.

Regional Anesthesia

There is no contraindication to the use of regional anesthesia in patients with porphyria. However, if a regional anesthetic is being considered, it is essential to perform a neurologic examination before initiating the blockade to minimize the likelihood that worsening of any preexisting neuropathy would be erroneously attributed to the regional anesthetic. Autonomic nervous system blockade induced by the regional anesthetic could unmask cardiovascular instability, especially in the presence of autonomic neuropathy, hypovolemia, or both. There is no evidence that any local anesthetic has ever induced an acute attack of porphyria or neurologic damage in porphyric individuals. Regional anesthesia has been safely used in parturient women with acute intermittent porphyria. However, regional anesthesia is used very infrequently in patients experiencing an attack of acute intermittent porphyria, owing to concerns about hemodynamic instability, mental confusion, and porphyria-related neuropathy.

General Anesthesia

Perioperative monitoring should consider the frequent presence of autonomic dysfunction and the possibility of blood pressure lability.

Based on current evidence, patients can receive benzodiazepines for preoperative anxiolysis and proton pump inhibitors and/or histamine (H_2) receptor blockers for aspiration prophylaxis.

Intravenous induction drugs, including barbiturates, etomidate, and ketamine, are contraindicated. Fortunately, propofol is well tolerated. Propofol could be given with or without midazolam, a narcotic, or dexmedetomidine.

Nitrous oxide is well established as a safe inhaled anesthetic in patients with porphyria. Safe use of isoflurane, sevoflurane, and desflurane is also established. Virtually all opioids for intravenous administration have been administered safely, though there are no specific data available about the safety of remifentanil. Naloxone is also a safe drug in these patients. Neither depolarizing nor nondepolarizing neuromuscular blocking drugs introduce any predictable risk when administered to these patients, nor do their reversal drugs.

Prophylaxis for postoperative nausea and vomiting can be safely accomplished with ondansetron and/or scopolamine. Safe oral analgesics for control of postoperative pain include codeine, oxycodone, hydrocodone, acetaminophen, and many nonsteroidal antiinflammatory drugs (NSAIDs). However, ketorolac is not safe. There is insufficient evidence to recommend the use of tramadol.

It is important to remember that many drugs other than anesthetic or analgesic drugs might be administered intraoperatively or postoperatively: antibiotics, bronchodilators, antihypertensives, drugs for heart rate control, anticoagulants and their reversals, antidysrhythmic, glucagon, octreotide, and others. The "safe" members of each drug class likely to be needed perioperatively should be determined preoperatively so timely administration of these drugs can occur whenever necessary.

Treatment of a Porphyric Crisis

The first step in treating an acute porphyric crisis is removal of triggering factors. Adequate hydration and carbohydrate loading are necessary. Sedation using a phenothiazine or benzodiazepine can be useful. Pain often necessitates administration of opioids. Nausea and vomiting are treated with conventional antiemetics. β blockers can be administered to control tachycardia and hypertension. Since many traditional anticonvulsants are regarded as unsafe, seizures may be treated with a benzodiazepine or propofol. Electrolyte disturbances, including hypomagnesemia, must be treated aggressively.

Because intravenous heme is more effective and its response rate quicker if heme treatment is given early in the course of an acute attack, it is no longer recommended that heme therapy for a severe attack be delayed pending a trial of glucose therapy. Now all patients with severe attacks should get heme therapy initially. Those with only a mild attack can be treated first with glucose. Heme is administered as hematin, heme albumin, or heme arginine. It is presumed that these forms of heme supplement the intracellular pool of heme and thus suppress ALA synthase activity via the negative feedback loop. Heme arginine and heme albumin lack the potential adverse effects associated with hematin (coagulopathy, thrombophlebitis). Recovery after an acute attack of porphyria depends on the degree of neuronal damage and usually is rapid if treatment is started early.

Gout

Gout is a disorder of purine metabolism and may be classified as primary or secondary. Primary gout is due to an inherited metabolic defect that leads to overproduction of uric acid. Secondary gout is hyperuricemia resulting from an identifiable cause, such as administration of chemotherapeutic drugs that cause rapid lysis of purine-containing cells. Gout is characterized by hyperuricemia with recurrent episodes of acute arthritis caused by deposition of urate crystals in joints. Deposition of urate crystals typically initiates an inflammatory response that causes pain and limited motion of the joint. At least half of the initial attacks of gout are confined to the first metatarsophalangeal joint—that is, the joint at the base of the great toe. Persistent hyperuricemia can also result in deposition of urate crystals in extraarticular locations, manifested most often as

nephrolithiasis. Urate crystal deposition can also occur in the myocardium, aortic valve, and extradural spinal regions. The incidence of systemic hypertension, ischemic heart disease, and diabetes mellitus is increased in patients with gout.

Treatment. Treatment of gout is designed to decrease plasma concentrations of uric acid by administration of uricosuric drugs (e.g., probenecid) or drugs that inhibit conversion of purines to uric acid by xanthine oxidase (e.g., allopurinol). Colchicine, which lacks any effect on purine metabolism, is considered the drug of choice for management of acute gouty arthritis. It relieves joint pain presumably by modifying leukocyte migration and phagocytosis. Side effects of colchicine include vomiting and diarrhea. Large doses of colchicine can produce hepatorenal dysfunction and agranulocytosis.

Management of anesthesia. Management of anesthesia in the presence of gout focuses on prehydration to facilitate continued renal elimination of uric acid. Administration of sodium bicarbonate to alkalinize the urine also facilitates excretion of uric acid. Even with appropriate precautions, acute attacks of gout often follow surgical procedures in patients with a history of gout.

Extraarticular manifestations of gout and side effects of drugs used to control the disease deserve consideration when formulating a plan for anesthetic management. Renal function must be evaluated, since clinical manifestations of gout usually increase with deteriorating renal function. The increased incidence of systemic hypertension, ischemic heart disease, and diabetes mellitus in patients with gout must be considered. Although rare, adverse renal and hepatic effects may be associated with use of probenecid and colchicine. Limited temporomandibular joint motion from gouty arthritis, if present, can make direct laryngoscopy difficult.

Lesch-Nyhan Syndrome

Lesch-Nyhan syndrome is a genetic disorder of purine metabolism that occurs exclusively in males. Biochemically the defect is characterized by decreased or absent activity of hypoxanthine-guanine phosphoribosyltransferase, which leads to excessive purine production and increased uric acid concentrations throughout the body. It has been called juvenile gout. Clinically, patients are often intellectually disabled and exhibit characteristic spasticity and self-mutilation. Self-mutilation often involves trauma to perioral tissues. Subsequent scarification around the mouth may cause difficulty with direct laryngoscopy for tracheal intubation. Seizures are associated with this syndrome. Spasticity of skeletal muscles can be significant. Athetoid dysphagia makes swallowing very difficult, and coexisting malnutrition is typically present. This dysphagia can also increase the likelihood of aspiration if vomiting occurs. Sympathetic nervous system responses to stress are often enhanced. Hyperuricemia is associated with nephropathy, urinary tract calculi, and arthritis. Death is often due to renal failure.

Management of anesthesia is influenced principally by potential airway difficulties and by the neurologic and renal dysfunction that is present.

DISORDERS OF CARBOHYDRATE METABOLISM

Disorders of carbohydrate metabolism typically reflect genetically determined enzyme defects (Table 18.5). Glycogen storage disease (GSD) type IA is the more severe form. It involves deficiency of the enzyme glucose-6-phosphatase itself. Death usually occurs in early childhood. GSD type IB is caused by an inability to translocate glucose-6-phosphatase across microsomal membranes.

Hypoglycemia and lactic acidosis are the most common signs of both type I GSDs and can result from even short periods of fasting. There may also be coagulation difficulties due to poor platelet adhesiveness. Long-term complications include gout due to hyperuricemia, hyperlipidemia leading to pancreatitis, ischemic heart disease, hepatic adenoma, renal dysfunction, and osteoporosis.

Management of anesthesia in patients with type I GSDs should include evaluation for the existence of disease complications such as renal dysfunction and heart disease. Arterial pH should be monitored perioperatively. Because even a short fast can induce hypoglycemia and metabolic acidosis, preoperative fasting must be minimized and glucose-containing infusions should be administered.

HEMOCHROMATOSIS

Hemochromatosis is a disease of total body iron overload. Primary hemochromatosis results from genetic mutation in the *HFE* gene, which leads to decreased hepcidin production. In this case, iron overload develops as a result of inappropriate iron absorption through the gastrointestinal track. Secondary hemochromatosis develops in transfusion-dependent patients, such as those with severe sickle cell disease, myelodysplastic syndrome, and β thalassemia. Iron release from repeated RBC transfusion eventually overwhelms iron loss resulting in excess iron deposit.

The most common organs affected by hemochromatosis are liver, pancreas, and heart. End-organ damage due to years of iron overload will typically manifest as cirrhosis, diabetes, and congestive heart failure after 40 years of age. Less commonly, bronzing of the skin and arthropathy will also develop.

Elevated serum ferritin level is common in hemochromatosis, although its specificity is low given its association with several other disease processes. However, serum ferritin level above 1000 μg/L is highly suggestive of hemochromatosis especially

TABLE 18.5 Disorders of Carbohydrate Metabolism

GSD type Ia (von Gierke disease)
GSD type Ib
GSD type II (Pompe disease)
GSD type V (McArdle disease)
Galactosemia
Fructose 1,3-diphosphate deficiency
Pyruvate dehydrogenase deficiency

GSD, Glycogen storage disease.

when associated with a fasting transferrin saturation of greater than 45%.

The mainstay of treatment of hemochromatosis is phlebotomy to physically remove iron from the body. Phlebotomy may be done once or twice a week at first, then tapered to less frequent treatment as the goal ferritin level is reached. Chelating agents such as deferoxamine remove less iron than phlebotomy and are used only when phlebotomy is not feasible. Certain complications of the iron deposition of hemochromatosis, such as skin pigmentation, hepatomegaly, and heart failure, can be improved with treatment. However, diabetes and cirrhosis, once established, cannot be reversed.

Due to end-organ damage accumulating in liver, pancreas, and heart, anesthetic management should focus on preoperative assessment of liver disease, diabetes mellitus, and the presence of cardiac dysfunction. Anesthetic technique, drug choice, and intraoperative monitoring should be tailored to severity of liver and cardiac involvement. In addition, transfusion of packed RBCs should be avoided if at all possible as this will worsen iron overload.

WILSON DISEASE

Wilson disease is a rare autosomal recessive disease of copper metabolism caused by a mutation in a gene necessary for copper transport. This defect in copper transport impairs biliary copper excretion and results in accumulation of copper, most prominently in the liver. As the disease progresses, copper accumulation can be seen in other organs such as the brain and heart.

Presentation of Wilson disease is often in the teenage years, and signs can range from abdominal pain and hepatitis to acute liver failure or cirrhosis. Neurologic and psychiatric signs and symptoms are seen later in the course of this disease. Movement disorders such as dystonia, tremors, and a Parkinson-like syndrome are often seen. Dysarthria and dysphagia are also common, as is autonomic neuropathy. Copper buildup in the heart leads to left ventricular thickening and high prevalence of benign supraventricular tachycardias.

The diagnosis of Wilson disease is best made by liver biopsy. Parenchymal copper level greater than 250 μg/g confirms the diagnosis. Serum ceruloplasmin levels may also be reduced, and urinary copper levels can be increased in heterozygotes. Kayser-Fleischer rings (brown rings around the rim of the cornea) are seen on slit lamp examination in virtually all patients with neuropsychiatric manifestations of Wilson disease but in fewer than 50% of patients who have not yet developed symptoms of the disease or those with only liver involvement.

Traditionally, Wilson disease was treated with the chelator agent penicillamine. However, this was associated with significant toxicity and the potential to worsen neurologic disease. Currently, if chelation is chosen as therapy, trientine is the drug of choice. For most patients with Wilson disease, zinc is the preferred treatment. Zinc blocks intestinal absorption of copper and induces sequestration of excess copper. Patients with more advanced disease (e.g., hepatic failure, neurologic signs) are treated with both zinc and chelators.

Anesthetic management includes a thorough preoperative evaluation disease severity and current treatment. Assessment of presence and degree of liver disease and neuropsychiatric involvement should be undertaken.

Intraoperative management should focus on avoiding drugs that could worsen affected organ. Care should be taken with anxiolytics, narcotics, and other sedatives, as their effects may be exaggerated in patients experiencing neurodepressive effects of Wilson disease. Drugs metabolized by the liver may have sustained effects secondary to liver dysfunction.

Although general anesthesia may theoretically increase the risk of further liver damage by causing vasodilation, hypotension, and decreased liver perfusion, it can be safely performed in patients with Wilson disease. Regional and neuraxial anesthesia are safe to perform, even in patients with advanced disease, since peripheral nerves are not affected by the copper overload.

KEY POINTS

- Acute attacks of porphyria are characterized by severe abdominal pain, autonomic nervous system instability, electrolyte disturbances, and neuropsychiatric manifestations. These can range from mild disturbances to life-threatening events.
- Skeletal muscle weakness that may progress to quadriparesis and respiratory failure is the most dangerous neurologic manifestation of an acute attack of porphyria. Seizures may also occur.
- Because carbohydrate administration can suppress porphyrin synthesis, carbohydrate supplementation preoperatively is recommended to reduce the risk of an attack of acute porphyria.
- Initial treatment of a severe acute porphyric crisis should include administration of heme. This will stop production of ALA synthase and production of the problematic porphyrin intermediate.
- Anesthetic management of a patient with hemochromatosis must focus on the severity of hepatic disease, diabetes mellitus, and congestive heart failure, which are the most common and important clinical features of the hereditary form of this disease. Red blood cell transfusion should be avoided if possible.
- Anesthetic management of a patient with Wilson disease must include careful consideration of the hepatic and neuropsychiatric dysfunction often present in untreated disease. Dysphagia may increase the risk of pulmonary aspiration of gastric contents. Severe dystonia may make the physical tasks of administering general anesthesia quite difficult. Positioning may be complicated by orthostatic hypotension.

RESOURCES

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19

Nutritional Diseases: Obesity and Malnutrition

Tiffany Sun Moon, Stephanie B. Jones

OUTLINE

Malnutrition can be caused by either an insufficient consumption of essential nutrients or an overconsumption of poor nutrients. Currently the most prevalent nutritional disease worldwide is obesity. About two-thirds of the world's population live in countries where being overweight and obese kills more people than being underweight. In the United States, obesity is considered a national epidemic and a serious public health threat. The prevalence of obesity remains substantial, with estimates indicating that 40% of adults in the US population have a body mass index (BMI) of 30 kg/m^2 or higher.

Obesity is due to a combination of genetic, environmental, psychological, and socioeconomic factors. Controlling the obesity epidemic depends on a better understanding of its causes as well as a systems-based approach to its medical and surgical management.

OBESITY

Definition

Obesity is defined as an abnormally high amount of adipose tissue compared with lean muscle mass that presents a risk to health. It is associated with increased morbidity and mortality due to a wide spectrum of associated medical and surgical diseases (Table 19.1). BMI is the most commonly used quantifier of obesity, although it does not measure adipose tissue directly. BMI is calculated as weight in kilograms divided by the square of the height in meters (BMI = kg/m^2). BMI is used because of its simplicity. However, there are flaws in the formula that should be taken into consideration when using the BMI clinically. For example, persons with an unusually high percentage of lean muscle mass (e.g., body builders) may have a high BMI that does not correlate with a high ratio of adipose tissue. In general, calculation of BMI provides a useful indicator of excess weight that may lead to comorbidity (Table 19.2).

Epidemiology

The global prevalence of obesity in 2016 reached an estimated 13% of adults aged 18 years or older and 7% of children and adolescents aged 5 to 19 years, corresponding to 650 million and 124 million adults and school-aged children, respectively. The estimates exhibit wide ranges at the regional, national, and international levels. Obesity prevalence trends over 40 years demonstrate universal and continuous growth across all demographics but disproportionate acceleration in low- and middle-income countries. In the United States, obesity affected 42% of the adult population in 2018, up from 30% in 2000. Individual patterns show disparities between groups, demonstrating the increasingly implicating systemic factors in the creation of the obesity pandemic. There are both gender and racial/ethnic disparities. Meeting public health goals requires approaching the patient with obesity in the wider setting of these social equity gaps.

Pathophysiology

Weight gain results when caloric intake exceeds energy expenditure. Energy expenditure is primarily determined by basal metabolic rate, which is responsible for maintaining homeostasis of bodily functions. Energy intake is coordinated by a complex hunger-satiety system (Fig. 19.1).

Fat Storage

A positive caloric balance is stored by the body as fat in adipocytes. This fat is primarily in the form of triglycerides. Triglycerides serve as an efficient form of energy storage because of their high caloric

TABLE 19-1 Medical and Surgical Conditions Associated With Obesity

Organ System	Comorbid Conditions
Respiratory system	Obstructive sleep apnea
	Obesity hypoventilation syndrome
	Restrictive lung disease
Cardiovascular system	Systemic hypertension
	Coronary artery disease
	Congestive heart failure
	Cerebrovascular disease, stroke
	Peripheral vascular disease
	Pulmonary hypertension
	Hypercoagulable syndromes
	Hypercholesterolemia
	Hypertriglyceridemia
	Sudden death
Endocrine system	Metabolic syndrome
	Diabetes mellitus
	Cushing syndrome
	Hypothyroidism
Gastrointestinal system	Nonalcoholic steatohepatitis
	Hiatal hernia
	Gallstones
	Fatty liver infiltration
	Gastroesophageal reflux disease
	Delayed gastric emptying
Musculoskeletal system	Osteoarthritis of weight-bearing joints
	Back pain
	Inguinal hernia
	Joint pain
Malignancy	Pancreatic
	Kidney
	Breast
	Prostate
	Cervical, uterine, endometrial
	Colorectal
Other	Kidney failure
	Depression
	Overall shorter life expectancy

TABLE 19-2 Weight Categories by Body Mass Index (BMI) and Waist Circumference

Category		COMORBIDITY RISK BY WAIST CIRCUMFERENCE	
		Men ≤ 40 Inches Women ≤ 35 Inches	Men > 40 Inches Women > 35 Inches
Adults	**BMI Range (kg/m²)**		
Underweight	< 18.5		
Normal	18.5–24.9		
	18.5–23.9 (US Asian populations)		
Overweight	25–29.9	Increased	High
	24.0–26.9 (US Asian populations)		
Obese class I	30–34.9	High	Very High
	27–31.9 (US Asian populations)		
Obese class II	35–39.9	Very High	Very High
	32–36.9 (US Asian populations)		
Obese class III (severe)	≥ 40	Extremely High	Extremely High
	≥ 37 (US Asian populations)		
Children (2–18 yr)			
Overweight	85th–94th percentile		
Obese	95th percentile or ≥ 30		
Severely obese	99th percentile		

density and hydrophobic nature. Adipocytes are able to increase to a maximum size and then begin dividing. As BMI increases from class I obesity (BMI between 30.0 and 34.9 kg/m^2), the relative risk for comorbidity and mortality directly increases. The increased risk correlates with an absolute increase in the total number of fat cells and with relative localization to abdominal (central) fat. The increase in metabolic activity of abdominal fat may contribute to the higher incidence of metabolic disturbances associated with central obesity. Central obesity is more common in men and is therefore known as android fat distribution. Peripheral fat around the hips and buttocks is more common in women and is known as gynecoid fat distribution. It is currently accepted that a waist-to-hip ratio of more than 1.0 in men and more than 0.8 in women is a strong predictor of ischemic heart disease, stroke, diabetes mellitus, and death, independent of the total amount of body fat. Environmental factors such as stress and cigarette smoking stimulate cortisol production, which may facilitate further deposition of extra calories as abdominal fat.

Environmental Factors

Environmental factors, consumption of high-calorie foods, decreased physical activity, and aging all contribute to the development of obesity. The technologic developments of the past 50 years have contributed significantly to decreased physical activity and sedentary lifestyles. There has also been a change in our food habits with the development of "fast food" and intense food marketing and industry competition. These new food habits amplify the obesity problem. Protein and carbohydrates

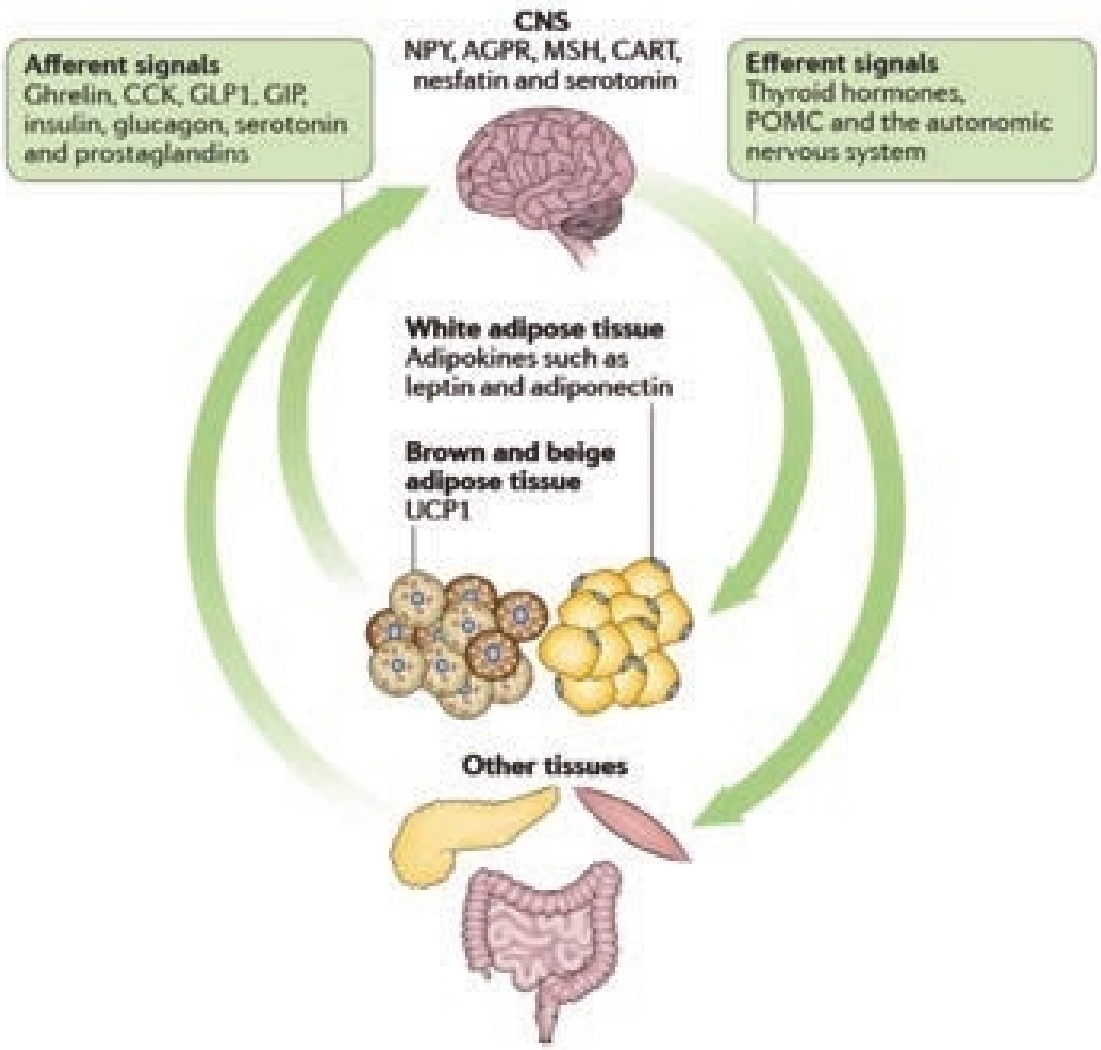

Fig. 19.1 Control of hunger and satiety. Hunger and satiety are controlled by complex interactions between the nervous system, nutrients, mechanical sensing, circadian rhythms, and hormones. Several neurotransmitters and neuropeptides in the hypothalamus are involved in the regulation of food intake. Neuropeptide Y *(NPY)* and agouti-related peptide *(AGRP)* stimulate food intake, whereas melanocyte-stimulating hormone *(MSH)*, cocaine- and amphetamine-regulated transcript protein *(CART)*, and proopiomelanocortin *(POMC)* suppress food intake. Nesfatin 1 regulates hunger and fat storage. Thyroid hormones (triiodothyronine and thyroxine) are involved in several physiologic processes, including regulation of the basal metabolic rate. (From Gonzalez-Muniesa P, Martinez-Gonzalez MA, Hu FB, et al. Obesity. *Nat Rev Dis Primers.* 2017;3:17034. doi:10.1038/nrdp.2017.34)

can be metabolically converted into fat. Evidence is lacking to support that changing the relative proportions of protein, carbohydrates, and fat in the diet without reducing overall caloric intake will promote weight loss. The bottom line is quite simple: If an individual is to lose weight and keep the weight off, daily energy expenditure must exceed daily caloric intake. If daily caloric (energy) intake exceeds energy expenditure by only 2%, the cumulative effect after 1 year is approximately a 5-lb increase in body weight. The critical elements of weight loss are both diet and exercise. Even slight exertion has been shown to provide some benefit to a highly sedentary adult, and the benefit is not exclusively related to weight loss. Exercise has a positive impact on cardiovascular health and glucose control. It limits the progressive decline in lean body tissue with age, decreases the risk of developing osteoporosis, and improves overall psychological well-being.

Psychological and Socioeconomic Factors

Throughout history, obesity has been viewed as a sign of wealth and elite socioeconomic status. Today, however, much more emphasis is placed on appearing slim and fit. Media and marketing pressures can lead overweight individuals, particularly women, to experiment with quick weight-loss schemes and to develop obsessive, unhealthy eating disorders to avoid discrimination. Nearly 37% of women in the United States are at risk of developing major depression related to obesity. Eating disorders linked to both depression and obesity include binge-eating disorder and night-eating syndrome. These eating disorders are seen in a large proportion of patients attending obesity clinics. It is important to recognize the characteristics of eating disorders, as well as signs of depression and anxiety, because psychological assessment and counseling are essential for treatment of these conditions. Use of antidepressants to treat depression

related to obesity can be risky because many of these drugs are associated with weight gain.

In the past, the US Food and Drug Administration (FDA) nutrition labeling policies allowed the food industry to sell packaged foods prepared with potentially harmful chemicals that prolonged shelf life and to add ingredients that increased the caloric density of the food without increasing its macronutrient content. In 2016, the FDA updated its requirements for nutrition facts labeling to support better-informed food choices by consumers.

Fast-food restaurants have made huge profits by attracting consumers with sugary and salty foods rich in fats, extracted sugars, and refined starches. All of these may taste good, but when eaten in large quantities, they are toxic to the body. Clever marketing trends to "supersize" meal portions to fool consumers into believing they are getting more value for their dollar have also led to an unhealthy and unnecessary increase in caloric consumption.

Diseases Associated With Obesity

Underlying the broad complications associated with obesity is the pathologic hijacking of the energy regulation system. Energy balance and tissue distribution require complex network signaling among organ systems to coordinate dynamic requirements and ensure appropriate nutritional needs are met. This framework tightly links the endocrine, cardiovascular, respiratory, gastrointestinal, immune, musculoskeletal, and nervous systems to peripherally dispersed adipocyte-mediated signaling in metabolic crosstalk. In obesity, adiposity increases to a state of excess cellular stress and hyperactivity that is passed downstream to create remote, widespread disease (Fig. 19.2).

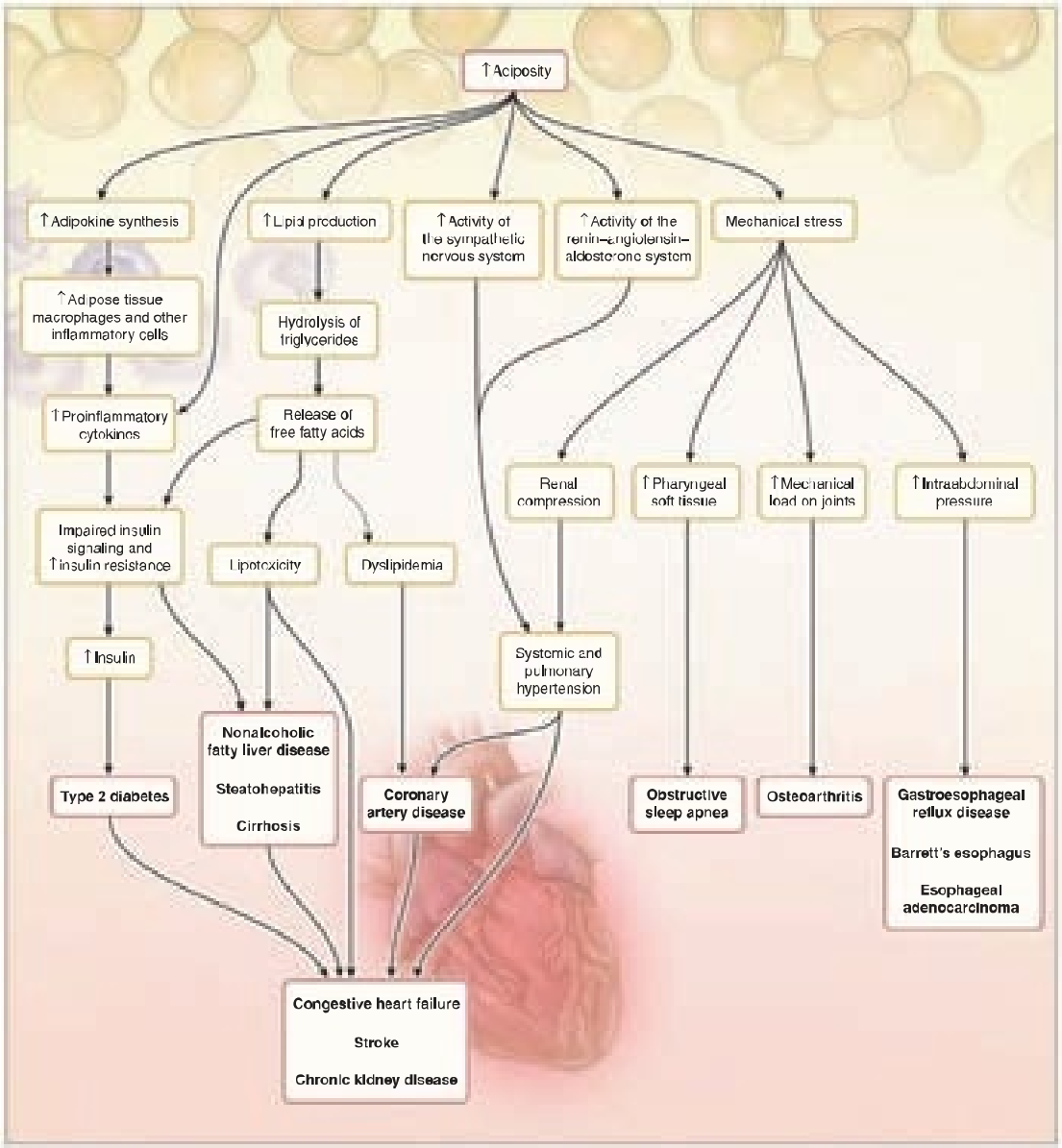

Fig. 19.2 Some pathways through which excess adiposity leads to major risk factors and common chronic diseases. (Copy of Figure 1 from Heymsfield SB, Wadden TA. Mechanisms, Pathophysiology, and Management of Obesity. *N Engl J Med*. 2017;376(3):254–266. doi:10.1056/NEJMra1514009.)

Metabolic syndrome. Increasing abdominal adiposity is the primary driver of the multidimensional obesity disease continuum. This visceral fat, located intraabdominally, and later ectopic fat, deposited around lean organs, reacts to anabolic signals beyond the physiologic limits of adipocyte accommodation. These cells release a proinflammatory, hyperinsulinemic, and immunogenic response with actions systemically. If the inflammatory state is prolonged, as in chronic overnutrition, individuals with epigenetic or existing environmental vulnerabilities can develop multisystem dysfunction known as metabolic syndrome (MetS). The diagnostic criteria include at least three of the following: (1) excess central obesity, (2) atherogenic dyslipidemia, (3) hypertension, and (4) dysglycemia. The individual definitions commonly in use are reported in Table 19.3. Patients in this state exhibit closely coupled disease processes that are strong risk factors for cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). Metabolic syndrome is also associated with a higher incidence of adverse perioperative outcomes, including higher infection and mortality rates, increased postoperative atelectasis, longer hospitalizations, and increased need for critical care and mechanical ventilation. Due to its wide range of adverse outcomes, it is important to preoperatively evaluate for any component of MetS and to treat each component individually.

Glucose intolerance and T2DM. Obesity is an important risk factor for the development of noninsulin-dependent (type 2) diabetes mellitus. Increased adipose tissue leads to increased resistance of peripheral tissues to the effects of insulin, which ultimately results in glucose intolerance and overt diabetes mellitus. Events that increase stress levels in these patients (e.g., surgery) may necessitate the use of exogenous insulin. Resolution of T2DM can be achieved in more than 75% of patients with obesity simply by weight loss.

Cardiovascular Disorders

Cardiovascular disease is a major cause of morbidity and mortality in individuals with obesity and may manifest as systemic hypertension, coronary artery disease, or heart failure. In patients with clinically severe obesity, cardiac function is best at rest, and exercise is poorly tolerated. Physical activity may cause exertional dyspnea and/or angina. Any increase in cardiac output is achieved by an increase in heart rate without an increase in stroke volume or ejection fraction. Changing position from sitting to supine is associated with an increase in pulmonary capillary wedge pressure and mean pulmonary artery pressure, as well as a decrease in heart rate and systemic vascular resistance. Individuals with obesity and cardiac dysfunction may choose to sleep sitting up in a chair to avoid symptoms of orthopnea and paroxysmal nocturnal dyspnea.

Systemic hypertension. Mild to moderate systemic hypertension is seen in approximately 50% to 60% of patients with obesity. The development of hypertension in obesity is multifactorial (Fig. 19.3). Obesity-induced hypertension is related to insulin's effects on the sympathetic nervous system and extracellular fluid volume. Hyperinsulinemia appears to increase circulating levels of norepinephrine, which has direct pressor activity and increases renal tubular reabsorption of sodium, resulting in hypervolemia. Cardiac output increases by an estimated 100 mL/min for each kilogram of adipose tissue weight gain. At the cellular level, insulin activates adipocytes to release angiotensinogen, which activates the renin-angiotensin-aldosterone pathway; this in turn leads to sodium retention and development of hypertension. An increase in circulating cytokines is seen in obesity, and this may cause damage to and fibrosis of the arterial wall, increasing arterial stiffness. If hypertension is not well controlled, a mixed eccentric and concentric left ventricular hypertrophy can develop that eventually leads to heart failure and pulmonary hypertension. Weight loss can significantly improve or even completely resolve this hypertension. In general, a decrease of 1% in body weight can decrease systolic blood pressure by 0.6 mm Hg and diastolic blood pressure by 0.2 mm Hg.

Coronary artery disease. Obesity is an independent risk factor for the development of ischemic heart disease, especially in individuals with central obesity. This risk is compounded by the presence of dyslipidemia, hypertension, and diabetes mellitus. Insulin resistance and abnormal glucose tolerance are associated with progression of atherosclerosis. Young patients with obesity have a significant incidence of single-vessel coronary artery disease, particularly in the right coronary artery.

TABLE 19.3 Common Consensus Guidelines for the Diagnosis of Metabolic Syndrome (MetS)

Criteria	AHA/NHLBI ATP III	IDF	JIS
Diagnostic	3 criteria	Central obesity is required + 2 any other	≥3 criteria
Central obesity (hWC)	M: ≥ 102 cm F: ≥ 88 cm	M: ≥ 94 cm F: ≥ 80 cm OR BMI ≥ 30 kg/m²	M/F: ≥ 90 cm[a]
Dyslipidemia (hTG)	≥ 150 mg/dL or treatment	≥ 150 mg/dL or treatment	≥ 150 mg/dL or treatment
Dyslipidemia (gHDL-C)	M: < 40 mg/dL F: < 50 mg/dL OR treatment	M: < 40 mg/dL F: <50 mg/dL OR treatment	M: <40 mg/dL F: < 50 mg/dL OR treatment
Hypertension	SBP ≥ 130 mm Hg OR DBP ≥85 mm Hg OR treatment	SBP ≥ 130 mm Hg OR DBP ≥ 85 mm Hg or treatment	SBP ≥ 130 mm Hg OR DBP ≥ 85 mm Hg OR treatment
Dysglycemia (FBS)	100 mg/dL OR treatment	100 mg/dL OR treatment OR history of T2DM	≥100 mg/dL OR treatment

AHA/NHLBI ATP III, American Heart Association/National Heart, Lung, and Blood Institute updates of Adult Treatment Panel III; *BMI,* body mass index; *DBP,* diastolic blood pressure; *FBS,* fasting blood sugar; *HDL-C,* high-density lipoprotein cholesterol; *IDF,* International Diabetes Federation; *JIS,* joint interim statement; *SBP,* systolic blood pressure; *T2DM,* type 2 diabetes mellitus; *WC,* waist circumference.
[a]Values specific to country/region-specific value.

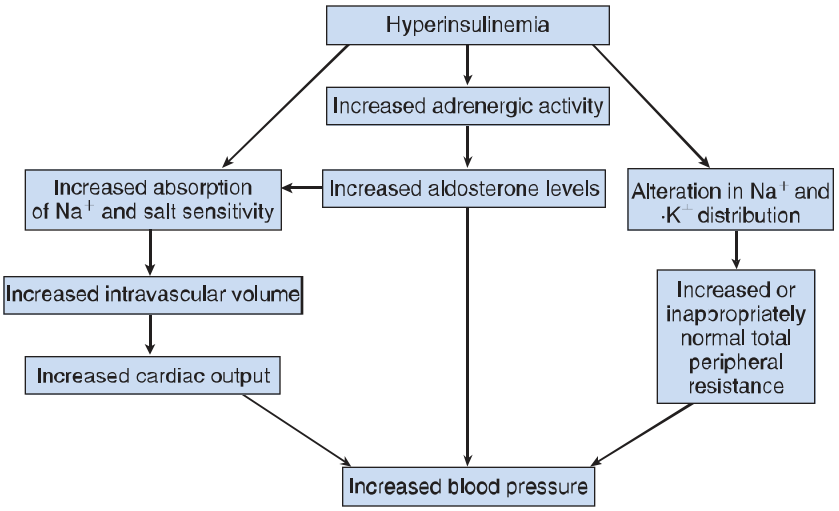

Fig. 19.3 Development of hypertension in obesity. (Adapted from Thakur V, Richards R, Reisin E. Obesity, hypertension, and the heart. *Am J Med Sci.* 2001;321:242–248.)

Obese men seem to be affected 10 to 20 years before women, which may reflect a protective effect from estrogen that dissipates after menopause.

Heart failure. Obesity is an independent risk factor for heart failure. In its staging of heart failure, the American College of Cardiology and the American Heart Association lists MetS and obesity as stage A of heart failure. This is defined as heart failure risk factors without symptoms or overt evidence of heart failure. Possible mechanisms for the development of heart failure are structural and functional modifications of the heart resulting from volume overload and vascular stiffness. These changes cause pressure overload that leads to concentric left ventricular hypertrophy, a progressively less compliant left ventricle that develops diastolic dysfunction, and finally systolic dysfunction. Increased metabolic demands and a larger circulating blood volume result in a hyperdynamic circulation. Right ventricular afterload may be increased because of associated sleep-disordered breathing and changes in right ventricular function (Fig. 19.4). Insulin resistance also appears to play a significant role in the development of heart failure. Cardiac steatosis, lipoapoptosis, and activation of specific cardiac genes that promote left ventricular remodeling and cardiomyopathy may contribute to obesity-related cardiomyopathy. The increased demands placed on the cardiovascular system by obesity decrease cardiovascular reserve and limit exercise tolerance. Cardiac dysrhythmias in obese individuals may be precipitated by arterial hypoxemia, hypercarbia, ischemic heart disease, obesity hypoventilation syndrome, or fatty infiltration of the cardiac conduction system. It is important to note that ventricular hypertrophy and dysfunction worsen with the duration of obesity. However, some of these structural and functional changes can be reversed with significant weight loss.

Respiratory Disorders

Respiratory derangements associated with obesity are related to the presence of redundant tissue in the upper airway, thorax, and abdomen that affects lung volumes, gas exchange, lung compliance, and work of breathing.

Lung volumes. Obesity can produce a restrictive pattern of ventilation due to the added weight of the thoracic cage, chest wall, and abdomen. The added weight impedes motion of the diaphragm, especially in the supine position, which results in an overall decrease in functional residual capacity (FRC), expiratory reserve volume, and total lung capacity. FRC declines exponentially with increasing BMI and may decrease to the point that small airway closure occurs (i.e., closing volume becomes greater than FRC) during normal tidal volume breathing. This results in ventilation/perfusion mismatching, right-to-left intrapulmonary shunting, and arterial hypoxemia. General anesthesia accentuates these changes. A 50% decrease in FRC occurs in anesthetized patients who are obese compared with a 20% decrease in nonobese individuals. Application of positive end-expiratory pressure (PEEP) can improve FRC and arterial oxygenation but at the potential expense of reducing venous return and cardiac output.

This decrease in FRC impairs the ability of patients to tolerate prolonged periods of apnea, such as during direct laryngoscopy for endotracheal intubation. They are more likely to experience oxygen desaturation following induction of anesthesia, even with adequate preoxygenation. This phenomenon reflects a decreased oxygen reserve due to the reduced FRC and increased oxygen consumption resulting from the increased metabolic activity of excess adipose tissue.

Gas exchange and work of breathing. Because of the obese patient's increased body mass, oxygen consumption and carbon dioxide (CO_2) production are increased. To maintain normocapnia, patients with obesity must increase minute ventilation, which also increases their work of breathing. Patients with obesity typically increase their minute ventilation by rapid, shallow breathing because this pattern uses the least amount of energy and helps prevent fatigue from the increased work of breathing. Individuals with clinically severe obesity

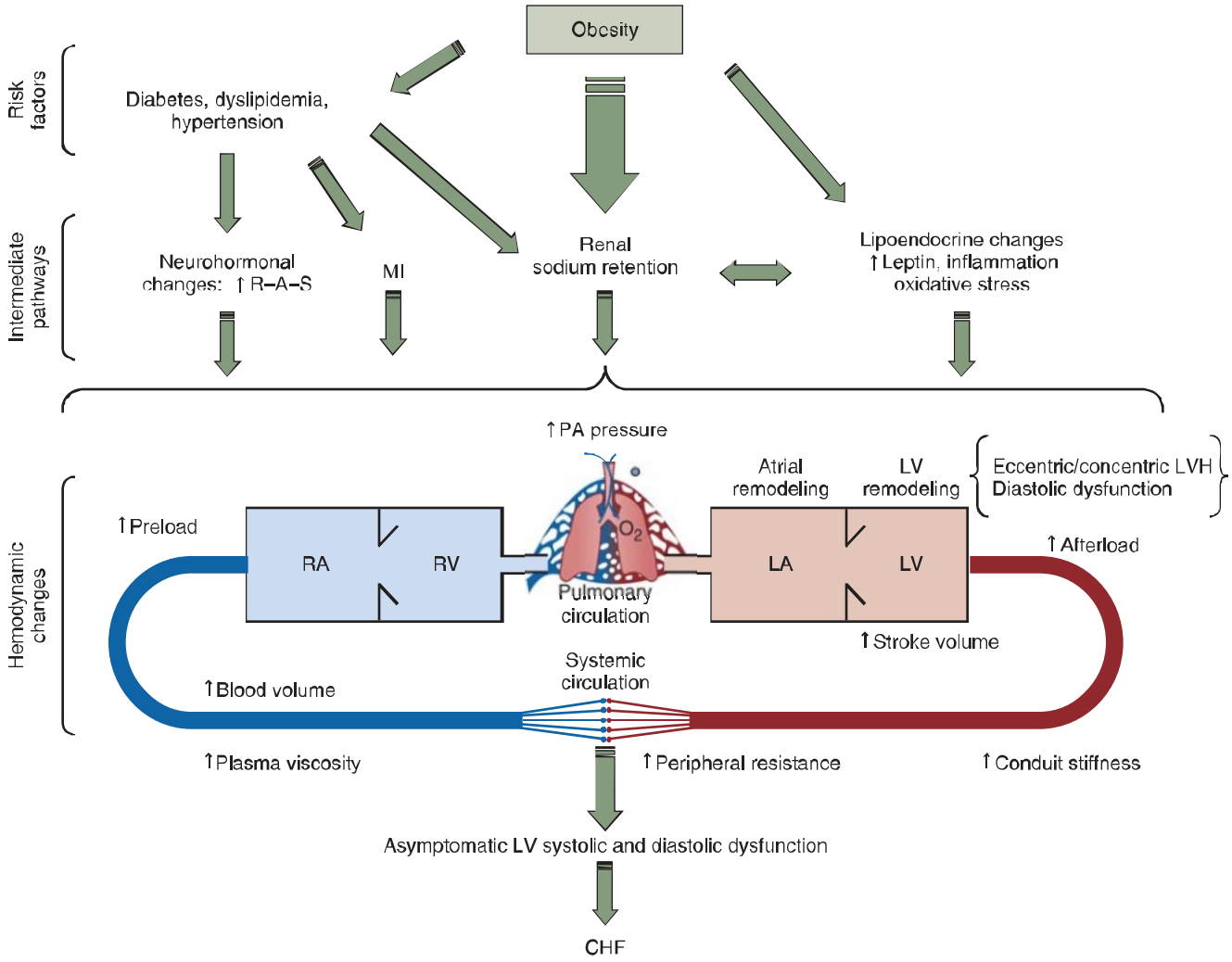

Fig. 19.4 Cardiac changes in obesity leading to heart failure. h, Increased; *CHF*, congestive heart failure; *LA*, left atrium; *LV*, left ventricle; *LVH*, left ventricular hypertrophy; *MI*, myocardial infarction; *PA*, pulmonary artery; *RA*, right atrium; *RAS*, renin-angiotensin system; *RV*, right ventricle. (Adapted from Vasan RS. Editorial: cardiac function and obesity. *Heart*. 2003;89:1127–1129.)

may exhibit only modest decreases in arterial oxygenation and modest increases in the alveolar-arterial oxygen gradient. The $Paco_2$ and ventilatory response to CO_2 remains within the normal range in obese patients, which reflects the high diffusing capacity and favorable characteristics of the CO_2 dissociation curve. However, arterial oxygenation may deteriorate markedly during induction of anesthesia (a period of increased oxygen consumption and decreased oxygen reserve) so that a higher fraction of inspired oxygen (F_{IO_2}) is required to maintain an acceptable level of oxygen saturation.

Lung compliance and airway resistance. Increased BMI is associated with decreased lung compliance and increased airway resistance. The decrease in lung compliance is due to accumulation of adipose tissue in and around the chest wall and abdomen as well as the added effect of an increased pulmonary blood volume. The decrease in lung compliance is associated with a decrease in FRC and impaired gas exchange. These changes are most evident when obese individuals assume the supine position.

Obstructive sleep apnea. Obstructive sleep apnea (OSA) is defined as cessation of breathing during sleep for periods lasting longer than 10 seconds. There may be frequent episodes of apnea and hypopnea during sleep. Hypopnea is a reduction in the size or number of breaths compared with normal ventilation and is associated with some degree of arterial desaturation. Apnea occurs when the pharyngeal tissues collapse. Pharyngeal patency depends on the action of dilator muscles that prevent upper airway collapse. Pharyngeal muscle tone is decreased during sleep, and in many individuals this reduction in tone leads to significant narrowing of the upper airway, resulting in turbulent airflow and snoring. In susceptible individuals, this may progress to severe snoring and ultimately to sleep apnea. Sleep fragmentation is the most likely explanation for daytime somnolence, which is associated with impaired concentration, memory problems, and an increase in motor vehicle accidents. Airway obstruction may induce physiologic changes that include arterial hypoxemia and hypercarbia, polycythemia, systemic hypertension, pulmonary hypertension, and right ventricular dysfunction. In addition,

patients may complain of morning headaches caused by nocturnal CO_2 retention and cerebral vasodilation. OSA is diagnosed using polysomnography, where episodes of apnea can be observed and quantified. The average number of incidents per hour measures the severity of OSA. More than five incidents per hour is considered evidence of sleep apnea syndrome. The main predisposing factors for development of OSA are male gender, middle age, and a BMI of 30 kg/m^2 or above. Additional factors such as evening alcohol consumption or use of pharmacologic sleep aids can worsen the problem. Treatment of OSA aims to apply enough positive airway pressure through a mask to sustain patency of the upper airway during sleep. Patients treated with positive airway pressure demonstrate improved neuropsychiatric function and reduced daytime somnolence. Patients with mild OSA who do not tolerate positive airway pressure may benefit from nighttime application of oral appliances designed to enlarge the airway by keeping the tongue in an anterior position or by displacing the mandible forward. Nocturnal oxygen therapy is another possibility for individuals who experience significant oxygen desaturation. In severe cases of sleep apnea, surgical treatment, including uvulopalatopharyngoplasty, tracheostomy, or maxillofacial surgery (i.e., genioglossal advancement) may be performed. In many instances, weight loss results in a significant improvement in or even complete resolution of OSA symptoms.

Obesity hypoventilation syndrome. Obesity hypoventilation syndrome (OHS) is the long-term consequence of OSA. It is defined as a combination of obesity, chronic daytime hypercapnia ($Paco_2$ 45 mm Hg), and sleep-disordered breathing. Severe cases of OHS can be characterized by obesity, daytime hypersomnolence, hypoxemia, hypercarbia, polycythemia, respiratory acidosis, pulmonary hypertension, and right ventricular failure. Even light sedation can cause complete airway collapse and/or respiratory arrest in a patient with OHS. All patients with a history of OSA or OHS must be thoroughly evaluated preoperatively. Obese patients without a documented history of sleep apnea should be screened preoperatively with a tool such as the STOP-Bang Questionnaire.

Gastrointestinal Disorders

Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. Obesity is the most important risk factor associated with nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). Obesity causes an excess of intrahepatic triglycerides, impaired insulin activity, and additional release of inflammatory cytokines. These factors can lead to destruction of hepatocytes and disruption of hepatic physiology and architecture. Because of the increasing prevalence of obesity, NASH has become one of the most common causes of end-stage liver disease in the United States. Approximately one-third of overweight children, adolescents, and adults have NAFLD, and 85% of severely obese adults have NAFLD. In most cases this form of hepatitis follows a benign course. However, in severe cases it may progress to cirrhosis, portal hypertension, and/or hepatocellular carcinoma requiring liver transplantation. Most patients are asymptomatic, but some may experience fatigue and abdominal discomfort. Liver function test results may be abnormal. Among patients with NAFLD, 22% also develop diabetes mellitus, 22% develop systemic hypertension, and 25% die of coronary heart disease within 5 to 7 years. Weight reduction, especially bariatric surgery–induced weight loss, has been shown to significantly improve the metabolic abnormalities associated with fatty liver disease or even cure this form of hepatic inflammation.

Gallbladder disease. Gallbladder disease is closely associated with obesity. Most commonly, patients with obesity have cholelithiasis resulting from supersaturation of bile with cholesterol due to abnormal cholesterol metabolism. Women with a BMI of more than 32 kg/m^2 have a three times higher risk of developing gallstones, and those with a BMI of more than 45 kg/m^2 have a seven times higher risk of gallstones than lean women. Paradoxically, rapid weight loss, especially after bariatric surgery, increases the risk of gallstones.

Gastric emptying and gastroesophageal reflux disease. Obesity per se is not a risk factor for delayed gastric emptying or gastroesophageal reflux disease (GERD). In the absence of gastroparesis or other comorbidities that affect gastric transit time and emptying, patients with obesity do not have delayed gastric emptying or higher gastric volumes compared to patients with normal BMIs. Standard preoperative fasting guidelines should be followed, and the routine use of pharmacologic agents to decrease aspiration risk is not recommended. If a fasting state is in question (e.g., active liraglutide therapy) or a nonfasting state is unavoidable (e.g., trauma), standard practice rapid-sequence intubation should be considered. Gastric point-of-care ultrasound (PoCUS) has demonstrated rapid, accurate identification of intragastric contents.

Cancer

The depressed immune function of the patient with obesity significantly increases the risk of developing certain cancers. The World Health Organization (WHO) International Agency for Research on Cancer estimates that obesity and lack of physical activity are responsible for 25% to 33% of breast, colon, endometrial, renal, and esophageal cancers. Prostate and uterine cancer are also seen in a higher percentage of overweight patients. Peripheral conversion of sex hormones in adipose tissue by aromatase, together with decreased concentrations of plasma steroid-binding globulin, may be responsible for the increased incidence of some of these cancers.

Thromboembolic Disorders

The risk of deep vein thrombosis in patients with obesity undergoing surgery is approximately double that of nonobese individuals. This increased risk presumably reflects the compounded effects of polycythemia, increased intraabdominal pressure, increased fibrinogen levels associated with a chronic inflammatory state, and immobilization leading to venostasis. At a cellular level, adipocytes produce excessive plasminogen activator inhibitor, and tissues have a decreased capacity for synthesis of tissue plasminogen activator. As a result, there is a decrease in fibrinolysis that renders the patient with obesity susceptible to thromboembolic disease. This phenomenon is worse in the perioperative period. The use of low-molecular-weight heparin (LMWH) perioperatively can decrease thromboembolic complications. The Society for Obesity and Bariatric Anaesthesia (SOBA) recommends a practical dosing schedule

TABLE 19.4 The Society for Obesity and Bariatric Anaesthesia (SOBA) Dosing Recommendations for Low-Molecular-Weight Heparins for Different Weight Categories

	50 kg	50–100 kg	100–150 kg	150 kg
Enoxaparin	20 mg once daily	40 mg once daily	40 mg twice daily	60 mg twice daily
Dalteparin	2500 U once daily	5000 U once daily	5000 U twice daily	7500 U twice daily
Tinzaparin	3500 U once daily	4500 U once daily	4500 U twice daily	6750 U twice daily

for postsurgical venous thromboembolic event (VTE) prevention for several LMWHs in different weight categories (Table 19.4). The volume of distribution of LMWH corresponds to plasma volume, which increases nonlinearly with total body weight. LMWH reaches plasma peak concentration 3 to 4 hours following subcutaneous administration and is mainly distributed via vascular tissue and blood.

The risk of stroke is increased in patients with obesity. Studies report an association between stroke and an increased waist:hip ratio and BMI. For every 1-unit increase above a normal BMI, there is a 4% increase in the risk of ischemic stroke and a 6% increase in the risk of hemorrhagic stroke. This increased stroke risk may be related to the prothrombotic and chronic inflammatory state that accompanies excess adipose tissue accumulation.

Musculoskeletal Disorders

Osteoarthritis and degenerative joint disease are being seen more frequently in men and women 40 to 60 years of age, a trend that closely parallels the incidence of obesity. Obesity leads to joint pain and arthritis of the hips, knees, and carpometacarpal joints, not only because of mechanical loading of weight-bearing joints but also because of the inflammatory and metabolic effects of increased adipose tissue. Coexisting disorders of glucose intolerance, lipid metabolism, hyperuricemia, gout, and vitamin D deficiency may further contribute to the problem of osteoarthritis in patients with obesity. Extra care must be taken in the intraoperative positioning of patients with arthritis or degenerative joint disease.

Nervous System

Patients with obesity, especially those affected by diabetes, may have symptoms of autonomic nervous system dysfunction and peripheral neuropathy. Deficiencies of essential micronutrients such as vitamin B_{12}, thiamine, folate, trace minerals, iron, and calcium, in combination with hyperglycemia, can lead to autonomic nervous system dysfunction. Weight loss in severely obese patients is associated with significant improvement in autonomic cardiac modulation. Because pressure sores and nerve injuries are more common in the superobese and diabetic populations, particular attention must be given to padding the extremities and protecting pressure-prone areas during surgery.

Treatment of Obesity

The benefits of weight loss are well documented. Medical and surgical weight loss plans should be aimed at decreasing the severity of obesity rather than meeting a cosmetic standard of thinness. A weight loss of only 5% to 10% total body weight can be associated with a decrease in systemic blood pressure and plasma lipid concentrations and better control of diabetes mellitus.

Lifestyle Therapy

The first step in any weight loss program is a reduction in caloric intake. Caloric restriction to 500 to 1000 kcal/day less than a regular diet promotes weight loss. Restricting caloric intake beyond this amount may initially help the patient lose weight faster, but the likelihood of long-term adherence to such a restricted diet is very low. Behavior modification therapy may be required to help patients stay motivated and adhere to lifestyle changes. The addition of exercise programs to dieting programs helps maintain successful long-term weight loss. Unfortunately, most patients with severe obesity do not maintain weight loss over time without pharmacologic or surgical intervention.

Medical Therapy

When administered in combination with low- to moderate-intensity lifestyle intervention counseling, pharmacotherapy with approved agents can produce modest weight loss and a reduction in relevant comorbidities. Patients with a BMI of 27 kg/m^2 or above and related comorbidities or a BMI of 30 kg/m^2 or above should be considered for pharmacotherapy to aid in the attainment and maintenance of a healthy weight. Drug monotherapy is not recommended for patients capable of instituting lifestyle interventions.

Weight loss from initial body weight at 1 year ranges from 5.8% to 8.8% (Table 19.5). Four drugs are included, all of which are approved by the FDA for obesity management. Patients should receive close follow-up after 3 months to evaluate for successful weight loss of 5% of the initial total body weight. If not present, the drug should be discontinued for an alternative or for referral to another modality. It bears noting that several older drugs acting through central nervous system (CNS) stimulant/sympathomimetic mechanisms are approved for the so-called short-term management of obesity. This strategy is not endorsed by US or European societies due to its ineffectiveness, and therefore the drugs are not generally endorsed as a component of medical weight-loss interventions.

When considering different long-term medications, the choice is narrowed by weight-loss goals and comorbidity-guided individualization. A meta-analysis of 29,000 participants showed the drug with greatest likelihood of achieving successful weight loss results, defined as 5% or more at 1 year, was once-daily phentermine/topiramate dosed at 15 mg/92 mg, which demonstrated an average weight loss of 8.8 kg (95% confidence interval [CI]: odds ratio [OR] −6.06 to −4.52 kg) in excess of placebo. Regardless, all were shown to be significantly superior to placebo in quantity of weight lost and in the likelihood of meeting weight-loss goals.

TABLE 19.5 US Food and Drug Administration–Approved Drugs for Obesity

Medication	Brand Names	↓Weight %	↑HbA_{1c} %	↓lipids %	↓SBP/↓DBP mm hg
Orlistat	Xenical	8.8	N/A	TC: 7.5; LDL-C: 9.3; HDL-C: 5.1; TGs: NS	2.1/ 1.1
Liraglutide	Saxenda Victoza	−2.7 to −6.0	↓0.1 to −1.0	TC: −2.0 to −6.0, LDL-C: −2.4; HDL-C: 1.9; TGs: ↓6.0 to ↓15.1	−2.4 to −3.1/−0.9 to ↓0.6
Phentermine/topiramate	Osymia	3.6 to 9.4	0.1 to 0.2	TC: 1.6 to 2.5 LDL-C: 2.8 to 5.0 HDL-C: 3.5 to 7.7 TGs: 13.1 to 14.5	2.3 to 3.75/ 1.1 to 1.9
Naltrexone/bupropion	Contrave	↓3.2 to ↓5.2	↓0.5	TC: NS LDL-C: ↑ 0.03 to ↓ 2.9; HDL-C: 0.1 to 7.2; TGs: ↓ 6.1 to ↓10.4	↑2.6 to ↓2.2/↓1.4 to ↑1.0

DBP, Diastolic blood pressure; *HbA1c*, glycosylated hemoglobin C; *HDL-C*, high-density lipoprotein-cholesterol; *LDL-C*, low-density lipoprotein-cholesterol; *SBP*, systolic blood pressure; *TC*, total cholesterol; *T2D*, type 2 diabetes; *TG*, triglyceride.

(Adapted from Filitsi E, Farr OM, Polyzos SA, et al. Pharmacotherapy of obesity: Available medications and drugs under investigation. *Metabolism*. 2019;92:170–192. doi:10.1016/j.metabol.2018.10.010)

A fifth drug, lorcaserin (Belviq), was approved in the United States in 2012 for obesity management. An FDA safety analysis of a large 4-year trial found an increased incidence of cancers associated with enrollment in the experimental arm. Consequently, it was removed from the market in 2020.

Several efforts are underway to develop an obesity vaccine. One research effort is directed against the hormone ghrelin, which stimulates appetite. The goal of this vaccine is to inactivate ghrelin by producing an antibody response against it, decreasing the amount of hormone available to enter the CNS and stimulate the appetite. This research is in phase II trials. Other obesity vaccine research is directed against somatostatin. Somatostatin has many effects in the body, including the ability to suppress pancreatic release of several hormones, including insulin and glucagon. Very early trials showed that this vaccine caused loss of 10% of body weight in the 4 days after its injection in mice. However, most of the weight was regained over time.

Surgical Therapy

Many patients have difficulty achieving meaningful weight loss with medical and lifestyle intervention, and few studies show sustained weight loss beyond 2 years. In addition, a growing percentage of the patient population with obesity are reaching BMI ranges that pose extreme risk for obesity or comorbidity-associated mortality. For these individuals, the weight-related complications may be a more significant risk than the risk of bariatric surgery. The 2019 consensus guidelines cosponsored by the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE), The Obesity Society, American Society for Metabolic & Bariatric Surgery (ASMBS), Obesity Medicine Association (OMA), and American Society of Anesthesiologists (ASA) recommend that patients with a BMI of 35.0 kg/m^2 or more and a severe, surgically remediable obesity-related complication (ORC) or any patient with a BMI of 40.0 kg/m^2 or more should be considered for bariatric surgery as part of an initial treatment plan that includes lifestyle and medical interventions. Patients with a BMI of 30.0 to 34.9 with poorly controlled T2DM despite optimal behavioral and medical therapy should also be considered for surgical treatment. For these patients, substantial data support bariatric intervention as a reliable approach to achieving substantial, long-term weight loss.

For patients with class I obesity and T2DM or MetS, insufficient data exist to include in the guidelines, but the ASMBS and AACE/ACE endorse consideration of these patients for bariatric procedures on case-by-case bases. This position is primarily driven by the high rate of T2DM remission and significant hemoglobin A_{1c} (HbA_{1c}) reduction accompanying weight loss. A randomized trial from Horwitz and colleagues showed that in 43 patients with T2DM and an average BMI of 32 kg/m^2, the 5-year postoperative diabetes resolution rates were as high as 38%, concurrent with significant decreases in HbA_{1c} and total body weight.

Since the first gastric bypass in the 1950s, the choices for interventions to support weight loss have continued to expand and modernize alongside surgery and, more recently, endoscopy. Regardless of invasiveness or technique, all are endorsed as component therapies to multimodal plans that include lifestyle strategies and medical management. Multidisciplinary care is recommended for all patients undergoing bariatric surgery during the pre- and postoperative period.

Weight-loss surgery. Between 2011 and 2018, primary metabolic and bariatric surgeries increased 40% from 143,000 to 202,000 cases annually in the United States. Four procedures are eligible for insurance consideration in the United States and endorsed by the ASMBS. Of these, the laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (RYGB) comprise approximately 70% and 25%, respectively. The remaining primary procedures include laparoscopic adjustable gastric banding (LAGB) (3%) and biliopancreatic diversion with duodenal switch (BPD/DS) (2%).

Traditionally, these procedures have been presented along two functional axes based on their perceived mechanism in treating obesity. These were restrictive procedures, those that physically restricted food intake, and malabsorptive procedures, those that acted to prevent the complete caloric utilization of a patient's diet. The mechanisms through which surgical intervention affects long-term change are increasingly appreciated for their complexities beyond these two paradigms. We include the division as it continues to emerge in the surgical literature and, increasingly, the endoscopic literature. These techniques are summarized visually in Fig. 19.5. Final decisions on strategy can be aided by establishing target weight-loss goals and relative contraindications (Table 19.6).

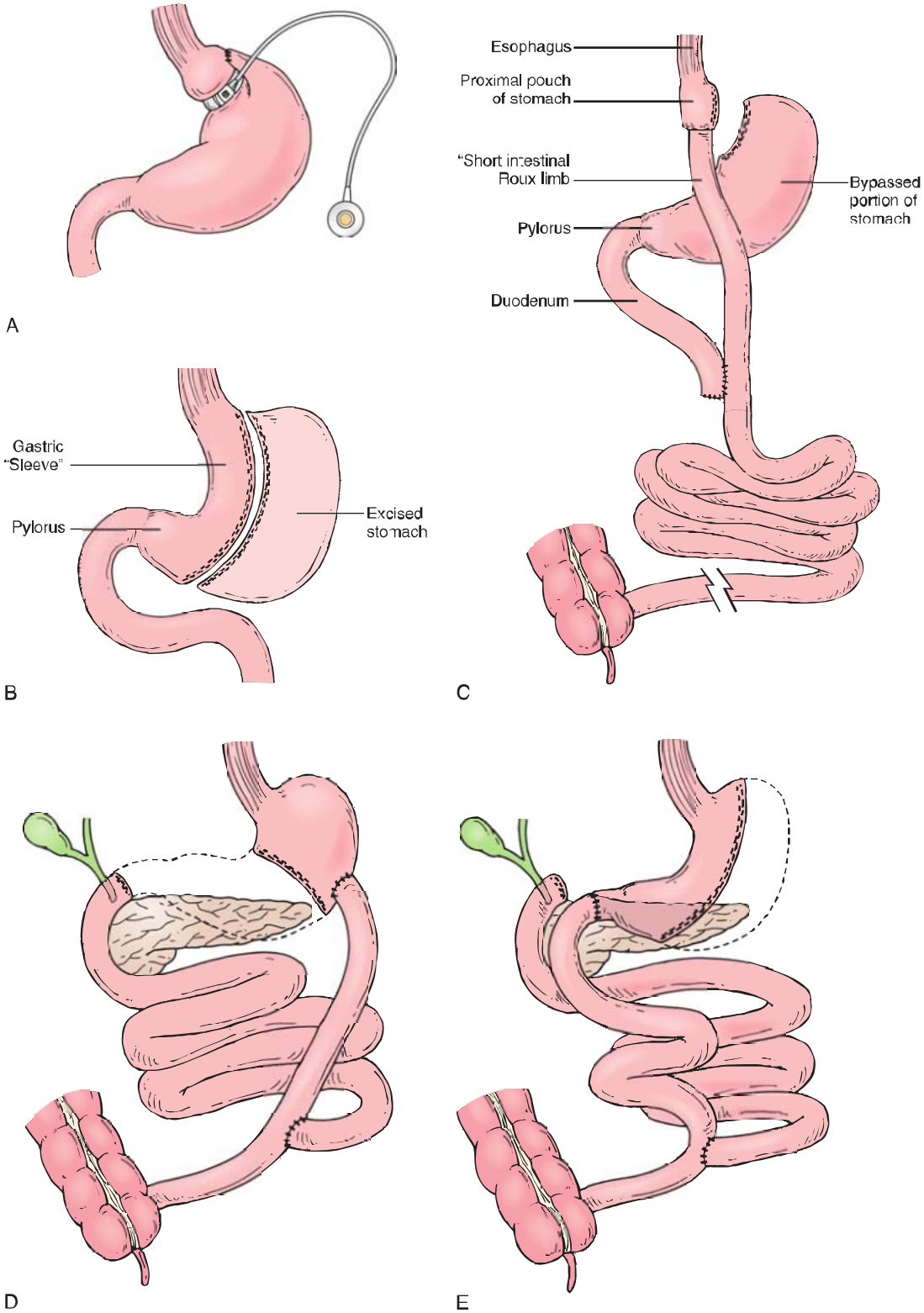

Fig. 19.5 (A) Adjustable gastric band (AGB). A silicone band is looped around the proximal stomach to create a 15- to 20-mL pouch with an adjustable outlet. The stomach is wrapped around the band anteriorly to prevent the band from slipping out of position. The band consists of a rigid outer ring and an inner inflatable balloon reservoir connected by tubing to a subcutaneous port that can be accessed through the skin to adjust the tightness. (B) Sleeve gastrectomy. A narrow gastric sleeve is created by stapling the stomach vertically. The fundus and greater curve of the stomach are removed from the abdomen. (C) Roux-en-Y gastric bypass (RYGB). A small gastric pouch (15–30 mL) is created by division of the upper stomach, connected to a 100- to 150-cm limb of jejunum called the Roux limb. The small gastric pouch results in restriction of food intake. (D) Biliopancreatic diversion (BPD). Most of the small bowel is bypassed, and only 50 to 100 cm of a common channel remains for absorption of calories and nutrients. The upper pouch is larger than that of the RYGB to allow for ingestion of larger amounts of protein to prevent malnutrition. (E) BPD with duodenal switch (BPD/DS). To avoid dumping syndrome and maintain the pylorus, the procedure was modified with the pouch based on the lesser curve of the stomach and an anastomosis at the first portion of the duodenum. (From Ding S, McKenzie T, Vernon A, et al. Bariatric surgery. In: Jameson JL, De Groot LJ, de Kretser DM, eds. *Endocrinology: Adult and Pediatric*. 7th ed. Philadelphia, PA: Elsevier; 2015:479.)

TABLE 19.6 Bariatric Procedures and Devices by Percentage of Total Weight Loss (%TWL) Goals, Risks, and Benefits[a]

Procedure	Type	Target %TWL	Favorable Aspects	Unfavorable Aspects
LAGB	Restrictive	20–25%	No anatomic alteration Removable Adjustable	High explant rate Erosion Slip/prolapse
LSG	Restrictive	25–30%	Easy to perform No anastomosis Few long-term complications Moderate metabolic effects Versatile for challenging patient populations	Leaks difficult to manage Little data beyond 5 years 20–30% incidence of GERD
RYGB	Malabsorptive/restrictive	30–35%	Strong metabolic effects Standardized techniques Higher complication rates Effective for GERD Can be used as second stage after LSG	Few proven revisional options for weight regain Marginal ulcers Internal hernias possible Long-term micronutrient deficiencies
BPD/DS	Malabsorptive/restrictive	35–45%	Very strong metabolic effects Durable weight loss Effective for patients with very high BMI Can be used as second stage after LSG	Malabsorptive 3–5% protein-calorie malnutrition GERD Potential for internal hernias Duodenal dissection Technically challenging Higher rate of micronutrient deficiencies than RYGB
IGB	Restrictive	10–12%	Endoscopic or swallowed Good safety profile FDA approved	Nausea, gastric reflux, pancreatitis. Not for use long term

BMI, Body mass index; *BPD/DS,* biliopancreatic diversion with duodenal switch; *GERD,* gastroesophageal reflux disease; *HTN,* hypertension; *IGB,* intragastric balloon; *LAGB,* laparoscopic adjustable gastric banding; *LSG,* laparoscopic sleeve gastrectomy; *MetS,* metabolic syndrome; *NAFLD,* nonalcoholic fatty liver disease; *NASH,* nonalcoholic steatohepatitis; *OSA,* obstructive sleep apnea; *PCOS,* polycystic ovarian syndrome; *RYGB,* Roux-en-Y gastric bypass; *T2DM,* type 2 diabetes mellitus.

[a] Guidance for weight-loss targets: (1) 0.5%–10% weight loss: T2DM, dyslipidemia, HTN, NAFLD, low testosterone, OSA/reactive airway disease, urinary stress incontinence, PCOS; and (2) 10%–15% weight loss: MetS, prediabetes, NASH, osteoarthritis, GERD, and depression.

Adapted from Mechanick JI, Apovian C, Brethauer S, et al. Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures – 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists. *Surg Obes Relat Dis.* 2020;16(2):175–247. doi:10.1016/j.soard.2019.10.025

Long-term efficacy and the risk of adverse events vary widely depending on the procedure, but large-scale studies with 5- or 10-year follow-up periods or longer support the overall superiority in long-term weight-loss results for all surgeries versus nonsurgical approaches. Meta-analyses of long-term studies showed pooled effect sizes on 10-year excess weight-loss percentage (%EWL; defined as the percent weight lost from the patient's initial total body weight minus the calculated maximum healthy weight at the initial visit for obesity) as high as 71.0% with BPD/DS, 60% with RYGB, and 49% with LAGB. Studies of LSG cases were too few to accommodate pooled effects analysis, but weighted mean difference reached 57% in the two included studies. Outcomes show large improvements when compared to one of the few longer-term behavioral intervention studies, the Look AHEAD trial, which achieved an approximate 15% EWL at 8 years with significant high-intensity interventional follow-up.

Types of bariatric surgery

Restrictive bariatric procedures. LAGB, LSG, and vertical banded gastroplasty are examples of restrictive weight-loss procedures in which a small gastric pouch with a small outlet is created. The mechanism of weight loss may be related to appetite suppression and early satiety or to vagal nerve compression or reduced secretion of gastric hormones such as ghrelin. LAGB places an adjustable silicone band around the upper end of the stomach, creating a small pouch and restrictive stoma that slows the passage of food into the small intestine. This procedure requires no cutting of, or entry into, the stomach or small intestine and should therefore be associated with a low complication rate. The gastric band is adjusted after surgery by injection of saline into a subcutaneous port (placed at the time of surgery) to adjust the stoma size. LSG involves resection of the greater curvature of the stomach, which compromises about 75% of the stomach. The smaller gastric reservoir produces early satiety, and the remnant stomach secretes decreased levels of gastric hormones. The normal absorptive physiology of the entire small intestine is left intact in all of these restrictive procedures. Therefore specific nutrient deficiencies are rare unless there is a significant change in eating habits or surgical complications occur.

Malabsorptive bariatric procedures. Malabsorptive procedures include distal gastric or jejunoileal bypass, BPD, and DS. These operations typically combine gastric volume reduction with

a bypass of various lengths of small intestine. After creation of a small gastric pouch, the small bowel is divided proximal to the ileocecal valve and connected directly to the gastric pouch, which produces a gastroileostomy. The remaining proximal limb of small intestine (biliopancreatic conduit) is anastomosed end-to-side to the distal ileum, proximal to the ileocecal valve. This provides a common channel that allows for mixture of nutrients with digestive enzymes in the ileum. The length of the common channel determines the degree of malabsorption. Because these procedures induce weight loss by extensively bypassing the small intestine and promoting malabsorption, they are associated with a high incidence of anemia, deficiency of fat-soluble vitamins, and protein-calorie malnutrition in the first year after surgery. Because of these risks of nutritional and metabolic complications, these operations are not performed as frequently as restrictive procedures.

Combined bariatric procedures. The combined bariatric procedure Roux-en-Y gastric bypass includes both gastric restriction and some degree of malabsorption. In the RYGB procedure, the surgeon creates a very small proximal gastric pouch that is connected to a Roux limb via an enteroenterostomy to the jejunum near the ligament of Treitz. The procedure bypasses the distal stomach, duodenum, and proximal jejunum, so there is a marked loss of absorptive surface area for nutrients, electrolytes, and bile salts.

Surgical complications. Complications and mortality rates for bariatric surgery depend on several factors: age, gender, BMI, existing comorbid conditions, procedure type and complexity, and experience of the surgeon and surgical center. Higher mortality rates have been associated with abdominal obesity, male gender, BMI of 50 kg/m^2 or more, diabetes mellitus, OSA, older age, and performance of the surgery at a lower-volume bariatric surgery center. Recent improvements in mortality rates are likely due to better perioperative care. Overall 30-day mortality for bariatric surgery ranges from 0.1% to 2%. LAGB has the lowest mortality rate. Mortality for RYGB and LSG is 0.5%. Malabsorptive operations are associated with a higher mortality rate. The mortality of RYGB ranges from 0.5% to 1.5%. The most severe complications of bariatric surgery include anastomotic leaks, stricture formation, pulmonary embolism, sepsis, gastric prolapse, and bleeding. Less common complications include wound dehiscence, hernia or seroma formation, lymphocele, lymphorrhea, and suture extrusion.

Nutritional complications are seen after malabsorptive and combined bariatric procedures. These complications are a result of the marked reduction in vitamin and mineral uptake. The majority of patients can maintain a relatively normal nutritional status after RYGB, but deficiencies of iron, vitamin B_{12}, and folate are common. Some patients develop subclinical micronutrient deficiency. Taking multivitamins with mineral supplements reduces but does not totally prevent development of vitamin or mineral deficiencies.

Additional complications of bariatric surgery include occurrence of an undesirable dumping syndrome in some patients. Other patients experience major nutritional complications. Three of the most clinically significant nutritional complications are protein-calorie malnutrition, Wernicke encephalopathy, and peripheral neuropathy. In the long term, patients are also at risk for metabolic bone disease. Pregnant women and adolescents are at higher risk for nutritional complications after RYGB because of their higher physiologic nutritional needs. Long-term nutritional follow-up is essential. Even when surgery-related mortality is considered, several studies have shown a significant survival benefit in patients who underwent bariatric surgery compared with those who did not. The survival benefit is specifically due to a decrease in the rate of myocardial infarction, resolution of diabetes mellitus, and fewer cancer-related deaths.

Protein-calorie malnutrition. Severe malnutrition is the most serious metabolic complication of bariatric surgery. Red meat is poorly tolerated after bariatric surgery because it is much harder to break down and pass through the small stomach outlet. If the patient does not consume enough alternative protein sources, such as milk, yogurt, eggs, fish, and poultry, protein malnutrition can develop. Protein-calorie malnutrition is generally more common with a BPD and very rare with vertical banded gastroplasty. Protein-caloric malnutrition has a reported incidence of 7% to 12% in patients who have undergone BPD. Hypoalbuminemia has been reported as early as 1 year after BPD. Mild to moderate cases usually respond to dietary counseling. In cases of severe malnutrition, enteral or parenteral nutritional therapy may be necessary. More frequent monitoring may be necessary for patients prone to protein-calorie malnutrition.

Fat malabsorption. Fat-soluble vitamin malabsorption and fat malabsorption (evidenced by steatorrhea) are common with RYGB and BPD. Indeed, this phenomenon is the principal means by which BPD promotes weight loss. However, the malabsorption of fat can lead to a deficiency of essential fatty acids and fat-soluble vitamins. The length of the common channel in BPD regulates the degree of fat absorption and determines the severity of malabsorption. In the United States, the common channel is typically 75 to 150 cm in length. Evidence has shown that a 100-cm common channel is better tolerated than a 50-cm channel and is associated with less diarrhea and steatorrhea and improved protein metabolism. Problems with fat-soluble vitamin imbalances and fat malabsorption are rarely seen with vertical banded gastroplasty.

Consideration of bariatric surgery in pediatric and adolescent patients. With over 10% of children now classified as overweight or obese, bariatric surgery in adolescents is becoming more prevalent. A National Institutes of Health (NIH) consensus statement indicated that bariatric surgery in adolescents is safe and effective for long-term sustained weight loss and resolution of comorbid conditions. The ASMBS has expanded the patient population suitable for bariatric surgery to include adolescents and possibly individuals with a BMI of 30 to 34.9 kg/m^2 who have associated comorbid conditions. The 2012 ASMBS Pediatric Best Practice Guidelines recommend that bariatric surgery be performed in adolescents with a BMI above 35 kg/m^2 and a severe comorbidity such as severe OSA, moderate to severe NASH, T2DM, pseudotumor cerebri, or adolescents with a BMI above 40 kg/m^2. The most common weight-loss operations in adolescents are sleeve gastrectomy and RYGB. Despite the lower complication rate seen with adjustable gastric banding, the FDA has approved this device for adults who have a

BMI between 30 and 40 kg/m^2 and at least one obesity-related comorbid condition.

Endoscopic and nonsurgical procedures. Currently, utilization of bariatric surgery among those who qualify is approximately 1% in the United States. This may be indicative of hesitation due to the invasiveness of weight-loss surgeries or misperceptions in the medical or patient community. Given the variable efficacy of medical-lifestyle interventions, minimally invasive techniques are increasingly used for weight loss. Bariatric endoscopy leverages the same principles as surgical approaches but is less invasive. The most common of these is the intragastric balloon (IGB), with multiple devices approved for use in patients with BMI between 30 and 40 kg/m^2.

IGBs are placed transorally or, for the Obalon (Obalon Therapeutics Inc.), swallowed. They are subsequently inflated with saline or gas in a space-occupying (or restrictive) technique that reduces caloric intake. These are short-term devices with removal no later than 6 months, but they can be reinserted if indicated. The most common complications are abdominal pain (33.7%) and nausea (29%), which are short term and may respond to medication. Rare, serious complications include dislodgement and small bowel obstruction (0.3%), perforation (0.1%), and death (0.08%).

Weight loss at 6 months is generally estimated to be around 10% total body weight, but there is significant debate on long-term efficacy. One study found as many as 78% of patients regained the weight loss in an average of 3.3 years. Notably, there appears to be consensus on the positive impact IGBs have on short-term comorbidities. In a systematic review and meta-analysis, the OR for diabetes remission was 1.4 (95% CI: 1.3–1.9), and there were significant decreases in multiple markers of comorbidity at 6 months; however, evidence quality was rated as low to moderate in all parameters. This is consistent with the observed neurohormonal changes with IGB use that resemble surgical gut manipulation. This is an active area of research with more data needed on long-term efficacy and comparison to invasive procedures.

Management of Anesthesia in Patients With Obesity

Patients with obesity have unique issues that may contribute to cardiovascular, pulmonary, and thromboembolic complications. High-risk patients should be identified early to ensure optimal management of coexisting diseases before surgery. A look at prior anesthetic records, with special attention to induction and intubation, may help identify problems with airway management and specify the weight of the patient at the time of the previous surgery.

Preoperative Evaluation

History. A thorough preoperative evaluation is necessary for all patients with clinically severe obesity presenting for surgery. Many of these patients lead sedentary lives, so eliciting symptoms associated with cardiorespiratory disease may be difficult. Even a thorough history and physical examination combined with an electrocardiogram (ECG) may underestimate the extent of cardiovascular disease. In some cases, more extensive preoperative diagnostic testing may include chest radiography, polysomnography, cardiac stress testing, transthoracic echocardiography, and room air arterial blood gas sampling. These may be necessary to fully evaluate the medical status of a patient with obesity.

The anesthesiologist should inquire about the presence of chest pain, dyspnea at rest or with exertion, palpitations, and the position in which the patient sleeps. The most common symptoms of pulmonary hypertension are exertional dyspnea, fatigue, and syncope, which reflect an inability to increase cardiac output during activity. If pulmonary hypertension is suspected, avoidance of nitrous oxide and other drugs that may further worsen pulmonary vasoconstriction is essential. Intraoperatively, inhaled anesthetics may be beneficial because they cause bronchodilation and decrease hypoxic pulmonary vasoconstriction.

Symptoms of OSA such as snoring, apneic episodes during sleep, daytime somnolence, morning headaches, and frequent sleep arousal should be sought. If a diagnosis of severe OSA or OHS is suspected, further evaluation is required. Symptoms of acid reflux, coughing, inability to lie flat without coughing, or heartburn may indicate GERD or delayed gastric emptying. If these symptoms are not already controlled with histamine (H_2) blockers or proton pump inhibitors, it may be necessary to start these medications preoperatively. In patients with a history of hypertension, eliciting symptoms such as frequent headaches and changes in vision can indicate whether the blood pressure is well controlled. In those with uncontrolled hypertension, referral to an internist for optimization should be considered. In diabetic patients, symptoms of claudication, peripheral neuropathy, renal dysfunction, retinopathy, or an elevated HbA_{1c} level should signal the possibility of advanced diabetes mellitus, poorly controlled blood glucose levels, and microvascular and/or macrovascular disease.

Physical examination and airway examination. The physical examination should attempt to identify signs suggestive of cardiac and respiratory disease. Signs of left or right ventricular failure (e.g., increased jugular venous pressure, extra heart sounds, rales, hepatomegaly, peripheral edema) may be very difficult to elicit in the patient with severe obesity because of body habitus. Pedal edema is a very common finding in patients with obesity and may be due to right-sided heart failure, varicose veins, or simply extravasation of intravascular fluid associated with decreased mobility.

A detailed assessment of the upper airway must be performed to look for the following anatomic features: full face and cheeks, short neck, large tongue, large tonsils, excessive palatal and pharyngeal soft tissue, limited cervical or mandibular mobility, short thyromental distance, large breasts, increased neck circumference, or a Mallampati score of 3 or higher. A history of sleep apnea should raise the possibility of upper airway abnormalities that may predispose to difficulties with mask ventilation and visualization of the glottic opening during direct laryngoscopy. When awake, these patients may compensate for their compromised airway anatomy by increasing the craniocervical angulation, which increases the space between the mandible and cervical spine and elongates the tongue and soft

tissues of the neck. This compensation is lost when the patient becomes unconscious.

Studies have not shown a statistically significant link between obesity per se and the likelihood of difficult intubation. Rather, physical examination findings such as a large neck circumference or a Mallampati score higher than 3 more reliably predict the possibility of a difficult intubation. In selected patients, awake endotracheal intubation using fiberoptic laryngoscopy may be the most appropriate method for securing the airway, but it is important to remember that neither clinically severe obesity nor a high BMI are absolute indications for awake intubation. Patients with obesity should also be evaluated for ease of peripheral intravenous (IV) catheter placement. If severe difficulty with IV access is anticipated, the patient should be informed of the possibility of placement of a central venous catheter before induction.

Preoperative diagnostic tests. ECG examination may demonstrate findings suggestive of right or left ventricular hypertrophy, cardiac dysrhythmias, or myocardial ischemia or infarction. It is important to keep in mind that the ECG may not always be reliable in the patient with clinically severe obesity because of morphologic features such as (1) displacement of the heart by an elevated diaphragm, (2) increased cardiac workload with associated cardiac hypertrophy, (3) increased distance between the heart and the recording electrodes caused by excess adipose tissue in the chest wall and possibly increased epicardial fat, and (4) the potential for associated chronic lung disease to alter the ECG. Chest radiographic examination may show signs of heart failure, increased vascular markings, pulmonary congestion, pulmonary hypertension, hyperinflated lungs, or other pulmonary disease. Transthoracic echocardiography is useful to evaluate left and right ventricular systolic and diastolic function as well as to identify pulmonary hypertension. In cases of severe OSA, the results of an arterial blood gas analysis on a sample drawn with the patient breathing room air may be helpful in guiding intraoperative and postoperative ventilatory management and oxygen supplementation.

Home medications. Most home medications should be continued preoperatively, except for oral hypoglycemics, anticoagulants (e.g., warfarin, aspirin, clopidogrel), and nonsteroidal antiinflammatory drugs (NSAIDs). Patients taking H_2 receptor blockers such as famotidine, nonparticulate antacids, or proton pump inhibitors should be counseled to take these medications on the morning of surgery. Patients with obesity are at high risk of acute postoperative pulmonary embolism because of their chronic inflammatory state, so perioperative deep vein thrombosis prophylaxis with either unfractionated or LMWH is indicated. If a continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) device is used at home, the patient should be advised to bring the device on the day of surgery so that this therapy can be continued in the postoperative period.

Intraoperative Management

Positioning. Specially designed operating tables may be required for patients with severe obesity. Regular operating room tables have a maximum weight limit of approximately 205 kg, but operating tables capable of holding up to 455 kg with extra width are also available. To transfer the patient from the stretcher to the operating table, some commercial devices are available to assist lateral transfer, reposition patients, and minimize injury to staff. Particular care should be paid to protecting pressure areas because pressure sores and nerve injuries are more common in patients with obesity. Brachial plexus, sciatic, and ulnar nerve palsies have been reported in patients with increased BMIs. Upper and lower limbs, because of their increased weight, have a higher likelihood of sliding off the operating table, which can produce peripheral nerve injuries. It is desirable to keep the arms in neutral position on the arm boards so their position can be monitored and excess pressure from tight tucking and draping can be avoided.

Laparoscopic surgery. The degree of intraabdominal pressure determines the effects of pneumoperitoneum on venous return, myocardial performance, and ventilatory status. There is a biphasic cardiovascular response to increases in intraabdominal pressure. At an intraabdominal pressure of approximately 10 mm Hg, there is an increase in venous return, probably from a reduction in splanchnic sequestration of blood. This is associated with an increase in cardiac output and arterial pressure. Hypovolemia, however, blunts this response. Compression of the inferior vena cava occurs at intraabdominal pressures of approximately 20 mm Hg, and this results in decreased venous return from the lower body, increased renal vascular resistance, decreased renal blood flow, and decreased glomerular filtration. Concomitantly, obese patients manifest a disproportionate increase in systemic vascular resistance caused not only by aortic compression but also by increased secretion of vasopressin. These patients have higher left ventricular end-systolic wall stress before pneumoperitoneum (caused by increased end-systolic left ventricular dimensions) and during pneumoperitoneum. Since higher left ventricular end-systolic wall stress is a determinant of myocardial oxygen demand, more aggressive control of blood pressure (ventricular afterload) may be needed in patients with clinically severe obesity to optimize myocardial oxygen supply and demand. Both pneumoperitoneum and Trendelenburg positioning can reduce femoral venous blood flow, increasing the risk of lower extremity thrombosis. High intraabdominal pressure in conjunction with placement in Trendelenburg position increases intrathoracic pressure and may impede adequate ventilation. Moreover, absorption of CO_2 can worsen hypercarbia and induce respiratory acidosis, thereby increasing pulmonary hypertension. Particular attention should be paid to adequate ventilation during laparoscopic procedures.

Choice of anesthesia. Regional and neuraxial techniques may be used as the primary anesthetic technique or as an adjunct when general anesthesia is necessary. Placement of an epidural or peripheral nerve block can significantly aid in managing postoperative pain and reduce the need for opioids, which decreases the incidence of postoperative respiratory depression.

Regional and neuraxial anesthesia. Regional and neuraxial anesthesia such as spinal anesthesia, epidural anesthesia, and peripheral nerve blocks may be technically difficult in patients

with obesity, since landmarks are obscured by excess adipose tissue. It is estimated that the risk of a failed block is about 1.5 times higher in patients with a BMI above 30 kg/m^2 than in patients with a normal BMI. There is also a higher likelihood of block-related complications. The success rate for blocks is significantly higher when ultrasonographic guidance is used to assist in needle placement. A distinct advantage of regional anesthesia in the patient with obesity is the ability to limit the amount of intraoperative and postoperative opioid use, which thereby limits the risk of respiratory depression and improves patient safety. Interestingly, patients with obesity require as much as 20% less local anesthetic for spinal or epidural anesthesia than nonobese patients, presumably because of fatty infiltration and vascular engorgement from increased intraabdominal pressure, which decreases the volume of the epidural or intrathecal space. It is difficult to reliably predict the sensory level of anesthesia that will be achieved by neuraxial blockade in these patients, and thus lower-than-normal doses should be used and titrated to effect.

General anesthesia. Induction of general anesthesia in the patient with obesity is associated with specific risks. The anesthetic plan, including all risks, benefits, and alternatives to general anesthesia, should be discussed thoroughly with the patient and surgeon before the operation. The possible need for postoperative respiratory support via CPAP, BiPAP, or mechanical ventilation should also be discussed.

Airway management. As mentioned, obesity by itself is not a strong predictor of a difficult airway. However, patients with obesity have higher oxygen requirements and a decreased FRC, which predisposes them to desaturation during induction before the airway is secured. An emergency airway cart that provides access to rescue intubating devices such as a bougie, supraglottic devices, and a flexible fiberoptic bronchoscope (FOB) should be immediately available. Intubating laryngeal mask airways can not only be useful for ventilation in a "cannot intubate, cannot ventilate" scenario but also have the option of facilitating endotracheal intubation. Use of a video laryngoscope may facilitate tracheal intubation by bypassing the upper pharyngeal structures and providing a superior view of the glottis, which may result in less work for visualization. Patients in whom difficult intubation or difficult ventilation is suspected should be considered for an awake fiberoptic intubation. For very high-risk patients with extremely limited pulmonary reserve or abnormal airway anatomy, a surgeon with considerable experience in performing tracheostomy should be immediately available to perform an emergency tracheostomy if needed.

Before intubation, the patient must be properly positioned and preoxygenated. Proper patient positioning is essential to successful intubation of the trachea. Often the large body habitus, particularly a large chest, short neck, or excess neck soft tissue, limits placement of the laryngoscope and glottic exposure. Successful intubation is contingent upon adequate alignment of the oral, pharyngeal, and laryngeal axes, also known as the sniffing position. To achieve this position, the obese patient may require ramping, in which a wedge-shaped device is placed behind the torso and a pillow is placed behind the head to slightly extend the neck so that the sternal notch is in line horizontally with the auditory meatus (Fig. 19.6). Adequate preoxygenation is critically important in patients with obesity, since they have a decreased FRC and higher oxygen consumption. Therefore they experience desaturation much faster than nonobese patients when they are apneic. Studies have shown that when patients undergo 5 minutes of preoxygenation with an Fio_2 of 100% via CPAP at a pressure of 10 cm H_2O, the time that apnea can be tolerated without oxygen desaturation increases by 50%, allowing more time for direct laryngoscopy and tracheal intubation. Techniques involving the use of apneic oxygenation have also been utilized to increase the safe apneic period in patients with obesity.

Management of ventilation. In the obese population, several factors can make controlled mechanical ventilation problematic. Patients with obesity have a decreased FRC and decreased pulmonary oxygen reserves and experience desaturation faster during periods of hypoventilation or apnea than do normal-weight individuals. Positioning for adequate surgical exposure (prone or Trendelenburg position) can worsen ventilation by decreasing chest wall compliance. If pneumoperitoneum is required for surgical exposure (laparoscopic or robotic surgery), ventilation may be impaired by the increased abdominal pressure, which worsens lung compliance. Recruitment maneuvers (e.g., Valsalva) can be used to prevent atelectasis. PEEP improves ventilation/perfusion matching and arterial oxygenation, but at high levels (15–20 cm H_2O) adverse effects on cardiac output and oxygen delivery may offset these benefits. Using pressure-controlled ventilation and increasing the inspiratory/expiratory ratio can help limit peak airway pressure. When spontaneous ventilation is resumed at the conclusion of surgery it is best to maintain the patient in a semiupright

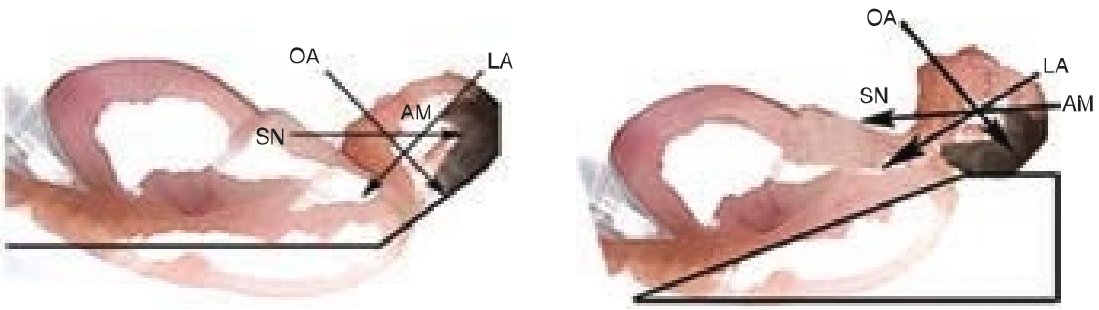

Fig. 19.6 Ramping to achieve proper positioning for airway management. *AM,* Auditory meatus; *LA,* laryngeal axis; *OA,* oral axis; *SN,* sternal notch. (Illustration by Brooke E. Albright, MD)

position and apply pressure support ventilation with PEEP to help reduce the risk of atelectasis. Currently there are no data to support the superiority of one mode of mechanical ventilation for patients with obesity.

Induction and Maintenance of Anesthesia

Any combination of drugs can be used for induction and maintenance of general anesthesia in patients with obesity, but some drugs appear to have a better pharmacokinetic profile than others.

The physiologic changes associated with obesity may lead to alterations in distribution, binding, and elimination of many drugs. The volume of distribution in individuals with obesity may be influenced by a variety of factors, including increased blood volume and cardiac output, decreased total body water (fat contains less water than other tissues), altered protein binding of drugs, and the lipid solubility of the drug being administered. The effect of obesity on protein binding is variable. Despite the occasional presence of liver dysfunction, hepatic clearance of drugs is usually not altered. Heart failure and decreased liver blood flow could slow elimination of drugs that are highly dependent on hepatic clearance. Renal clearance of drugs may increase in obese individuals because of increased renal blood flow and glomerular filtration rate.

The impact of obesity on dosing of injected drugs is difficult to predict. Total blood volume is likely to be increased, which would tend to decrease the plasma concentration achieved following IV injection of a drug. However, fat has relatively low blood flow, so an increased dose of drug calculated based on total body weight could result in an excessive plasma concentration. Cardiac output is increased in the patient with obesity, which affects drug distribution and dilution in the first minute after administration. Since both cardiac output and plasma volume are increased, an initially higher dose of a drug may be required for loading to attain peak plasma concentration. The most clinically useful approach is to calculate the initial dose of drug based on lean body weight rather than total body weight. Lean body weight is total body weight minus fat weight (Fig. 19.7). In clinically severe obesity, lean body weight is increased and accounts for 20% to 40% of excess body weight. Ideal body weight does not take into account the increase in lean body weight in severely obese patients. Therefore lean body weight is more highly correlated with cardiac output and drug clearance and should be used for initial dosing. Subsequent doses of drugs should be based on the pharmacologic response to the initial dose. Repeated injections of a drug, however, can result in cumulative drug effects and prolonged responses, reflecting storage of drugs in fat and subsequent release from this inactive depot into the systemic circulation as the plasma concentration of drug declines. It is important to note that oral absorption of drugs is not influenced by obesity.

An increased incidence of NASH in patients with obesity warrants caution when selecting drugs that have been associated with postoperative liver dysfunction. Awakening of obese patients is more prompt after exposure to desflurane or sevoflurane than after administration of either isoflurane or propofol. The rapid elimination of nitrous oxide is useful, but the frequent need for increased supplemental oxygen limits the usefulness of nitrous oxide in patients with obesity.

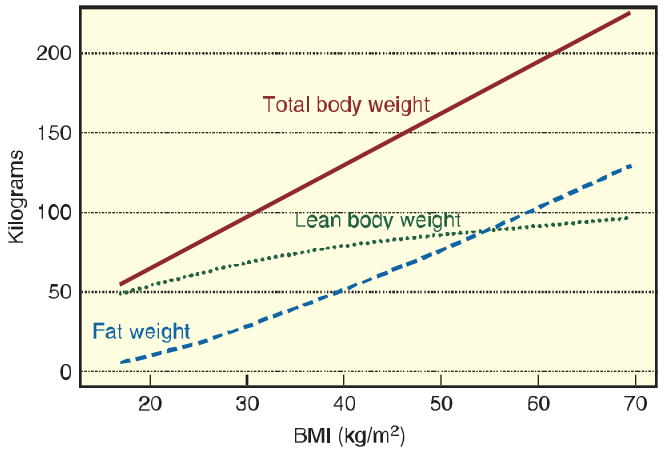

Fig. 19.7 Comparison of total body weight, lean body weight, and fat weight with increasing body mass index *(BMI)* in a male of standard height. (Adapted from Lemmens H. Perioperative pharmacology in morbid obesity. *Curr Opin Anaesthesiol.* 2010;23:485–491.)

Maintenance of anesthesia is best managed with drugs with minimal potential for accumulation in adipose tissue. Propofol, benzodiazepines, cisatracurium, and opioids such as sufentanil and fentanyl are highly lipophilic and accumulate in fatty tissue when administered by infusion over a long period. Usually, highly lipophilic drugs show a significant increase in volume of distribution in obese patients, and dosing of these should be based on total body weight. However, because most of these drugs have the potential to accumulate in adipose tissue over time, a prolonged effect can be seen. An exception is remifentanil. This drug is also highly lipophilic; however, because it is rapidly metabolized by plasma esterases, it has limited potential for accumulation in fat tissue. Ketamine and dexmedetomidine may also be useful anesthetic adjuncts in patients who are susceptible to opioid-induced respiratory depression. Dosing of common anesthetic drugs is presented in Table 19.7.

Administration of hydrophilic substances such as muscle relaxants should be based on lean body weight, since the peak plasma concentrations are independent of the volume of distribution. The large volume of distribution is due to the high ratio of extracellular to intracellular fluid, since the water content of adipose tissue is almost completely extracellular. Because the effect of this increased extracellular fluid on neuromuscular blockade is unclear, it is recommended that neuromuscular blockers be dosed based on lean body weight and that the degree of blockade be carefully monitored with a peripheral nerve stimulator or quantitative monitor.

The pharmacokinetics of succinylcholine are unique. Because the volume of distribution and plasma pseudocholinesterase levels are increased, patients with obesity have larger absolute succinylcholine requirements than normal-weight patients. Therefore, to achieve adequate neuromuscular blockade and facilitate intubation, administration of succinylcholine should be based on total body weight rather than lean body weight.

TABLE 19-7 Recommended Weights for Dosing of Common Anesthetic Drugs in Obese Patients

Total Body Weight	Lean Body Weight
Propofol: loading	Propofol: maintenance
Midazolam (titrate to effect)	Rocuronium
Succinylcholine	Vecuronium
Cisatracurium and atracurium: loading	Cisatracurium and atracurium: maintenance
	Sufentanil
	Remifentanil
	Fentanyl

Recent studies suggest sugammadex (Bridion) may be a better agent than neostigmine in reversing neuromuscular blockade in obese patients, since it has an improved ability to prevent postoperative recurarization. To reverse neuromuscular blockade at less than two twitches on train-of-four (TOF) stimulation, 4 mg/kg is suggested. For patients who have reached the second twitch in response to TOF stimulation, sugammadex should be given at a dose of 2 mg/kg. These dosages are recommended to be based on total body weight per the package insert.

Monitoring. The extent of surgery and concomitant comorbid conditions should be the primary factors that determine the need for and extent of monitoring beyond routine monitors. For surgery performed under local or regional anesthesia with moderate sedation, the ASA Practice Guidelines recommend continuous capnography monitoring to decrease the risk of undetected airway obstruction, which is especially prevalent in the obese population. For surgery performed under general anesthesia, invasive hemodynamic monitoring may be needed in selected patients. The technical difficulty of placing invasive hemodynamic monitors may be increased in this patient population. If noninvasive blood pressure cuffs are used, it is important to fit a correctly sized cuff. If the cuff is too small, blood pressure measurements may be falsely elevated. Alternatives to standard blood pressure cuffs include noninvasive blood pressure monitoring systems that detect blood pressure in the radial artery or finger. An intraarterial catheter should be inserted if noninvasive monitoring is inadequate or if the obese patient has concurrent cardiopulmonary disease. When IV access is problematic, use of ultrasonography to guide the placement of peripheral and/or central lines may increase the success rate and decrease the complication rate associated with these procedures. Transesophageal echocardiography (TEE) and pulmonary artery catheterization can be performed intraoperatively in patients with heart failure, pulmonary hypertension, or other medical conditions that make continuous assessment of volume status or cardiac function necessary. Continuous TEE monitoring allows immediate detection of alterations in cardiac function as well as accurate assessment of volume status to guide fluid management. However, TEE monitoring requires expensive equipment and trained personnel and may not be readily available in all settings.

Fluid management. Calculation of fluid requirements in patients with obesity should be based on lean body weight. Achieving this goal may be very difficult because there is a high association between severe obesity and diastolic dysfunction. In patients with preexisting cardiac disease, large volume loads may not be well tolerated, and development of pulmonary edema is more likely. During laparoscopic surgery, decreased urine output does not necessarily reflect hypovolemia, and liberal fluid administration may have a negative impact on overall outcome.

Emergence. Tracheal extubation is considered when patients with obesity are fully awake and alert and have recovered from the depressant effects of the anesthetics. Any degree of neuromuscular blockade should be reversed. Quantitative demonstration of a TOF of 90% is preferred over use of a peripheral nerve stimulator and visual assessment. Although there are no specific studies to guide the practice of tracheal extubation in obese patients, certain maneuvers can facilitate better respiratory mechanics before extubation. These include placement in the semiupright position (~30 degrees head up), provision of pressure support ventilation with PEEP or CPAP until extubation, oxygen supplementation, and placement of a nasopharyngeal airway to help maintain airway patency. A history of OSA or OHS mandates strict postoperative respiratory monitoring to ensure a patent upper airway and acceptable oxygenation and ventilation. In certain high-risk patients, placement of a tube exchanger before extubation may be prudent.

Postoperative Management

Although episodic arterial hypoxemia may occur at any time from the immediate postoperative period to as late as 2 to 5 days after surgery, no data support routine intensive care unit admission for patients with obesity. Early episodic arterial hypoxemia may be due to perioperative opioid use. The patients at highest risk for developing postoperative hypoxemia are those with a history of OSA. The sitting position is a useful posture to improve arterial oxygenation. Routine administration of oxygen during the postoperative period is controversial because oxygen administration can mask hypoxia and increase the duration of apnea by delaying the arousal effect produced by arterial hypoxemia. Therefore it is preferable to provide supplemental oxygen only if arterial oxygen desaturation occurs. Once the patient's saturation can be maintained at baseline levels at or above 90% on room air with adequate pain control, pulse oximetry may be discontinued.

Before transport from the operating room to the recovery room, the obese patient should be fully awake and alert, sitting in a semiupright position (unless contraindicated), receiving supplemental oxygen, and monitored with pulse oximetry. Verbal contact should be maintained throughout transport to assess wakefulness and adequacy of respiratory effort.

Postoperative analgesia. Because opioid-induced ventilatory depression is a concern, a multimodal approach to postoperative pain control is usually employed. This includes use of techniques that decrease opioid use. Peripheral and central nerve block with continuous infusions of local anesthetic with or without small doses of opioids is an effective method of postoperative analgesia in patients with obesity. Supplementation with NSAIDs, Γ_2-receptor agonists, N-methyl-d-aspartate

(NMDA) receptor antagonists, sodium channel blockers, or other nonopioid analgesics is also recommended, since these drugs do not contribute to postoperative respiratory depression. Ketorolac is an NSAID that has been used successfully to reduce pain in the postoperative period. The principal side effects are GI discomfort and the potential for increased operative site bleeding. Ketorolac is not suitable for use in patients who have undergone RYGB because these patients are at especially high risk for development of GI bleeding. IV acetaminophen can serve as an excellent adjunct to multimodal analgesia in patients with obesity. Dosing of IV acetaminophen for patients who weigh more than 50 kg should be 1 g IV every 6 hours as needed, not to exceed 4 g in 24 hours. Because acetaminophen is metabolized by the liver and excreted in the urine, dosage should be decreased in patients with liver or kidney disease. Both dexmedetomidine, a selective α_2-receptor agonist, and clonidine, a less selective α_2-receptor agonist, have been shown to reduce opioid requirements if administered by continuous infusion in the perioperative period. Ketamine has been shown to enhance the analgesic effects of morphine by inhibiting opioid activation of NMDA receptors. Given in small doses postoperatively, ketamine can decrease pain and increase wakefulness and oxygen saturation. If opioids are required to control postoperative pain, patient-controlled analgesia is a good option. There should not be a basal infusion rate, and dosages of opioids should be based on lean body weight. In addition, local anesthetic wound infiltration or ultrasound-guided transversus abdominis plane (TAP) blocks after laparoscopic bariatric surgery and other abdominal surgery can be used as part of multimodal pain control therapy.

Respiratory and cardiovascular monitoring and management. If a patient is on CPAP or BiPAP at home, this device should be brought in on the day of surgery so that it may be used postoperatively. If the patient has not been diagnosed with sleep apnea preoperatively but experiences frequent airway obstruction and hypoxemic episodes in the recovery room, CPAP or BiPAP can be initiated. There should be strict respiratory monitoring in the first few postoperative hours. Any sign suggestive of respiratory fatigue or cardiovascular instability should be evaluated and treated immediately. If patients with obesity require reintubation, it is best performed in a controlled fashion rather than under emergent conditions.

Discharge to an unmonitored setting. The decision about when to discharge patients to a regular hospital room or to their home can be difficult in some patients with obesity, but it is generally considered safe to discharge a patient to an unmonitored setting (regular hospital bed or home) when pain is adequately controlled without the use of opioids and the patient is no longer at significant risk of postoperative respiratory depression.

Postoperative complications. Postoperative morbidity and mortality rates are higher in patients with obesity than in nonobese patients. This is due primarily to the presence of preexisting medical illnesses. Wound infection is twice as common in patients with obesity. Postoperative mechanical ventilation is often needed in obese patients who have a history of CO_2 retention and have undergone prolonged surgery. The hazards of OSA and OHS may extend several days into the postoperative period. The maximum decrease in Pao_2 typically occurs 2 to 3 days postoperatively. Weaning from mechanical ventilation may be difficult because of an increased work of breathing, decreased lung volumes, and ventilation/perfusion mismatching. The likelihood of deep vein thrombosis and pulmonary embolism is increased, which emphasizes the importance of early postoperative ambulation and the need for prophylactic anticoagulation. Patients with obesity tend not to be able to mobilize their fat stores during critical illness and need to rely on carbohydrates for energy. This increased carbohydrate metabolism raises the respiratory quotient and accelerates protein catabolism. If these patients take nothing by mouth for a prolonged period, a protein malnutrition syndrome may develop.

Enhanced Recovery After Surgery (ERAS) protocols, also known as fast-track protocols, are designed to reduce morbidity after surgery and to decrease hospital length of stay. These protocols were initially introduced in the setting of elective colorectal surgery but have been adapted for other surgeries, including bariatric procedures. Bariatric ERAS protocols consist of several evidence-based perioperative care interventions, such as using laparoscopic techniques, avoiding prophylactic nasogastric tubes and abdominal drains, early postoperative feeding and ambulation, implementation of multimodal analgesia and antiemetic therapy, and thromboprophylaxis. The results of a large case-matched study conducted by Meunier and colleagues using a propensity score analysis suggest that implementation of an ERAS program significantly reduces length of hospital stay without a significant increase in overall morbidity and readmission rates.

The Outpatient With Obesity

Ambulatory surgery has been shown to be safe for many procedures in patients with obesity. Some early studies reported increased mortality and complications that posed a relative contraindication for surgery at an ambulatory surgery center (ASC). Some of the primary challenges included cardiac comorbidity, OSA, and the perception of difficult airway management. Updated recommendations and evidence suggest that many of these patients and procedures can be safely performed at ASCs if certain guidelines are followed. One of the key factors in deciding if a patient is appropriate for the ASC is identification of comorbidities (Table 19.8).

MALNUTRITION AND MICRONUTRIENT ABNORMALITIES

Malnutrition and micronutrient deficiencies are historically regarded as distinct from diseases of overnutrition. Globally, efforts in all major regions to curb the two entities have resulted in a plateau or decline in the prevalence of underweight individuals. Nutritional inadequacy in developed countries is present across all age groups and affects patients from all BMI categories. Identifying and managing these patients have become fundamental components in the perioperative movement toward safe, rapid recovery and in reducing complications, morbidity, and mortality.

TABLE 19.8 Comorbidities of a Patient With Obesity to Consider Prior to Ambulatory Surgery

Concern	Potential Testing	Population	Considerations
hCardiac morbidity	Functional capacity	All patients should be screened for possible cardiomyopathy	Patients with obesity may have difficulty characterizing their functional status, warranting escalation of investigation due to frequent equivocal responses.
	Exercise testing	In patients with equivocal results from functional capacity screening	
	Electrocardiogram	In patients with severe obesity with one other risk factor for heart disease	Signs of right ventricular hypertrophy suggests pulmonary hypertension Left bundle branch block may suggest occult heart disease
	Exercise or pharmacologic stress echo	Patients with ¯3 coronary artery disease (CAD) risk factors	Patients with significant CAD are not appropriate for ambulatory surgery
hPulmonary morbidity	Chest radiograph	If prior testing indicates risk factors	Cardiac chamber enlargement or abnormal pulmonary vascularity may be indicative of undiagnosed heart failure or pulmonary hypertension, respectively.
Obstructive sleep apnea	STOP-Bang Questionnaire	All patients should be screened	Multimodal, opioid-sparing analgesia Early postoperative positive airway pressure device
Difficult airway	Thyromental distance Upper lip bite test Neck circumference Mallampati classification	All patients should be screened	Adjunct airway equipment should be available Consider apneic oxygenation

Malnutrition

Major surgery creates a substantial stress response that results in a significant metabolic burden. Patients with unmet nutritional requirements risk exhausting their physiologic reserve, potentially leading to lean muscle catabolism. This imbalance of protein-energy malnutrition impairs functioning of many homeostatic systems. Biomolecular studies show malnutrition, with or without an inflammatory component, causes mitochondrial malfunction, generation of reactive oxygen species, proinflammatory cytokine release, and impaired leukocyte mobilization. The immune system can be severely affected and may progress to lymph organ atrophy. Over time, lymphopenia may develop in proportion to malnutrition. Consequently, there is a well-documented elevated risk for perioperative infection in malnourishment. Decreased total lymphocyte count has been used intermittently in studies as a malnutrition marker (Γ 1500 cells/mL^3), but there is disagreement in the field on its specificity and sensitivity. Serum albumin, prealbumin, and transferrin levels are commonly used risk tools (Table 19.9).

Undernourished patients experience more surgical complications, longer lengths of stay, higher hospital costs, increased 30-day readmission rates, and greater perioperative and postoperative morbidity and mortality. Malnourishment is present in an estimated one-third of hospitalized cases on admission, but only around 20% of hospitals formalize protocols for screening, diagnosis, and intervention for perioperative malnutrition. Increasing evidence indicates that early standardized care initiated during the preoperative period can create significant improvement in morbidity and complications. Key components of this expanding perioperative care movement are risk identification and subsequent preparation to minimize the effect of surgery. This preprocedure period is referred to as nutritional prehabilitation or nutritional optimization.

TABLE 19.9 Characteristics of Visceral Serum Markers of Malnutrition in Use by Nutritional Indices

Protein	Half-Life	Prognostic Threshold	Nonnutritive Confounding
Albumin	20 days	3.0–3.5 g/dl	g Albumin: infection, burns, fluid overload, liver failure, cancer, nephrotic syndrome
Prealbumin[a]	2 days	15 mg/dl	h Prealbumin: renal dysfunction, corticosteroid treatment g Prealbumin: physiologic stress, infection
Transferrin	10 days	_ 150–200 mg/dL	Altered results: liver disease, fluid status, stress, illness

[a]Prealbumin levels require parallel C-reactive protein 115 mg/L to rule out inflammatory sources of elevated prealbumin.

Screening and Diagnosis

International consensus guidelines on diagnosis and staging of malnutrition are presented in Table 19.10 and recommended diagnosis of malnutrition after positive screening followed by one etiologic and one phenotypic criterion. Five broad clinical criteria indicating malnutrition were determined: (1) nonvolitional weight loss, (2) low BMI, (3) reduced muscle mass, (4) reduced food intake or assimilation, and (5) disease burden/

TABLE 19.10 Global Leadership Initiative on Malnutrition (GLIM) Phenotypic and Etiologic Criteria for the Diagnosis of Malnutrition

PHENOTYPIC CRITERIA[a]			ETIOLOGIC CRITERIA	
Weight Loss (%)	**Low BMI (kg/m²)**	**Reduced Muscle Mass[b]**	**Reduced Food Intake or Assimilation[c,d]**	**Inflammation[e,f,g]**
5% within past 6 months, or 10% beyond 6 months	20 if 70 years, or 22 if 70 years Asians: 18.5 if 70 years, or 20 if 70 years	Reduced by validated body composition measuring techniques[b]	50% of ER 1 week, or any reduction for 2 weeks, or any chronic GI condition that adversely impacts food assimilation or absorption[c,d]	Acute disease/injury[e,f] or chronic disease related[f,g]

BMI, Body mass index; *ER*, energy requirements; *GI*, gastrointestinal.

[a]Requires at least one phenotypic criterion and one etiologic criterion for diagnosis of malnutrition.

[b]For example, fat-free mass index (kg/m²) by dual-energy absorptiometry or corresponding standards using other body composition methods such as bioelectrical impedance analysis, computed tomography, or magnetic resonance imaging. When not available or by regional preference, physical examination or standard anthropometric measures such as midarm muscle or calf circumferences may be used. Thresholds for reduced muscle mass need to be adapted to race (e.g., Asians). Functional assessments such as hand-grip strength may be considered as a supportive measure.

[c]Consider GI symptoms as supportive indicators that can impair food intake or absorption (e.g., dysphagia, nausea, vomiting, diarrhea, constipation, or abdominal pain). Use clinical judgment to discern severity based on the degree to which intake or absorption is impaired. Symptom intensity, frequency, and duration should be noted.

[d]Reduced assimilation of food/nutrients is associated with malabsorptive disorders such as short bowel syndrome, pancreatic insufficiency, and postbariatric surgery. It is also associated with disorders such as esophageal strictures, gastroparesis, and intestinal pseudoobstruction. Malabsorption is a clinical diagnosis manifest as chronic diarrhea or steatorrhea. Malabsorption in those with ostomies is evidenced by elevated volumes of output. Use clinical judgment or additional evaluation to discern severity based on frequency, duration, and quantitation of fecal fat and/or volume of losses.

[e]Acute disease/injury related. Severe inflammation is likely to be associated with major infection, burns, trauma, or closed head injury. Other acute disease/injury-related conditions are likely to be associated with mild to moderate inflammation.

[f]Chronic disease related. Severe inflammation is not generally associated with chronic disease conditions. Chronic or recurrent mild to moderate inflammation is likely to be associated with malignant disease, chronic obstructive pulmonary disease, congestive heart failure, chronic renal disease, or any disease with chronic or recurrent inflammation. Note that transient inflammation of a mild degree does not meet the threshold for this etiologic criterion.

[g]C-reactive protein may be used as a supportive laboratory measure.

Recreated from Jensen GL, Cederholm T, Correia M, et al. GLIM criteria for the diagnosis of malnutrition: A consensus report from the global clinical nutrition community. JPEN J *Parenter Enteral Nutr.* 2019;43(1):32–40. doi:10.1002/jpen.1440

inflammation. The collaborative strongly supported universal screening for malnutrition risk among patients undergoing major surgery. The American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (PQI) developed and validated the perioperative nutrition screen (PONS), which can be easily integrated into the preoperative period (Fig. 19.8).

Early preoperative screening can identify the broader set of patients that includes those who are malnourished as well as those who are less likely to retain a positive energy balance in the perioperative period. The PONS places a participant into the high-risk group based on any positive screen. Additional methods of predicting risk have focused on the likelihood, presence, or adjunct indication of sarcopenia, or very low lean body mass (LBM). Of particular importance is the integration of clinical dieticians into the care team at earlier stages.

Malnourished Obesity, A Double Burden

In the United States, overweight and obesity affect more people than underweight. There is a disproportionate burden placed upon ethnic, racial, and gender minorities. The public health literature finds these groups form communities with poor access to affordable, high-quality nutrition that meets minimum micronutrient recommendations (so-called food deserts). It follows that a significant portion of the excess energy balance in obesity may be sourced from less nutritious, caloric-dense foods, thus facing an underappreciated multiplied risk profile in the perioperative setting.

With expanding access to large data repositories such as the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP), the interaction of obesity and malnutrition is becoming evident. Several studies of orthopedic procedures used these databases to evaluate the coexistence of obesity and malnutrition in relation to arthroplasties. The connection between the two may be indicated by the observation of significantly higher rates of hypoalbuminemia in patients with obesity compared to patients with a normal BMI during the preoperative period. Fieber and colleagues published findings of a 106,000-patient cohort and found that 6% of patients undergoing bariatric surgery were hypoalbuminemic with an increased risk of complications. They additionally found that in those patients with hypoalbuminemia, as high as 3.00 to 3.49 g/dL, weight loss above 10% of the starting body weight was synergistic with the risk caused by hypoalbuminemia in causing death or serious morbidity after surgery. This emphasizes the importance of incorporating all patients, regardless of BMI, into a preoperative care pathway that includes screening for malnutrition.

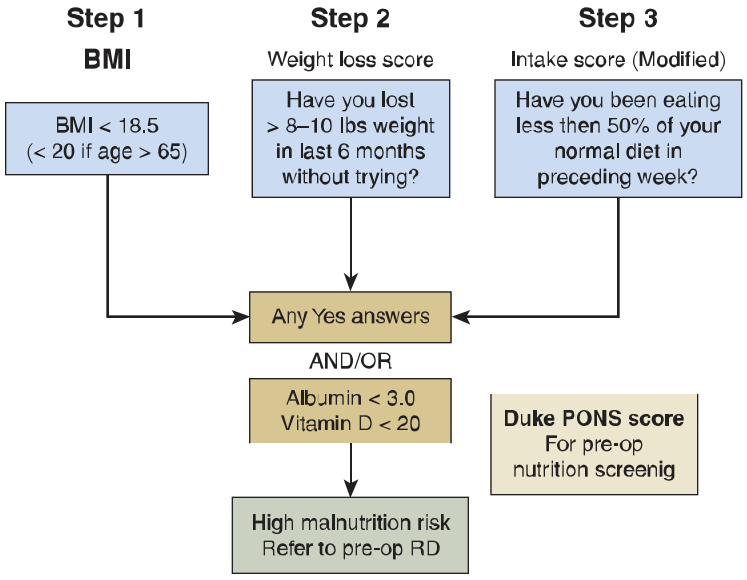

Fig. 19.8 Modified perioperative nutrition screen (PONS) for identifying patients who will likely benefit from thorough nutritional assessment and intervention before a major surgery.

Micronutrient Deficiency

Enteral Nutrition

When the GI tract is functioning, enteral nutrition can be provided by means of a nasogastric tube or gastrostomy tube feedings or by postpyloric methods such as nasojejunal tubes or feeding jejunostomy tubes. Continuous infusion is the usual method for administering enteral feedings. The rate, composition, and volume of the feeding solution are individualized based on laboratory data and patient circumstances.

The question of when to stop postpyloric feedings in patients with upcoming surgery is unclear. However, nasogastric and orogastric feedings should be stopped 8 hours before surgery, and the stomach should be suctioned before the patient is taken to the operating room. Complications of enteral feedings are infrequent but include hyperglycemia, causing osmotic diuresis and hypovolemia. Exogenous insulin administration may be a consideration if blood glucose concentrations are elevated. The osmolarity of elemental diets (i.e., tube feedings) is high at 550 to 850 mOsm/L; they often cause diarrhea.

Parenteral Nutrition

Parenteral nutrition is indicated when the GI tract is not functioning. Peripheral parenteral nutrition using an isotonic solution delivered through a peripheral vein is limited by osmolality and volume constraints. It may be useful as a supplement to oral intake or when the anticipated need for nutritional support is less than 14 days. Total parenteral nutrition (TPN) is used when the daily caloric requirements exceed 2000 kcal or prolonged nutritional support is required. In such cases, a catheter is inserted into a central vein to permit infusion of hypertonic solutions in a daily volume of approximately 40 mL/kg.

Potential complications of TPN are numerous (Table 19.11). Blood glucose concentrations must be monitored because hyperglycemia is very common and may require treatment with exogenous insulin. Hypoglycemia may occur if the TPN infusion is abruptly discontinued, since increased circulating endogenous concentrations of insulin may persist. Hyperchloremic metabolic acidosis may occur because of the liberation of hydrochloric acid during the metabolism of amino acids present in most parenteral nutrition solutions. Parenteral feeding of patients with compromised cardiac function is associated with the risk of congestive heart failure from fluid overload. Increased production of CO_2 resulting from metabolism of large amounts of glucose may result in the need to initiate mechanical ventilation or failure to wean from mechanical ventilation.

TABLE 19.11 Complications of Total and Peripheral Parenteral Nutrition

Hypokalemia
Hypophosphatemia
Bacterial translocation from the gastrointestinal tract
Renal dysfunction
Nonketotic hyperosmolar hyperglycemic coma
Hypomagnesemia
Venous thrombosis
Osteopenia
Hyperchloremic metabolic acidosis
Hypocalcemia
Infection, sepsis
Elevated liver enzyme levels
Fluid overload
Refeeding syndrome

Vitamin Deficiencies

Table 19.12 lists the more common vitamin deficiencies.

TABLE 19.12 Vitamin Deficiencies

Vitamin Deficiency	Causes of Deficiency	Signs of Deficiency
Thiamine (B_1) (beriberi)	Chronic alcoholism, which results in decreased intake of thiamine	Low systemic vascular resistance; high cardiac output; polyneuropathy (demyelination, sensory deficit, paresthesia); exaggerated blood pressure response to hemorrhage, change in body position, positive pressure ventilation
Riboflavin (B_2)	Almost always caused by dietary deficiency, photodegradation of milk or other dairy products	Magenta tongue, angular stomatitis, seborrhea, cheilosis
Niacin (B_3)	Carcinoid tumor; niacin (nicotinic acid) is synthesized from tryptophan; in carcinoid tumor, tryptophan is used to form serotonin instead of niacin, which makes patients with these tumors more susceptible to deficiency	Mental confusion, irritability, peripheral neuropathy, achlorhydria, diarrhea, vesicular dermatitis, stomatitis, glossitis, urethritis, excessive salivation
Pyridoxine (B_6)	Alcoholism, isoniazid therapy	Seborrhea, glossitis, convulsions, neuropathy, depression, confusion, microcytic anemia
Folate (B_9)	Alcoholism; therapy with sulfasalazine, pyrimethamine, or triamterene	Megaloblastic anemia, atrophic glossitis, depression, increased homocysteine level
Cyanocobalamin (B_{12})	Gastric atrophy (pernicious anemia), terminal ileal disease, strict vegetarianism	Megaloblastic anemia, loss of vibratory and positional sense, abnormal gait, dementia, impotence, loss of bladder and bowel control, increased levels of homocysteine and methylmalonic acid
Biotin	Ingestion of raw egg whites (contain the protein avidin, which strongly binds the vitamin and reduces its bioavailability)	Mental changes (depression, hallucinations), paresthesias; a scaling rash around the eyes, nose, and mouth; alopecia
Ascorbic acid (C)	Smoking, alcoholism	Capillary fragility, petechial hemorrhage, joint and skeletal muscle hemorrhage, poor wound healing, catabolic state, loosened teeth and gangrenous alveolar margins, low potassium and iron levels
A	Dietary lack of leafy vegetables and animal liver, malabsorption	Loss of night vision, conjunctival drying, corneal destruction, anemia
D (rickets)	Limited sun exposure, inflammatory bowel disease and other fat malabsorption syndromes	Thoracic kyphosis, which can lead to hypoventilation; parathyroid hormone activity, which leads to increased osteoclastic activity and bone resorption
E	Occurs only with fat malabsorption or genetic abnormalities of vitamin E metabolism or transport	Peripheral neuropathy, spinocerebellar ataxia, skeletal muscle atrophy, retinopathy
K	Prolonged antibiotic therapy that eliminates the intestinal bacteria that form the vitamin; failure of fat absorption	Bleeding

KEY POINTS

- Obesity is the most prevalent nutritional disease and is considered one of the most preventable causes of illness worldwide.
- Obesity leads to an increased incidence of glucose intolerance, diabetes mellitus, systemic hypertension, coronary artery diseases, heart failure, cancer, and thromboembolic events. A waist:hip ratio higher than 1.0 in men and 0.8 in women is a strong predictor of ischemic heart disease, stroke, diabetes, and death.
- Compared with the normal-weight population, the risk of premature death is doubled and the risk of death resulting from cardiovascular disease is increased fivefold in the obese population.
- Bariatric surgery results in significant and sustained weight loss as well as a reduction in obesity-related comorbid conditions. It is associated with a survival benefit.
- Regional anesthesia may be more technically challenging in patients with obesity. Use of ultrasonography significantly increases the success rate of regional anesthesia in this population.
- Airway management can be a challenge associated with general anesthesia in patients with obesity. Mask ventilation can be difficult owing to the presence of increased soft tissue in the head, neck, and chest. Proper positioning, apneic oxygenation, and the use of video laryngoscopy can improve the safety and efficacy of tracheal intubation.
- In the obese population, pneumoperitoneum during laparoscopic surgery may have significant deleterious effects on cardiopulmonary performance, including decreased cardiac output and stroke volume, increased systemic vascular resistance, and decreased functional residual capacity.
- The impact of obesity on appropriate dosing of intravenous anesthetic drugs is difficult to predict. A useful clinical approach is to calculate the initial dose of drug based on lean body weight rather than total body weight.
- A multimodal approach to postoperative pain control is usually employed to decrease the risk of opioid-induced respiratory depression.
- Current guidelines recommend screening and monitoring for signs of malnutrition in all patients admitted to the hospital. In situations in which oral intake is prohibited and treatment of malnutrition is needed, supplementation can be provided by initiating enteral or parenteral nutrition.

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20

Fluid, Electrolyte, and Acid-Base Disorders

Robert B. Schonberger

OUTLINE

Alterations of water, osmolal, and electrolyte content and distribution as well as acid-base disturbances are common in the perioperative period and rarely happen in isolation because they are inherently interrelated. They both affect and are affected by the function and stability of several organ systems. Central nervous system (CNS) impairment, cardiac dysfunction, and neuromuscular changes are especially common in the presence of water, osmolal, electrolyte, and acid-base disturbances. Several perioperative events can exacerbate such alterations (Table 20.1). Management of patients with these disturbances is based on an assessment of the cause and severity of the condition, an understanding of the interrelationships among these disturbances, and an awareness of the patient's comorbid conditions.

ABNORMALITIES OF WATER, OSMOLALITY, AND ELECTROLYTES

Water and Osmolal Homeostasis

In the nonobese adult, total body water comprises approximately 60% of body weight (obesity decreases this proportion). Body water is divided into intracellular fluid (ICF) and extracellular fluid (ECF) compartments according to the location of the water relative to cell membranes (Fig. 20.1). ECF consists primarily of an interstitial compartment (three-fourths of ECF) and an intravascular plasma compartment (one-fourth of ECF). Water shifts between compartments according to the balance of hydrostatic and oncotic pressure across membranes, and thus water homeostasis relies on the maintenance of osmolality within a narrow physiologic range. The integrity of living cells depends on preservation of water homeostasis as well as on the energy-intensive maintenance of intracellular and extracellular concentrations of ions termed *electrolytes*. These electrolytes, in addition to being a major determinant of both osmolality and acid-base balance, are responsible for electrical potentials across cell membranes. Changes in electrolyte homeostasis especially impact excitable cells in the CNS and musculature that rely on action potentials for rapid and organized transfer of information.

Water and osmolal homeostasis are predominantly mediated by osmolality-sensing neurons located in the anterior hypothalamus. In response to osmolal elevations, these neurons stimulate thirst and cause pituitary release of vasopressin (antidiuretic hormone). Vasopressin is stored as granules in the posterior pituitary and acts through G protein–coupled receptors in the collecting ducts of the kidney to cause water retention, which in turn decreases serum osmolality. Vasopressin receptors are also present in other tissues and, most noticeably for the anesthesiologist, are present in high density on vascular smooth muscle cells where they induce vasoconstriction. As a major site of vasopressin effects, the kidney is responsible for maintaining water homeostasis by excreting urine with large

TABLE 20.1 Common Causes of Water, Osmolal, Electrolyte, and Acid-Base Disturbances During the Perioperative Period

- Disease states
  - Endocrinopathies
  - Nephropathies
  - Gastroenteropathies
- Drug therapy
  - Diuretics
  - Corticosteroids
- Nasogastric suction
- Surgery
  - Transurethral resection of the prostate
  - Translocation of body water due to tissue trauma
  - Resection of portions of the gastrointestinal tract
- Management of anesthesia
  - Intravenous fluid administration
  - Alveolar ventilation
  - Hypothermia

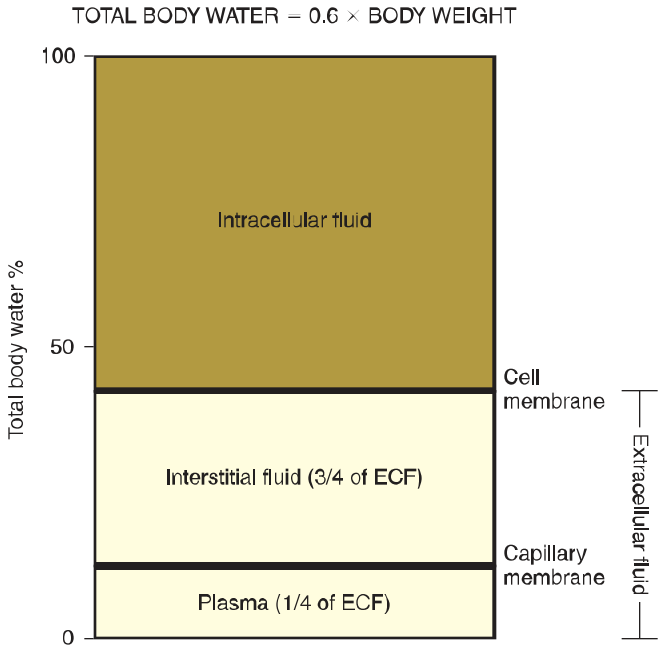

Fig. 20.1 Total body water (≈ 60% of total body weight) is designated as intracellular fluid (ICF) or extracellular fluid (ECF) depending on the location of the water relative to cell membranes. ECF is further divided into interstitial and plasma compartments depending on its location relative to vascular walls. Two-thirds of total body water is ICF. Of ECF, 75% is interstitial, 25% is intravascular.

variations in total osmolality. Under normal circumstances, serum osmolality is tightly regulated by thirst and renal control of water excretion. The normal range of serum osmolality is 280 to 290 mOsm/kg.

The osmolality of serum represents the total number of osmotically active particles (i.e., solutes) per kilogram of solvent. When osmolality is assessed, a shorthand indirect measurement of expected serum osmolality can easily be calculated as 2[Na] [Glucose]/18 + [Blood urea nitrogen (BUN)]/2.8, and this calculated value should always be compared with direct laboratory-measured actual osmolality. A significant difference in these values (known as an osmolal gap) should alert the clinician to the presence of unmeasured osmotically active particles. Increases in serum osmolality may be encountered as a result of free water depletion (e.g., dehydration or diabetes insipidus) or the presence of additional solutes (most commonly from ingestion of ethanol or other toxins, hyperglycemia, or iatrogenic administration of osmolal loads such as mannitol or glycine). Perioperative attempts to induce fluid shifts by deliberate administration of osmolal loads should take into consideration the patient's preexisting serum osmolality to avoid extreme increases in serum osmolality (> 320 mOsm/kg). Mannitol should not be administered to an intoxicated patient with elevated intracranial pressure, for example, without prior consideration of the preexisting effects of ethanol molecules and water diuresis on the osmolal state of the patient.

Although vasopressin is predominantly secreted in response to increased osmolality, its release is also stimulated by large isoosmolar decreases in effective circulating volume. In addition, the pain and stress of the perioperative period are upregulators of vasopressin release, and the stress response to critical illness can include water retention, oliguria, and dilutional hyponatremia (Table 20.2).

TABLE 20.2 Factors and Drugs Affecting Vasopressin Secretion

Stimulation of Vasopressin Release	Inhibition of Vasopressin Release	Drugs That Stimulate Vasopressin Release and/or Potentiate Renal Action of Vasopressin
Contracted ECF volume	Expanded ECF volume	Amitriptyline
Hypernatremia	Hyponatremia	Barbiturates
Hypotension	Hypertension	Carbamazepine
Nausea and vomiting		Chlorpropamide
Congestive heart failure		Clofibrate
Cirrhosis		Morphine
Hypothyroidism		Nicotine
Angiotensin II		Phenothiazines
Catecholamines		Selective serotonin reuptake inhibitors
Histamine		
Bradykinin		

ECF, Extracellular fluid.

In contrast to osmolal homeostasis, the homeostatic response to isotonic changes in total body water relies on juxtaglomerular sensation of changes in effective circulating volume and consequent changes in kidney renin excretion. Renin converts angiotensinogen into angiotensin I, which is converted to angiotensin II in the lung. Angiotensin II induces adrenal release of aldosterone, which promotes sodium reabsorption and potassium loss in the distal tubules and leads to increases in water resorption. Elevations in circulating volume also cause increased release of natriuretic peptides that promote a return to water homeostasis.

Fluid resuscitation in patients with hypovolemia necessitates consideration of the cause and severity of the hypovolemia and patient comorbid conditions. Crystalloid administration should take into consideration a patient's electrolyte and acid-base balance as well as concerns regarding the acute cardiovascular effects of additional volume and the neurologic effects of changes in volume, osmolality, and glucose levels.

Regarding the choice of crystalloid solution in the absence of compelling physiologic patient needs, a recent large pragmatic clinical trial in critically ill intensive care unit (ICU) adults demonstrated a lower rate of the composite outcome of death, new renal-replacement therapy, or persistent renal dysfunction when using balanced crystalloid as opposed to normal saline.

Infusion of colloids, including blood products, should be done in the context of appropriate goals for hemoglobin concentration, platelet numbers, and coagulation factors and must take into consideration the course of any ongoing blood loss and the health status of the patient. Synthetic volume expanders have been advocated to achieve volume expansion with reduced tissue edema compared to crystalloids. However, there is no good evidence that they provide advantages in outcomes in comparison to appropriately balanced crystalloid solutions. Indeed, some have been associated with increased bleeding and a higher incidence of renal dysfunction in addition to their increased cost in comparison with crystalloids.

DISORDERS OF SODIUM

As the ion with the highest concentration in the ECF, sodium contributes most of the effective osmoles to serum. This underlying connection between serum sodium concentration and osmolality is critical for understanding disorders of sodium homeostasis. Under normal circumstances, serum sodium concentration is maintained between 136 and 145 mmol/L, primarily by the action of vasopressin on water and osmolal homeostasis.

Variations in measured sodium concentration frequently occur along with derangements in total body water. Assessment and treatment of changes in sodium concentration must therefore consider osmolality as well as the total body water of the patient. Total body water can be increased, normal, or decreased in the context of derangements in sodium concentration, and the cause and treatment of serum sodium disorders depend on the osmolality and volume status of the patient.

Hyponatremia

Hyponatremia commonly exists in concert with hypoosmolality when water retention or water intake exceeds renal excretion of dilute urine. Hyponatremia exists in approximately 15% of hospitalized patients, most commonly as a dilutional effect in the setting of increased vasopressin release. In the outpatient setting, hyponatremia is more likely to be a result of chronic disease, and in heart failure it has been shown to be an independent predictor of 30-day and 1-year mortality.

Signs and Symptoms

The signs and symptoms of hyponatremia depend on the rate at which the hyponatremia has developed and are less pronounced in chronic cases. In addition, younger patients appear to tolerate a decrease in serum sodium better than elderly patients.

Anorexia, nausea, and general malaise may occur early, but CNS signs and symptoms predominate later in the course and in acutely deteriorating cases of hyponatremia (Table 20.3). As mentioned, hyponatremia usually occurs along with extracellular hypotonicity. The associated osmolal gradient allows water to move into brain cells, which results in cerebral edema and increased intracranial pressure. Brain cells may compensate over time by lowering intracellular osmolality by movement of potassium and organic solutes out of brain cells. This reduces water movement into the intracellular space. However, when adaptive mechanisms fail or hyponatremia progresses, CNS dysfunction can manifest as a change in sensorium, seizures, brain herniation, or death.

Diagnosis

Although hyponatremia usually coexists with hypoosmolality, osmolality should be measured in all cases of hyponatremia, particularly to avoid overlooking a pathologic hyperosmolar state caused by dangerous concentrations of glucose or exogenous toxins, or iatrogenic infusions of osmolal loads.

In such hyperosmolal situations, plasma volume expands as interstitial and intracellular water migrate into the intravascular space, causing a relative dilution of the serum sodium concentration without a reduction in the amount of total body sodium. Total body water may be increased, unchanged, or decreased depending on the competing effects of water administered with the osmolal load and the likely presence of an osmotic diuresis.

In patients with normal osmolality, a pseudohyponatremia can be seen as a laboratory artifact in cases of severe hyperlipidemia or hyperproteinemia when plasma volume is increased in the presence of normal serum sodium concentrations. Measuring sodium

TABLE 20.3 Symptoms and Signs of Hyponatremia

Symptoms	Signs
Anorexia	Abnormal sensorium
Nausea	Disorientation, agitation
Lethargy	Cheyne-Stokes breathing
Apathy	Hypothermia
Muscle cramps	Pathologic reflexes
	Pseudobulbar palsy
	Seizures
	Coma
	Death

concentrations in serum rather than in plasma avoids this misinterpretation of laboratory data.

Once the two situations of hyperosmolality and normal osmolality have been excluded, the approach to the diagnosis of hypoosmolal hyponatremia includes evaluation of the severity of the electrolyte derangement and the underlying volume status of the patient. Hypervolemic hyponatremia suggests the possibility of renal failure, congestive heart failure, or a hypoalbuminemic state such as cirrhosis or nephrotic syndrome. Euvolemic hyponatremia is commonly seen in the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or in situations of habitual ingestion of hypotonic solutions (e.g., water), as seen in psychogenic polydipsia. Hypovolemic hyponatremia should prompt an investigation into the source of free water loss. This free water loss may be from renal losses (e.g., from diuretics, mineralocorticoid deficiency, or other salt-wasting nephropathy) or extrarenal losses (e.g., gastrointestinal [GI] losses or third spacing).

Often the clinical context of hyponatremia offers the principal clue to its cause. For example, massive absorption of irrigating solutions that do not contain sodium, such as during transurethral resection of the prostate, is a relatively common cause of intraoperative hyponatremia. When the clinical context does not lead to a diagnosis, urinary sodium concentration measured from a spot urine sample can help further differentiate among the various causes of hyponatremia (Fig. 20.2).

Treatment

Treatment of hypotonic hyponatremia will depend on the volume status of the patient. In hypovolemic hyponatremia, appropriate volume resuscitation should be pursued, usually with normal saline. If renal sodium losses are suspected, mineralocorticoid deficiency and the possibility of adrenal insufficiency should not be overlooked. Cases of massive third spacing, such as often accompany pancreatitis or burns, require tailored resuscitation based on the totality of electrolyte and hematologic derangements.

In euvolemic or hypervolemic patients, treatment involves withholding free water and encouraging free water excretion with a loop diuretic. Administration of saline is necessary only if significant symptoms are present. In these as in all cases of hyponatremia, the rate of correction depends on whether the development of hyponatremia was acute (i.e., occurred in ∃48 hours) or chronic.

Acute symptomatic hyponatremia must be treated promptly. Solute-free fluids are withheld, and hypertonic saline (3% NaCl) and furosemide are administered to enhance renal excretion of free water. Serum electrolyte levels should be checked frequently

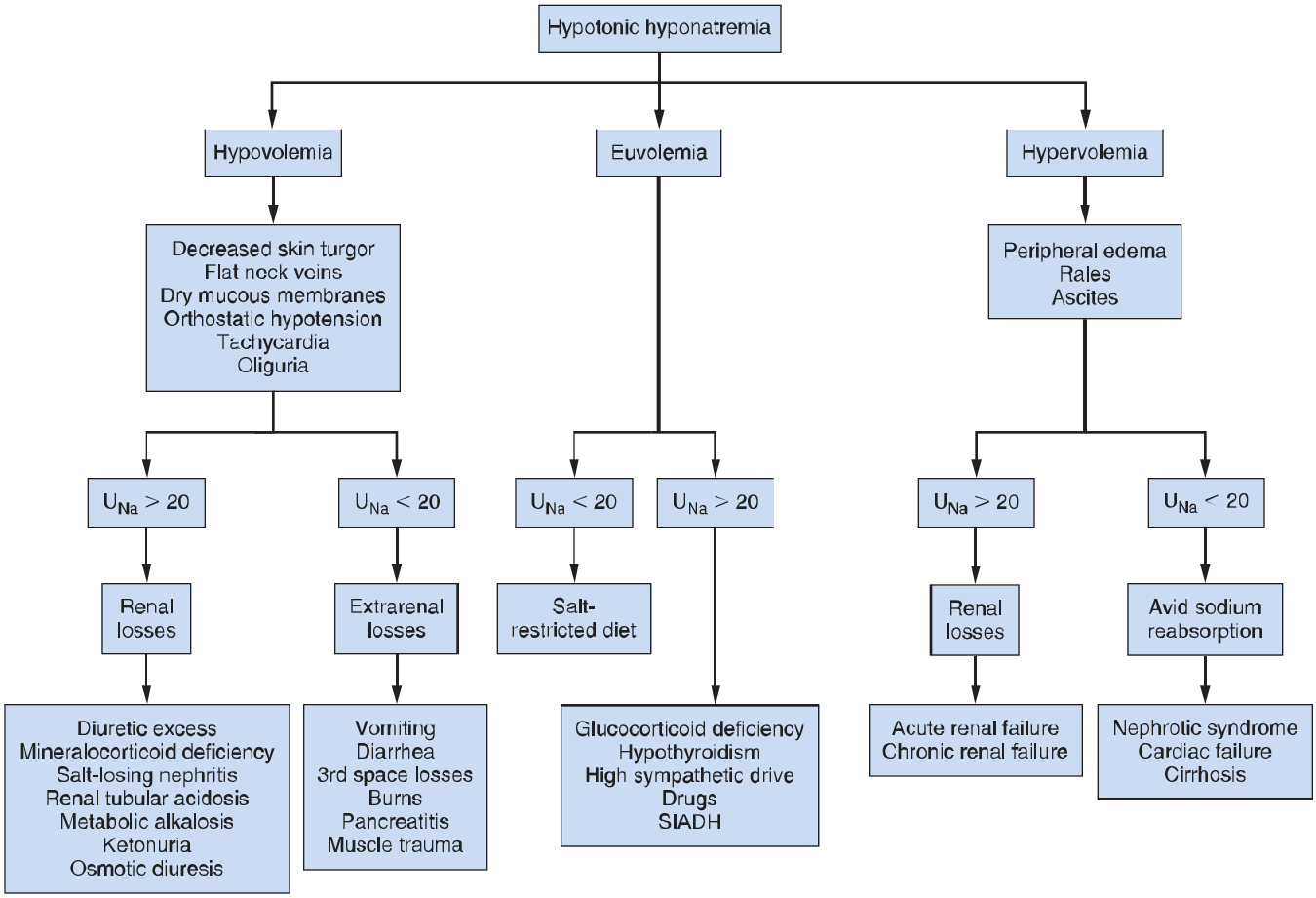

Fig. 20.2 Diagnostic algorithm for hypotonic hyponatremia. *SIADH*, Syndrome of inappropriate antidiuretic hormone secretion; U_{Na}, urinary sodium concentration (mEq/L) in a spot urine sample. (Adapted from Schrier RW. *Manual of Nephrology*. ed. 6. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)

and this treatment continued until symptoms disappear, which will likely occur before the serum sodium concentration returns to normal.

Chronic symptomatic hyponatremia should be corrected slowly to avoid the risk of osmotic demyelination. During the development of chronic hyponatremia, brain cells retain their normal intracellular volume as the serum sodium decreases by exporting effective osmoles. Approximately half of these effective osmoles are potassium ions and anions, and the remainder are small organic compounds. While hyponatremia is being corrected, brain cells must reaccumulate these effective osmoles or water will move out of the cells into the now relatively hypertonic ECF, causing cell shrinkage. Such shrinkage can trigger central pontine myelinolysis, which can result in quadriplegia, seizures, coma, and death. The risk of osmotic demyelination is higher in patients who are malnourished or potassium depleted. Guidelines for correction of chronic symptomatic hyponatremia call for an initial correction in serum sodium concentration of approximately 10 mEq/L. Thereafter, correction should not exceed 1 to 1.5 mEq/L/hr or a daily maximum increase of 12 mEq/L.

Treatment of chronic asymptomatic hyponatremia should consider the underlying cause of the electrolyte disturbance. Appropriate sodium intake and volume restriction are often the cornerstones of treatment. Patients with hypervolemic hyponatremia due to congestive heart failure respond very well to the combination of an angiotensin-converting enzyme inhibitor and a loop diuretic.

Management of Anesthesia

If at all possible, significant hyponatremia, especially if symptomatic, should be corrected before surgery. If the surgery is urgent, appropriate corrective treatment should continue throughout the surgery and into the postoperative period. Frequent measurement of serum sodium concentration is necessary to avoid overly rapid correction of hyponatremia with resultant osmotic demyelination or overcorrection resulting in hypernatremia. If the treatment of hyponatremia includes hypertonic sodium infusion during surgery, it should be infused via a pump while losses caused by the surgery are replaced with standard crystalloid or colloid solutions as required. Treatment of the underlying cause of the hyponatremia should also continue throughout the perioperative period.

Induction and maintenance of anesthesia in patients with hypovolemic hyponatremia are fraught with the risk of hypotension. In addition to fluid therapy, vasopressors and/or inotropes may be required to treat the hypotension, and these should be available before the start of induction. Hypervolemic hyponatremic patients, particularly those with heart failure, may benefit from invasive hemodynamic monitoring to assess cardiac function and guide fluid therapy.

Transurethral Resection of the Prostate (TURP) Syndrome

Benign prostatic hyperplasia is often treated surgically by TURP. This procedure involves resection via a cystoscope, with continuous irrigation of the bladder to aid visualization of the surgical field and removal of blood and resected material. The irrigating fluid is usually a nearly isotonic nonelectrolyte fluid containing glycine or a mixture of sorbitol and mannitol. This irrigating fluid can be absorbed rapidly via open venous sinuses in the prostate gland and can cause volume overload and hyponatremia. The constellation of findings associated with absorption of bladder irrigation solution is known as TURP syndrome. This syndrome is more likely to occur when resection is prolonged (> 1 hour), when the irrigating fluid is suspended more than 40 cm above the operative field, when hypotonic irrigation fluid is used, and when the pressure in the bladder is allowed to increase above 15 cm H_2O. TURP syndrome (Table 20.4) manifests principally with cardiovascular signs of fluid overload and neurologic signs and symptoms of hyponatremia. Use of hypotonic irrigating solutions can also induce hemolysis because red blood cells encounter a significant influx of free water from hypotonic ECF. Hypertension and pulmonary edema are common. If a glycine irrigant is used, transient blindness can occur that is thought to result from the inhibitory neurotransmitter effects of glycine on several populations of retinal ganglion cells. Glycine breaks down into glyoxylic acid and ammonia, and excessive ammonia levels are themselves known to cause encephalopathy.

TABLE 20.4 Signs and Symptoms of TURP Syndrome

System	Signs and Symptoms	Cause
Cardiovascular	Hypertension, reflex bradycardia, pulmonary edema, cardiovascular collapse	Rapid fluid absorption (reflex bradycardia may be secondary to hypertension or increased ICP)
	Hypotension	Third spacing secondary to hyponatremia and hypoosmolality; cardiovascular collapse
	ECG changes (wide QRS, elevated ST segments, ventricular dysrhythmias)	Hyponatremia
Respiratory	Tachypnea, oxygen desaturation, Cheyne-Stokes breathing	Pulmonary edema
Neurologic	Nausea, restlessness, visual disturbances, confusion, somnolence, seizures, coma, death	Hyponatremia and hypoosmolality causing cerebral edema and increased ICP, hyperglycinemia, hyperammonemia
Hematologic	Disseminated intravascular hemolysis	Hyponatremia and hypoosmolality
Renal	Renal failure	Hypotension, hyperoxaluria (oxalate is a metabolite of glycine)
Metabolic	Acidosis	Deamination of glycine to glyoxylic acid and ammonia

ECG, Electrocardiogram; *ICP*, intracranial pressure; *TURP*, transurethral resection of the prostate.

Monitoring for the development of TURP syndrome includes direct neurologic assessment in patients under regional anesthesia and measurement of hemodynamics, serum sodium concentration, and osmolality in patients under general anesthesia. Treatment consists of terminating the surgical procedure so no more fluid is absorbed, administration of loop diuretics if needed for relief of cardiovascular symptoms, and administration of hypertonic saline if severe neurologic symptoms or signs are present or the serum sodium concentration is less than 120 mEq/L.

Hypernatremia

Hypernatremia is defined as a serum sodium concentration above 145 mEq/L. It is much less common than hyponatremia because the vasopressin-driven thirst mechanism is very effective in responding to the hypertonic state of hypernatremia. Even in patients with renal disorders of sodium retention or severe water loss, patients will regulate their serum sodium concentration close to or within the normal range if they have access to water. Therefore hypernatremia is much more likely to be seen in the very young, the elderly, and those people who are debilitated, have altered mental status, or are unconscious.

In the perioperative setting, hypernatremia is most likely a result of iatrogenic overcorrection of hyponatremia or treatment of acidemia with sodium bicarbonate. Free water losses from diabetes insipidus and extrarenal GI losses may also lead to hypernatremia. Because sodium is the major contributor to ECF osmolality, hypernatremia induces the movement of water across cell membranes into the ECF. Hypernatremia and the associated hyperosmolality will always lead to cellular dehydration and shrinkage.

Signs and Symptoms

Signs and symptoms of hypernatremia can vary from mild to life threatening (Table 20.5). The earliest signs and symptoms include restlessness, irritability, and lethargy. As hypernatremia progresses, muscular twitching, hyperreflexia, tremors, and ataxia may develop. The signs and symptoms progress as the osmolality increases above 325 mOsm/kg. Muscle spasticity, seizures, and death may ensue. The very young, the very old, and those with preexisting CNS disease exhibit more severe symptoms at any given serum sodium concentration or degree of hyperosmolality.

The most prominent abnormalities in hypernatremia are neurologic. Dehydration of brain cells occurs as water shifts out of the cells into the hypertonic interstitium. Capillary and venous congestion as well as venous sinus thrombosis have all been reported. As the brain cells shrink, cerebral blood vessels may stretch and tear, which results in intracranial hemorrhage.

Usually the signs and symptoms are more severe when hypernatremia is acute rather than chronic and when excessive elevations in serum sodium levels are present. Mortality rates of up to 75% have been reported in adults with severe acute hypernatremia (serum sodium concentration ¯ 160 mEq/L), and survivors of severe acute hypernatremia often have permanent neurologic deficits. During the development of chronic hypernatremia, brain cells generate idiogenic osmoles that restore intracellular water in spite of the ongoing hypernatremia and protect against brain cell dehydration. If chronic hypernatremia is corrected too rapidly, these idiogenic osmoles predispose to the development of cerebral edema.

TABLE 20.5 Symptoms and Signs of Hypernatremia

Symptoms	Signs
Polyuria	Muscle twitching
Polydipsia	Hyperreflexia
Orthostasis	Tremor
Restlessness	Ataxia
Irritability	Muscle spasticity
Lethargy	Focal and generalized seizures
	Death

Diagnosis

The diagnosis and treatment of hypernatremia should focus on the severity of the derangement and the volume status of the patient. The presence of hypervolemia, euvolemia, or hypovolemia dictates the appropriate diagnostic and treatment modalities (Fig. 20.3).

In hypovolemic hypernatremia the patient has lost more water than sodium via renal or extrarenal routes. This may occur as a result of excessive diuresis, GI losses, or insensible fluid losses from burns or sweating.

Patients with hypervolemic hypernatremia will show signs of ECF volume expansion, such as jugular venous distention, peripheral edema, and pulmonary congestion. The differential diagnosis includes a history of hypertonic fluid administration, oral intake of salt tablets, and endocrine abnormalities marked by excessive aldosterone secretion.

Euvolemic and hypovolemic hypernatremia occur secondary to water loss without salt loss and may be seen with either extrarenal pathologic conditions (e.g., GI tract losses or insensible losses from burns or sweating) or from renal losses (e.g., diabetes insipidus, loop diuretics, or osmotic diuresis).

As with hyponatremia, testing of a spot urine sample for sodium concentration and osmolality can help distinguish among the causes of hypernatremia (see Fig. 20.3).

Treatment

Treatment is determined by how severe the hypernatremia is, how rapidly it developed, and whether the ECF volume is increased or decreased.

In hypovolemic hypernatremia the water deficit is replenished with normal saline or a balanced electrolyte solution until the patient is euvolemic, and then the plasma osmolality is corrected with hypotonic saline or 5% dextrose solution.

In patients with hypervolemic hypernatremia the primary treatment is diuresis with a loop diuretic unless the cause is renal failure, in which case hemofiltration or hemodialysis may be needed.

Patients with euvolemic hypernatremia require water replacement either orally or with 5% dextrose intravenously. Treatment of diabetes insipidus depends on whether there is a

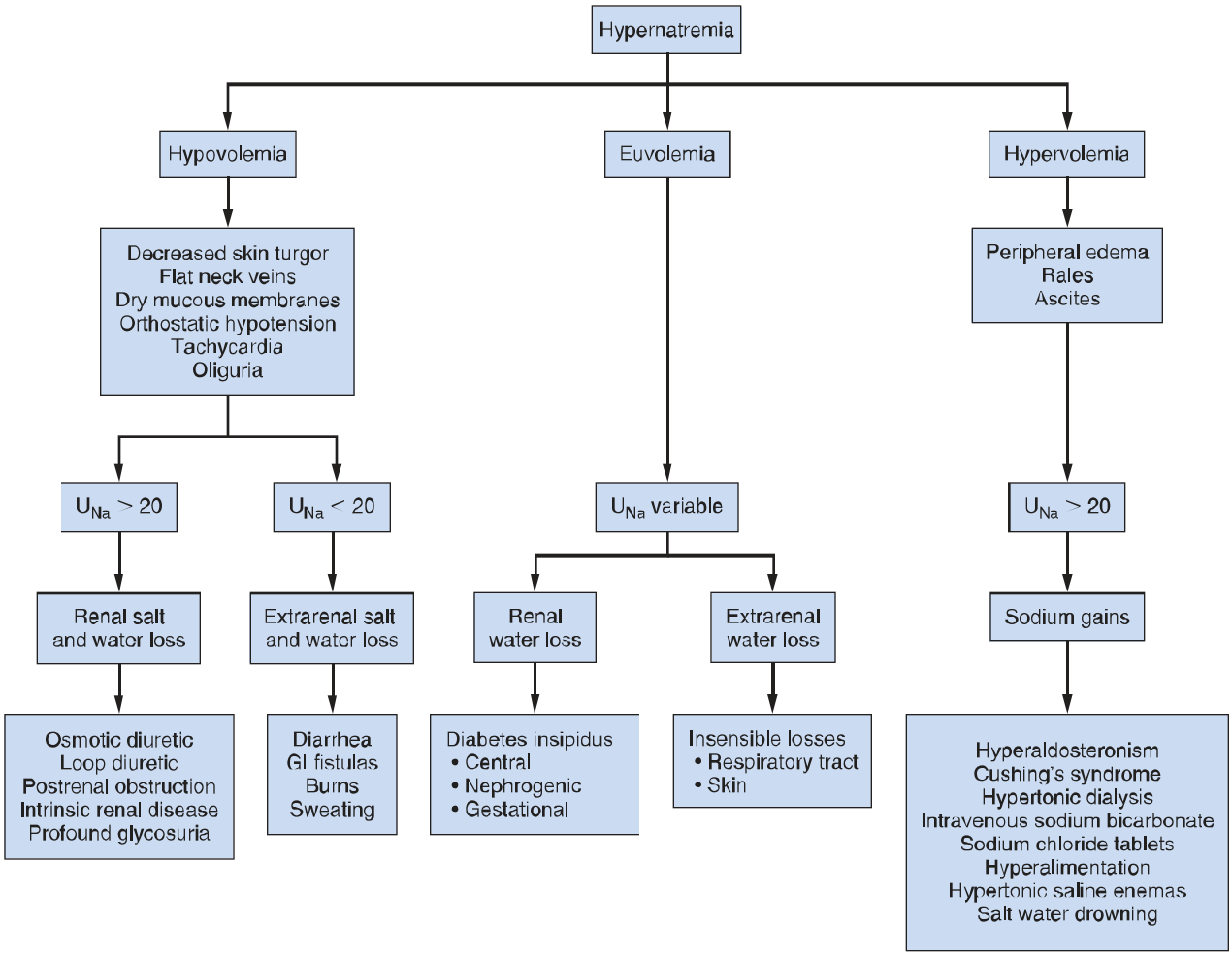

Fig. 20.3 Diagnostic algorithm for hypernatremia. *GI*, Gastrointestinal; U_{Na}, urinary sodium concentration (mEc/L) in a spot urine sample. (Adapted from Schrier RW. *Manual of Nephrology*. ed. 6. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)

central deficit of vasopressin release or a renal insensitivity to vasopressin's actions.

Acute hypernatremia should be corrected over several hours. However, to avoid cerebral edema, chronic hypernatremia should be corrected more slowly over 2 to 3 days. Ongoing sodium and water losses should also be calculated and replaced.

Management of Anesthesia

If at all possible, surgery should be delayed until the hypernatremia has been corrected and its associated symptoms have abated. Frequent serum sodium measurement and urine output monitoring will be required perioperatively, and invasive hemodynamic monitoring may be useful to assess volume status. Hypovolemia will be exacerbated by induction and maintenance of anesthesia, and prompt correction of hypotension with fluids, vasopressors, and/or inotropes may be required. The volume of distribution of hydrophilic drugs will be altered in hypovolemia and hypervolemia. However, the accentuated hemodynamic responses to anesthetic drug administration are most likely a consequence of the vasodilation and negative inotropic effects of anesthetic drugs rather than the result of changes in their volume of distribution.

DISORDERS OF POTASSIUM

Potassium is the major intracellular cation. The normal total body potassium content depends on muscle mass; it is maximal in young adults and decreases progressively with age. Less than 1.5% of total body potassium is found in the extracellular space. Therefore serum potassium concentration is more a reflection of factors that regulate transcellular potassium distribution than of total body potassium. Total body potassium is regulated over long periods of time, principally by the distal nephron in the kidneys; the distal nephron secretes potassium in response to aldosterone, which leads to an increase in urine volume and nonresorbable anions and metabolic alkalosis. More than 90% of potassium taken in by diet is excreted in the urine, and most of the remainder is eliminated in the feces. As the glomerular filtration rate decreases in renal failure, the amount of potassium excreted by the GI route increases.

Hypokalemia

Signs and Symptoms

Signs and symptoms of hypokalemia are generally restricted to the cardiac and neuromuscular systems and include dysrhythmias, muscle weakness, cramps, paralysis, and ileus.

Diagnosis

Hypokalemia is diagnosed by the presence of a serum potassium concentration below 3.5 mmol/L and results from decreased net potassium intake, intracellular shifts, or increased potassium losses. The differential diagnosis requires determining whether the hypokalemia is acute and secondary to intracellular potassium shifts, such as might be seen with hyperventilation or alkalosis, or whether the hypokalemia is chronic and associated with depletion of total body potassium stores (Table 20.6). If the hypokalemia is the result of potassium losses, a spot urinary potassium reading will guide the diagnosis to either renal or extrarenal causes. Appropriately low urine potassium concentrations in the setting of hypokalemia point to a normally functioning kidney in the setting of inadequate potassium intake or GI losses. Renal potassium losses are indicated by a spot urinary potassium value of more than 15 to 20 mEq/L despite the presence of hypokalemia. In cases of renal potassium loss, assessment of the transtubular potassium concentration gradient, hemodynamics, and acid-base status will further help to elucidate the diagnosis. Hypertension with hypokalemia is usually the result of a hyperaldosterone state. Renal losses in the setting of acidemia point to a diagnosis of renal tubular acidosis or diabetic ketoacidosis. Renal losses in the setting of alkalemia can indicate a response to diuretics or can be seen in genetic disorders such as Liddle syndrome (associated with hypertension and excess sodium resorption) or Bartter syndrome (which presents with polyhydramnios, normal to low blood pressure, and neonatal polyuria and polydyspsia with tubular effects similar to those of loop diuretics). Hypomagnesemia can also exacerbate renal potassium losses. Hypokalemia without a change in total body potassium stores can be caused by familial hypokalemic periodic paralysis.

TABLE 20.6 Causes of Hypokalemia

Hypokalemia Due to Increased Renal Potassium Loss
- Thiazide diuretics
- Loop diuretics
- Mineralocorticoids
- High-dose glucocorticoids
- Antibiotics (penicillin, nafcillin, ampicillin)
- Drugs associated with magnesium depletion (aminoglycosides)
- Surgical trauma
- Hyperglycemia
- Hyperaldosteronism

Hypokalemia Due to Excessive Gastrointestinal Loss of Potassium
- Vomiting and diarrhea
- Zollinger-Ellison syndrome
- Jejunoileal bypass
- Malabsorption
- Chemotherapy
- Nasogastric suction

Hypokalemia Due to Transcellular Potassium Shift
- L-adrenergic agonists
- Tocolytic drugs (ritodrine)
- Insulin
- Respiratory or metabolic alkalosis
- Familial periodic paralysis
- Hypercalcemia
- Hypomagnesemia

Adapted from Gennari JF. Hypokalemia. *N Engl J Med.* 1998;339: 451–458.

Treatment

Treatment of hypokalemia depends on the degree of potassium depletion and the underlying cause. If the hypokalemia is profound or is associated with life-threatening signs, potassium must be administered intravenously. In the presence of paralysis or malignant dysrhythmias, the rate of potassium repletion can be as high as 20 mEq over 30 minutes (via an infusion pump) and repeated as needed. If a malignant dysrhythmia appears during potassium repletion, the rate of potassium administration may be the cause. Therefore electrocardiographic (ECG) monitoring is required whenever rapid potassium repletion is undertaken. In the setting of urgent potassium repletion, potassium solutions without dextrose are preferred. Otherwise the insulin secretion stimulated by the glucose will induce intracellular potassium transfer.

The enteral route of potassium repletion is preferred in cases of nonemergent potassium repletion to avoid the risks of high-dose intravenous (IV) potassium administration. If IV repletion is chosen in a nonemergency situation, it should proceed at a rate of less than 20 mEq/h. Peripheral infusion of a concentrated potassium solution will result in pain and/or inflammation at the IV site, so administration via a central venous catheter is preferred.

Management of Anesthesia

Whether or not to treat hypokalemia before surgery is an ongoing subject of debate and depends on the chronicity and severity of the deficit. Because of the limitations on the rate of potassium repletion and the large total body potassium deficits that accompany chronic hypokalemia, safe repletion of total body potassium stores often requires days. Although total body depletion is variable in its relationship to serum potassium concentrations, chronic hypokalemia with serum concentrations of less than 3.0 mEq/L may require delivery of 600 mEq or more of potassium to achieve a normal total body potassium. It is therefore unlikely that administration of small aliquots of potassium immediately before surgery will make any significant difference in potassium balance. Moreover, such interventions carry the risk of inadvertent hyperkalemia that may exacerbate the risk of dysrhythmias in the perioperative period. However, it has been suggested that even small improvements in potassium balance may help normalize transmembrane potentials and reduce the incidence of perioperative dysrhythmias. Recommendations on this controversial issue are based more on expert opinion, clinical judgment, and local practice patterns than on evidence from peer-reviewed studies.

It may be prudent to correct significant hypokalemia in patients with other risk factors for dysrhythmias, such as those with congestive heart failure, those taking digoxin, and those with ECG evidence of hypokalemia. ECG abnormalities

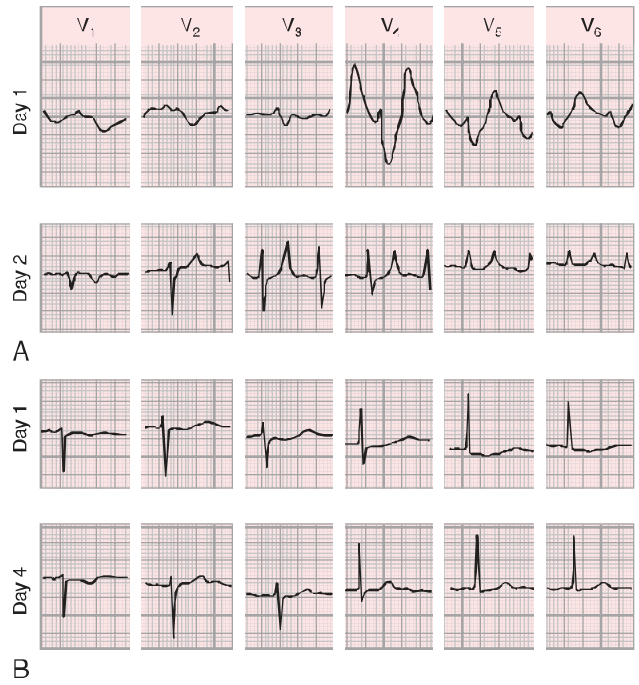

Fig. 20.4 Electrocardiographic changes in hyperkalemia (A) and hypokalemia (B). (A) On day 1, at a K^+ level of 8.6 mEq/L, the P wave is no longer recognizable and the QRS complex is diffusely prolonged. Initial and terminal QRS delays are characteristic of K^+-induced intraventricular conduction slowing and are best illustrated in leads V_2 and V_6. On day 2, at a K^+ level of 5.8 mEq/L, the P wave is recognizable, with a PR interval of 0.24 second; the duration of the QRS complex is approximately 0.10 second, and the T waves are characteristically "tented." (B) On day 1, at a K^+ level of 1.5 mEq/L, the T and U waves are merged. The U wave is prominent, and the QU interval is prolonged. On day 4, at a K^+ level of 3.7 mEq/L, the tracing is normal. (From Bonow R, Mann D, Zipes D, et al., eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. ed. 9. Philadelphia, PA: Saunders; 2011. Courtesy Dr. C. Fisch.)

associated with potassium derangement are illustrated in (Fig. 20.4). Classically, U waves are seen. Anesthetic management of patients with significant hypokalemia should prevent further decreases in serum potassium concentration by avoiding administration of insulin, glucose, β-adrenergic agonists, bicarbonate, and diuretics as well as by avoiding hyperventilation and respiratory alkalosis.

Because of the effect of hypokalemia on skeletal muscle, there is the theoretical possibility of prolonged action of muscle relaxants. Doses of neuromuscular blockers should, as always, be guided by nerve stimulator testing.

Potassium levels should be measured frequently if repletion is ongoing or changes resulting from drug administration, surgical progress, or ventilation are expected.

Hyperkalemia

Hyperkalemia is defined as a serum potassium concentration of more than 5.5 mEq/L. As with hypokalemia, hyperkalemia can result from transcellular movement of potassium out of cells or from alterations in potassium intake or excretion. In hospitalized patients, hyperkalemia is frequently the result of iatrogenic potassium loads (Table 20.7).

TABLE 20.7 Causes of Hyperkalemia

Increased Total Body Potassium Content
- Acute oliguric renal failure
- Chronic renal disease
- Hypoaldosteronism
- Drugs that impair potassium excretion
  - Triamterene
  - Spironolactone
  - Nonsteroidal antiinflammatory drugs
- Drugs that inhibit the renin-angiotensin-aldosterone system

Altered Transcellular Potassium Shift
- Succinylcholine
- Respiratory or metabolic acidosis
- Lysis of cells resulting from chemotherapy
- Iatrogenic bolus

Pseudohyperkalemia
- Hemolysis of blood specimen
- Thrombocytosis/leukocytosis

Signs and Symptoms

Signs and symptoms of hyperkalemia depend on the acuity of the increase. Chronic hyperkalemia is often asymptomatic, and dialysis-dependent patients can withstand considerable variations in serum potassium concentration between dialysis sessions (usually 2–3 days) with remarkably few symptoms. Chronic hyperkalemia may be associated with nonspecific symptoms such as general malaise and mild GI disturbances. More acute or significant increases in serum potassium manifest as complications of a change in membrane depolarization, and neuromuscular and cardiac changes (including weakness, paralysis, nausea, vomiting, bradycardia, or asystole) may result.

Diagnosis

The first step in the diagnosis of hyperkalemia is to rule out a spuriously high potassium level due to hemolysis of the specimen. A spuriously high potassium level may also occur with thrombocytosis and leukocytosis because potassium may leak from these cells in vitro. True hyperkalemia can be identified on ECG first as a peaked T wave, followed in more severe cases by disappearance of the P wave and prolongation of the QRS complex, which progresses to sine waves and then eventually to asystole (see Fig. 20.4).

Common causes of hyperkalemia in the perioperative period include acidosis, rhabdomyolysis, and succinylcholine administration. If the increase in serum potassium level is thought to be associated with increased total body potassium, decreased renal excretion or increased potassium intake is likely. Measurement of the urinary potassium excretion rate can aid in the differential diagnosis between cellular potassium shifts and problems with potassium excretion.

Treatment

Immediate treatment of hyperkalemia is required if life-threatening dysrhythmias or ECG signs of severe hyperkalemia are present. This treatment is aimed at antagonizing the effects of a

high potassium level on the transmembrane potential and redistributing the potassium intracellularly. Calcium chloride or calcium gluconate is administered intravenously to stabilize cellular membranes. The onset of action is immediate. Potassium can be driven intracellularly by the action of insulin with or without glucose. This measure will be effective within 10 to 20 minutes. Other adjuvant therapies include sodium bicarbonate administration and hyperventilation to promote alkalosis and movement of potassium intracellularly. Potassium driven intracellularly may eventually move out of the cells again, so therapy may need to continue beyond acute correction of the derangement.

When hyperkalemia is due to increased total body stores of potassium, potassium must be eliminated from the body. This can be achieved by administration of a loop diuretic such as furosemide, infusion of saline to encourage diuresis, or use of an ion exchange resin. The primary potassium exchange resin in use is sodium polystyrene sulfonate (Kayexalate) given either orally or by enema. Dialysis may be required to remove potassium in cases of emergent hyperkalemia or in patients with poor renal function.

Management of Anesthesia

It is recommended that the serum potassium concentration be less than 5.5 mEq/L for elective surgery. Correction of hyperkalemia before surgery is preferable, but if this is not feasible, then steps should be taken to lower the potassium level immediately before induction of anesthesia by one or more of the methods indicated previously. Potassium levels may influence selection of drugs for induction and maintenance of anesthesia because preoperative medications that induce some degree of hypoventilation and respiratory acidosis may cause further transcellular potassium shifts. Also, succinylcholine (which only increases serum potassium concentration by 0.5 mEq/L in healthy patients) is best avoided in the absence of an urgent need for it. The effects of muscle relaxants may be exaggerated if there is muscle weakness from the hyperkalemia. Both respiratory and metabolic acidosis must be avoided, since either will exacerbate the hyperkalemia and its effects. Potassium-containing IV fluids such as lactated Ringer solution (which contains 4 mEq/L of potassium) and Normosol (which contains 5 mEq/L of potassium) should be avoided. Dialysis patients who are scheduled for surgery in which intraoperative potassium loads are anticipated can be managed preoperatively by decreasing the potassium content of the dialysate to reduce serum potassium levels in anticipation of surgery.

DISORDERS OF CALCIUM

Only 1% of total body calcium is present in the ECF. The remainder is stored in bone. In the ECF, 60% of calcium is free or coupled with anions and is thus filterable, and the remaining 40% is bound to proteins, mainly albumin. Only the ionized calcium in the extracellular space is physiologically active. Ionized calcium concentrations are affected by both albumin concentration and the pH of plasma. Net calcium balance occurs when absorption from the diet equals losses of calcium in feces and urine. Several hormones regulate calcium metabolism: parathyroid hormone, which increases bone resorption and renal tubular reabsorption of calcium; calcitonin, which inhibits bone resorption; and vitamin D, which augments intestinal absorption of calcium. The activity of these hormones is altered in response to changes in plasma ionized calcium concentration. Other hormones, including thyroid hormone, growth hormone, and adrenal and gonadal steroids, also affect calcium homeostasis, but their secretion is determined by factors other than plasma calcium concentration.

Hypocalcemia

Hypocalcemia is defined as a reduction in serum ionized calcium concentration. It is important to note that many blood chemistry analysis systems measure total calcium rather than ionized calcium. Several formulas exist to convert total calcium to ionized calcium, but none of these is totally reliable.

Binding of calcium to albumin is pH dependent, and acid-base disturbances can change the bound fraction and therefore the concentration of ionized calcium without changing total body calcium. Alkalosis reduces the ionized calcium concentration, so ionized calcium may be significantly reduced after bicarbonate administration or in the setting of hyperventilation. Many hospitalized patients are also hypoalbuminemic, and the reduction in bound calcium will reduce the measured serum calcium level. When serum calcium concentration is interpreted in the setting of a low albumin level, corrected calcium concentration can be calculated as follows: measured calcium (mg/dL) ⊥ 0.8 [4 ⊥ albumin (mg/dL)].

Signs and Symptoms

The signs and symptoms of hypocalcemia depend on the rapidity and degree of reduction in ionized calcium. Most of these signs and symptoms are evident in the cardiovascular and neuromuscular systems and include paresthesias, irritability, seizures, hypotension, and myocardial depression. ECG changes associated with hypocalcemia are marked by prolongation of the QT interval (Fig. 20.5). In the postoperative period following thyroid or parathyroid resection, hypocalcemia-induced laryngospasm can be life threatening.

Diagnosis

Hypocalcemia is often caused by decreased parathyroid hormone secretion, end-organ resistance to parathyroid hormone, or disorders of vitamin D metabolism. These are usually seen clinically as complications of thyroid or parathyroid surgery, magnesium deficiency, and renal failure. In the operating room, acute hypocalcemia is often encountered as a result of calcium binding to the citrate preservative in blood products during massive transfusion.

Treatment

Acute symptomatic hypocalcemia with seizures, tetany, and/or cardiovascular depression must be treated immediately with IV calcium. The duration of treatment will depend on serial calcium measurements. Treatment of hypocalcemia in the presence of hypomagnesemia is ineffective unless magnesium is

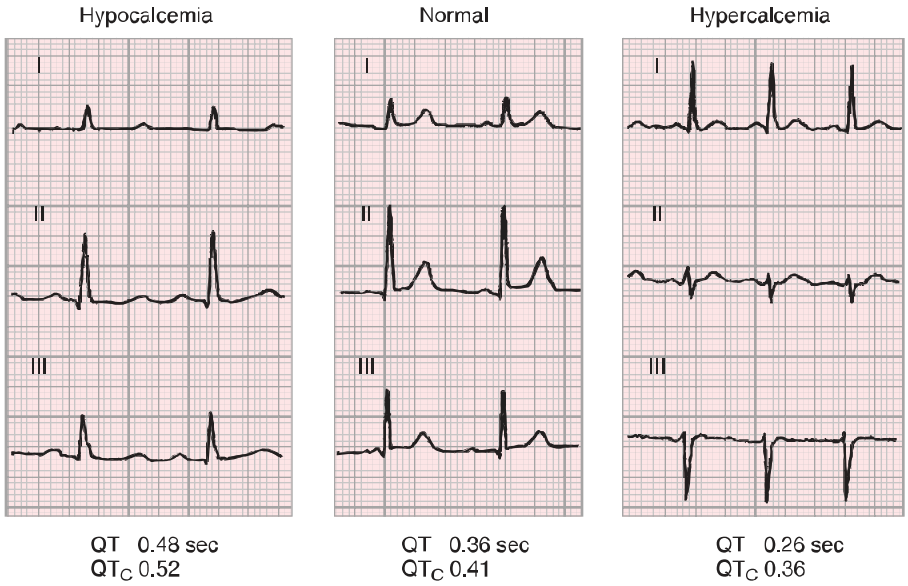

Fig. 20.5 Electrocardiographic changes in calcium disorders. Prolongation of the QT interval (ST-segment portion) is typical of hypocalcemia. Hypercalcemia may cause abbreviation of the ST segment and shortening of the QT interval. QT_C, Corrected QT interval. (Data from Goldberger AL. *Clinical Electrocardiography: A Simplified Approach*. ed. 6. St Louis, MO: Mosby; 1999.)

also replenished. Metabolic or respiratory alkalosis should be corrected. If metabolic or respiratory acidosis is present with hypocalcemia, the calcium level should be corrected before the acidosis is treated; correcting an acidosis with bicarbonate or hyperventilation will only exacerbate the hypocalcemia.

Less acute and asymptomatic hypocalcemia may be treated with oral calcium and vitamin D supplementation.

Management of Anesthesia

Symptomatic hypocalcemia must be treated before surgery, and every effort must be made to minimize any further decrease in serum calcium level intraoperatively, as might occur with hyperventilation or administration of bicarbonate. A decrease in ionized calcium levels should always be considered during massive transfusion of blood containing citrate. Hypothermia, liver disease, and renal failure impair citrate clearance and further increase the likelihood of significant hypocalcemia in transfusion recipients.

Sudden decreases in ionized calcium levels may be seen in the early postoperative period after thyroidectomy or parathyroidectomy and may precipitate laryngospasm.

Hypercalcemia

Hypercalcemia results from increased calcium absorption from the GI tract (milk-alkali syndrome, vitamin D intoxication, granulomatous diseases such as sarcoidosis), decreased renal calcium excretion in renal insufficiency, and increased bone resorption of calcium (primary or secondary hyperparathyroidism, malignancy, hyperthyroidism, and immobilization).

Signs and Symptoms

Hypercalcemia is associated with neurologic and GI signs and symptoms such as confusion, hypotonia, depressed deep tendon reflexes, lethargy, abdominal pain, and nausea and vomiting, especially if the increase in serum calcium level is relatively acute. A shortened ST segment and QT interval are seen on ECG (see Fig. 20.5). Chronic hypercalcemia is often associated with polyuria, hypercalciuria, and nephrolithiasis.

Diagnosis

Almost all patients with hypercalcemia have either hyperparathyroidism or cancer. Primary hyperparathyroidism is typically associated with a serum calcium concentration below 11 mEq/L and no symptoms, whereas malignancy often presents with acute symptoms and a serum calcium level higher than 13 mEq/L.

Treatment

Treatment of hypercalcemia is directed toward increasing urinary calcium excretion and inhibiting bone resorption and further GI absorption of calcium.

Since hypercalcemia is frequently associated with hypovolemia secondary to polyuria, volume expansion with saline not only corrects the fluid deficit but also increases urinary excretion of calcium along with the administered sodium. Loop diuretics also enhance urinary excretion of both sodium and calcium but should be used only after appropriate volume resuscitation.

Calcitonin, bisphosphonates, or mithramycin may be required in disorders associated with osteoclastic bone resorption. Hydrocortisone may reduce GI absorption of calcium in granulomatous disease, vitamin D intoxication, lymphoma, and myeloma. Oral phosphate may also be given to reduce GI uptake of calcium if renal function is normal. Dialysis may be required for life-threatening hypercalcemia. Surgical removal of the parathyroid glands may be required to treat primary or secondary hyperparathyroidism.

Management of Anesthesia

Management of anesthesia for emergency surgery in a patient with hypercalcemia is aimed at restoring intravascular volume before induction and increasing urinary excretion of calcium with loop diuretics. (Note: Thiazide diuretics should be avoided because they increase renal tubular reabsorption of calcium.) Ideally, surgery should be postponed until calcium levels have normalized.

Central venous pressure or pulmonary artery pressure monitoring may be advisable in some patients requiring fluid resuscitation and diuresis as part of the perioperative treatment of hypercalcemia. Dosing of muscle relaxants must be guided by neuromuscular monitoring if muscle weakness, hypotonia, or loss of deep tendon reflexes is present.

DISORDERS OF MAGNESIUM

Magnesium is predominantly found intracellularly and in mineralized bone. Between 60% and 70% of serum magnesium is ionized, with 10% complexed to citrate, bicarbonate, or phosphate and approximately 30% bound to protein, mostly albumin. There is little difference between extracellular and intracellular ionized magnesium concentrations, so there is only a small transmembrane gradient for ionized magnesium. It is the ionized fraction of magnesium that is associated with clinical effects.

Magnesium is absorbed from and secreted into the GI tract and filtered, reabsorbed, and excreted by the kidneys. Renal reabsorption and excretion are passive, following sodium and water.

Hypomagnesemia

Some degree of hypomagnesemia occurs in up to 10% of hospitalized patients. An even higher percentage of patients in ICUs, especially those receiving parenteral nutrition or dialysis, have hypomagnesemia. Coronary care unit patients with hypomagnesemia have a higher mortality rate than those with normal serum levels of magnesium.

Signs and Symptoms

Signs and symptoms of hypomagnesemia are similar to those of hypocalcemia and involve mostly the cardiac and neuromuscular systems. Dysrhythmias, weakness, muscle twitching, tetany, apathy, and seizures can be seen. Hypokalemia and/or hypocalcemia that had been refractory to supplementation will respond after correction of hypomagnesemia.

Diagnosis

Hypomagnesemia is most commonly due to reduced GI uptake (reduced dietary intake or reduced absorption from the GI tract) or to renal wasting of magnesium. These entities can be differentiated by measuring the urinary magnesium excretion rate. Much less frequently, hypomagnesemia is due to intracellular shifts of magnesium with no overall change in total body magnesium, to hungry bone syndrome after parathyroidectomy, or to exudative cutaneous losses after burn injury.

Treatment

Treatment of hypomagnesemia depends on the severity of the deficiency and the signs and symptoms that are present. If cardiac dysrhythmias or seizures are present, magnesium is administered intravenously as a bolus (2 g of magnesium sulfate = 8 mEq of magnesium), and the dose is repeated until symptoms abate. After life-threatening signs have resolved, a slower infusion of magnesium sulfate can be continued for several days to allow for equilibration of intracellular and total body magnesium stores. If renal wasting is present, supplementation must be increased to account for the magnesium lost in urine.

Hypermagnesemia is a potential side effect of the treatment of hypomagnesemia, so the patient should be monitored for signs of hypotension, facial flushing, and loss of deep tendon reflexes.

Management of Anesthesia

Management of anesthesia in patients with hypomagnesemia includes attention to the signs of magnesium deficiency, magnesium supplementation, and treatment of refractory hypokalemia or hypocalcemia if needed. If the hypomagnesemia is secondary to malnutrition or alcoholism, the anesthetic implications of these diseases must also be considered. Intraoperative magnesium supplementation to reduce postoperative dysrhythmias has been suggested but was recently found to make no difference in rates of postoperative atrial fibrillation in a randomized trial of cardiac surgery patients.

Ventricular dysrhythmias (typically polymorphic ventricular tachycardia) should be anticipated and treated as necessary. Muscle relaxation should be guided by the results of peripheral nerve stimulation, since hypomagnesemia can be associated with both muscle weakness and muscle excitation. Fluid loading (particularly with sodium-containing solutions) and diuretic use should be avoided because renal excretion of magnesium passively follows sodium excretion.

Hypermagnesemia

Hypermagnesemia (i.e., serum magnesium concentration >2.5 mEq/L) is much less common than hypomagnesemia because a magnesium load can be briskly excreted if renal function is normal. Even patients with renal failure rarely have symptomatic hypermagnesemia unless there is a significant increase in dietary or IV intake. However, milder elevations in serum magnesium levels are frequently found in ICU and dialysis patient populations. Hypermagnesemia may be a complication of magnesium sulfate administration to treat preeclampsia/eclampsia or to provide perinatal neurologic protection in premature delivery. Magnesium infusion during pheochromocytoma surgery is popular in some centers but may also result in hypermagnesemia.

Signs and Symptoms

Signs and symptoms of hypermagnesemia begin to occur at serum levels of 4 to 5 mEq/L and include lethargy, nausea and vomiting, and facial flushing. At levels above 6 mEq/L, a loss of deep tendon reflexes and hypotension occur. Paralysis, apnea,

heart block, and/or cardiac arrest are likely if the magnesium level exceeds 10 mEq/L.

Diagnosis

Evaluation of hypermagnesemia involves assessing renal function (creatinine clearance) and detecting any source of excess magnesium intake, such as parenteral infusion, oral ingestion of antacids, and administration of magnesium-based enemas or cathartics. Once these have been excluded, less common causes of hypermagnesemia, including hypothyroidism, hyperparathyroidism, Addison disease, and lithium therapy, can be considered.

Treatment

Life-threatening signs of hypermagnesemia may be temporarily ameliorated with IV calcium administration, but hemodialysis may be required. Lesser degrees of hypermagnesemia can be treated with forced diuresis with saline and loop diuretics to increase renal excretion of magnesium.

Management of Anesthesia

Invasive cardiovascular monitoring may be necessary perioperatively to measure and treat the hypotension and vasodilation associated with hypermagnesemia and to guide fluid resuscitation and ongoing replacement of fluids during forced diuresis. Acidosis exacerbates hypermagnesemia, so careful attention must be paid to ventilation and arterial pH. Initial and subsequent doses of muscle relaxants should be reduced in the presence of muscle weakness and guided by results of peripheral nerve stimulation. Hypermagnesemia and skeletal muscle weakness are not uncommon causes of failure to wean from mechanical ventilation in the ICU setting, especially in patients with renal failure.

ACID-BASE DISORDERS

Arterial acid-base balance is normally tightly regulated within the pH range of 7.35 to 7.45 to ensure optimal conditions for cellular enzyme function. Values of arterial blood pH less than 7.35 are termed *acidemia*, and values higher than 7.45 are termed *alkalemia*. The related terms *acidosis* and *alkalosis* refer to acid-base derangements that produce either excess H^+ or excess OH^-, respectively, which may be present regardless of arterial pH. Intracellular pH is lower than extracellular pH and is maintained at a closely regulated level of 7.0 to 7.3. Acid-base regulation in the setting of normal metabolism requires handling of the continuous production of acidic metabolites, totaling approximately 1 mEq/kg body weight per day.

Stability of pH is accomplished by a system of intracellular and extracellular buffers, most importantly the HCO_3/CO_2 buffer pair. Carbon dioxide can enter or leave the body via the lungs, and bicarbonate can enter or leave the body via the kidneys. Maintenance of a normal bicarbonate concentration relative to carbon dioxide tension results in an optimal ratio of approximately 20:1. Maintenance of this 20:1 ratio allows for a relatively normal pH despite deviations from normal of either bicarbonate concentration or carbon dioxide tension. Other buffers include proteins, bone apatite, and phosphate ions.

The relationship of the CO_2/HCO_3 buffer system to pH is expressed by the Henderson-Hasselbalch equation: $pH = 6.1 + \log(\text{serum bicarbonate concentration}/0.03 \times Paco_2)$.

Changes in respiration regulate carbon dioxide tension, whereas renal regulation adjusts bicarbonate concentration. These changes may be the cause of a primary acid-base disorder or can occur as a compensatory mechanism in response to another underlying disorder. In non–mechanically ventilated, nonsedated patients, compensatory respiratory or renal responses can normalize an altered pH but will not overcompensate and alter the pH to the point of reversing the primary disorder. This is not always true in the operating room, where mechanical ventilation and sedation/unconsciousness allow for potential overcompensation or undercompensation of acid-base disorders. Familiarity with the clinical history is then a key part of understanding the patient's primary acid-base abnormality.

Renal compensation for acid-base derangements may include increases in resorption or secretion of filtered bicarbonate in the proximal tubule. In addition, protons (i.e., hydrogen ions) can be reabsorbed in the distal tubule and collecting duct or excreted into the urine. Hydrogen ion excretion in the urine regenerates the bicarbonate originally consumed by buffering a hydrogen ion in the ECF. The excreted hydrogen ions are themselves buffered by titratable renal buffers (mainly ammonia) and lost in the urine.

Evaluation of acid-base disturbances begins with a determination of the primary pH derangement by measurement of arterial pH, $Paco_2$, and HCO_3. A high or low pH will demonstrate the primary acid-base disorder and allow evaluation of whether there is appropriate compensation. In cases of normal pH there may still be chronic compensated acidosis or alkalosis that can offer insight into a patient's comorbid condition.

Identification of acid-base disturbance follows a series of steps:

1. Identify whether the pH is increased or decreased. An increase defines alkalemia, and a decrease defines acidemia.
2. Identify the change in $Paco_2$ and bicarbonate from their normal levels of 40 mm Hg and 24 mEq/L, respectively.
3. If both $Paco_2$ and bicarbonate change in the same direction (i.e., both are increased or both are decreased), there is a primary acid-base disorder with a compensatory secondary disorder that brings the ratio of bicarbonate to carbon dioxide tension back toward 20:1.
4. If bicarbonate and $Paco_2$ change in opposite directions, there is a mixed acid-base disorder.
5. Determine the primary acid-base disorder by comparing the fractional change of the measured bicarbonate or carbon dioxide tension to the normal value.
6. There are equations and nomograms that calculate the expected change in one of the three parameters involved in acid-base determination (pH, bicarbonate, or carbon dioxide tension) for a given change in one of the other two parameters (Fig. 20.6). If the actual change is markedly different from the expected change, there is a mixed acid-base disorder.

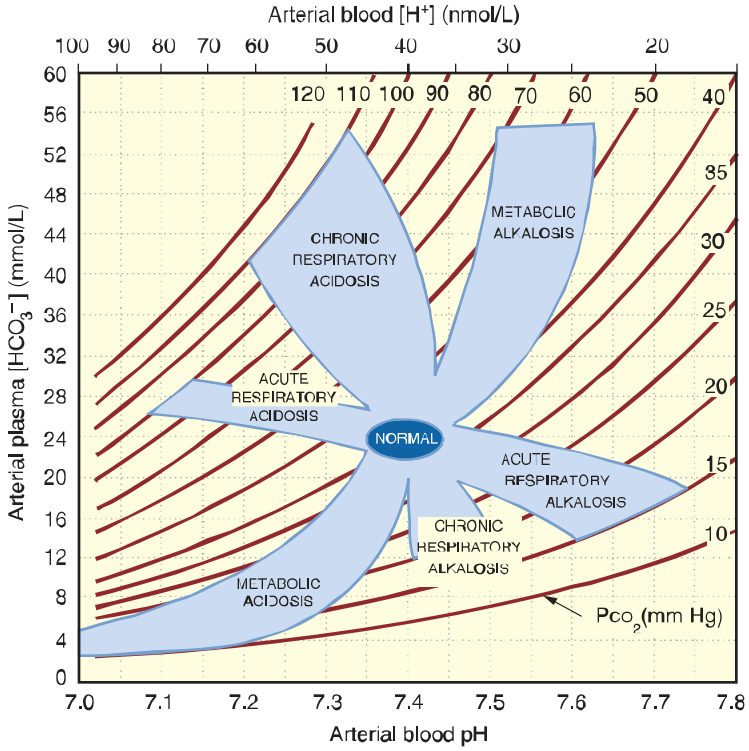

Fig. 20.6 Acid-base nomogram (map). Shaded areas represent the 95% confidence limits of the normal respiratory and metabolic compensations for primary acid-base disturbances. Data falling outside the shaded areas denote a mixed disorder if a laboratory error is not present. (Data from Brenner B, Clarkson M, Oparil S, et al., eds. *Brenner and Rector's The Kidney*. ed. 8. Philadelphia, PA: Saunders; 2007.)

7. Finally, calculate the anion gap to determine whether there is an anion gap metabolic acidosis. Elevation in the anion gap requires subsequent identification of the unmeasured anion.

Signs and Symptoms

Major adverse consequences of severe systemic acidosis (pH ⊐ 7.2) can occur independently of whether the acidosis is of respiratory, metabolic, or mixed origin (Table 20.8). The effects of acidosis are particularly detrimental to the cardiovascular system. Acidosis decreases myocardial contractility, although clinical effects are minimal until the pH decreases to less than 7.2, which perhaps reflects the effects of catecholamine release in response to the acidosis. When the pH is less than 7.1, cardiac responsiveness to catecholamines decreases and compensatory inotropic effects are diminished. The detrimental effects of acidosis may be accentuated in those with underlying left ventricular dysfunction or myocardial ischemia and in those in whom sympathetic nervous system activity is impaired, such as by ∃-adrenergic blockade or general anesthesia.

Major adverse consequences of severe systemic alkalosis (pH ⊐ 7.60) reflect impairment of cerebral and coronary blood flow caused by arteriolar vasoconstriction (Table 20.9). Associated decreases in serum ionized calcium concentration probably contribute to the neurologic abnormalities associated with systemic alkalosis. Alkalosis predisposes patients, especially those with coexisting heart disease, to significant and even refractory ventricular dysrhythmias. Alkalosis depresses ventilation and can frustrate efforts to wean patients from mechanical ventilation.

TABLE 20.8 Adverse Consequences of Severe Acidosis

Nervous System
Obtundation
Coma

Cardiovascular System
Impaired myocardial contractility
Decreased cardiac output
Decreased arterial blood pressure
Sensitization to reentrant cardiac dysrhythmias
Decreased threshold for ventricular fibrillation
Decreased responsiveness to catecholamines

Ventilation
Hyperventilation
Dyspnea
Fatigue of respiratory muscles

Metabolism
Hyperkalemia
Insulin resistance
Inhibition of anaerobic glycolysis

Adapted from Adrogué HJ, Madias NE. Management of life-threatening acid-base disorders. *N Engl J Med*. 1998;338:26–34.

Hypokalemia accompanies both metabolic and respiratory alkalosis but is more prominent in the presence of metabolic alkalosis. Alkalosis stimulates anaerobic glycolysis and increases the production of lactic acid and ketoacids. Although alkalosis can

TABLE 20.9 Adverse Consequences of Alkalosis

Nervous System
Decreased cerebral blood flow
Seizures
Lethargy
Delirium
Tetany

Cardiovascular System
Arteriolar vasoconstriction
Decreased coronary blood flow
Decreased threshold for angina pectoris
Predisposition to refractory dysrhythmias

Ventilation
Hypoventilation
Hypercarbia
Arterial hypoxemia

Metabolism
Hypokalemia
Hypocalcemia
Hypomagnesemia
Hypophosphatemia
Stimulation of anaerobic glycolysis

Adapted from Adrogué JH, Madias NE. Management of life-threatening acid-base disorders. *N Engl J Med.* 1998;338:107–111.

decrease the release of oxygen to the tissues by tightening the binding of oxygen to hemoglobin, chronic alkalosis negates this effect by increasing the concentration of 2,3-diphosphoglycerate in erythrocytes.

Respiratory Acidosis

Respiratory acidemia is present when a decrease in alveolar ventilation results in an increase in the $Paco_2$ sufficient to decrease arterial pH to less than 7.35 (Table 20.10). The most likely cause of respiratory acidosis during the perioperative period is drug-induced depression of ventilation by opioids, general anesthetics, or neuromuscular blockers. Respiratory acidosis may be complicated by metabolic acidosis when renal perfusion is decreased to the extent that reabsorption mechanisms in the renal tubules are impaired. For example, cardiac output and renal blood flow may be so decreased in patients with chronic obstructive pulmonary disease and cor pulmonale as to lead to metabolic acidosis.

TABLE 20.10 Causes of Respiratory Acidosis

Drug-induced ventilatory depression
Permissive hypercapnia
Upper airway obstruction
Status asthmaticus
Restriction of ventilation (rib fractures/flail chest)
Disorders of neuromuscular function
Malignant hyperthermia
Hyperalimentation

Respiratory acidosis is treated by correcting the disorder responsible for hypoventilation. Mechanical ventilation is necessary when the increase in $Paco_2$ is marked and carbon dioxide narcosis is present. It must be remembered that rapid lowering of chronically increased $Paco_2$ levels by mechanical ventilation decreases body stores of carbon dioxide much more rapidly than the kidneys can produce a corresponding decrease in serum bicarbonate concentration. The resulting metabolic alkalosis can cause neuromuscular irritability and excitation of the CNS, including seizures. It is best to decrease the $Paco_2$ slowly to permit sufficient time for renal tubular elimination of bicarbonate.

Metabolic alkalosis may accompany respiratory acidosis when the body stores of chloride and potassium are decreased. For example, decreased serum chloride concentrations facilitate renal tubular reabsorption of bicarbonate, which leads to metabolic alkalosis. Hypokalemia stimulates renal tubules to excrete hydrogen, which may produce metabolic alkalosis or aggravate a coexisting alkalosis caused by chloride deficiency. Treatment of metabolic alkalosis associated with these electrolyte disturbances requires administration of potassium chloride.

Respiratory Alkalosis

Respiratory alkalosis is present when an increase in alveolar ventilation results in a decrease in $Paco_2$ sufficient to increase the pH to greater than 7.45 (Table 20.11). The most likely cause of acute respiratory alkalosis during the perioperative period is iatrogenic hyperventilation. Respiratory alkalosis occurs normally during pregnancy and is an important adaptive response to high altitude.

Treatment of respiratory alkalosis is directed at correcting the underlying disorder responsible for alveolar hyperventilation. During anesthesia this is most often accomplished by adjusting the ventilator to decrease alveolar ventilation. The hypokalemia and hypochloremia that may coexist with respiratory alkalosis may also require treatment.

Metabolic Acidosis

Metabolic acidosis lowers blood pH, which stimulates the respiratory center to hyperventilate and lower carbon dioxide tension. Respiratory compensation does not in general fully counterbalance the increased acid production, but the pH will return toward normal.

Acidoses of metabolic origin are typically divided into those with a normal anion gap and those with a high anion gap.

A high anion gap occurs when a fixed acid is added to the extracellular space. The acid dissociates, the hydrogen ion combines with bicarbonate forming carbonic acid, and the decreased

TABLE 20.11 Causes of Respiratory Alkalosis

Iatrogenic (mechanical hyperventilation)
High altitude
Central nervous system injury
Hepatic disease
Pregnancy
Salicylate overdose

bicarbonate concentration produces an increased anion gap. Lactic acidosis, ketoacidosis, renal failure, and the acidoses associated with many poisonings are examples of high–anion gap metabolic acidoses.

Non–anion gap metabolic acidosis is the result of a net increase in chloride concentration. Bicarbonate loss is counterbalanced by a net gain of chloride ions to maintain electrical neutrality. Therefore a normal anion gap acidosis is often called a hyperchloremic metabolic acidosis. The most common causes of a normal–anion gap acidosis are IV infusion of sodium chloride and GI and renal losses of bicarbonate (diarrhea, renal tubular acidosis, early renal failure).

Signs and Symptoms

Since acidosis is secondary to an underlying disorder, the presentation of acidosis is complicated by the signs and symptoms of the causative disorder. Derangements of pH have wide-ranging effects on tissue, organ, and enzyme function, and the signs and symptoms attributable to an acidosis relate to these effects. The clinical features of metabolic acidosis depend also on the rate of development of acidosis and are likely to be more dramatic in rapidly developing acidosis in which compensatory respiratory or renal changes are not able to limit the fall in pH.

Diagnosis

Diagnosis depends on a high index of suspicion and laboratory testing. Most commonly, arterial blood is analyzed for pH, carbon dioxide tension, bicarbonate concentration, and anion gap. Common causes of metabolic acidosis are listed in Table 20.12.

Metabolic acidosis can be of renal or extrarenal origin. Metabolic acidosis of renal origin involves a primary disorder of renal acidification. This occurs when the kidneys are unable to regenerate sufficient bicarbonate to replace that lost by the buffering of normal endogenous acid production (distal renal tubular acidosis) or when an abnormally high fraction of filtered bicarbonate is not reabsorbed in the proximal tubule and is subsequently lost in the urine (proximal renal tubular acidosis or acetazolamide use). Combined defects occur in renal failure. The most common causes of extrarenal sources of metabolic acidosis are GI bicarbonate losses, ketoacidosis, and lactic acidosis.

Treatment

Treatment of metabolic acidosis includes treatment of the cause of the acidosis—for example, insulin and fluids for diabetic ketoacidosis and improvement in tissue perfusion for lactic acidosis. Administration of sodium bicarbonate for acute treatment of metabolic acidosis is very controversial. Many recommend that bicarbonate be given only if the pH is less than 7.1 or the bicarbonate concentration is less than 10 mEq/L. There is concern that the bicarbonate reacts with hydrogen ions, generating carbon dioxide, which diffuses into cells and lowers intracellular pH even more than before the bicarbonate treatment. It is also postulated that administration of bicarbonate to patients with chronic metabolic acidosis may result in transient tissue hypoxia because acute changes in pH toward normal (or alkalosis) may negate the rightward shift of the oxyhemoglobin dissociation curve caused by acidemia (Bohr effect) and result in increased hemoglobin affinity for oxygen, which reduces oxygen delivery at the tissue level.

The 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care do *not* recommend administering sodium bicarbonate routinely during cardiac arrest and cardiopulmonary resuscitation. However, sodium bicarbonate may be considered for life-threatening hyperkalemia or cardiac arrest associated with hyperkalemia, or for cardiac arrest associated with a significant prearrest metabolic acidosis.

Management of Anesthesia

Elective surgery should be postponed until an acidosis has been treated. For urgent surgery in a patient with metabolic acidosis, invasive hemodynamic monitoring should be considered to guide fluid resuscitation and monitor cardiac function in marked acidosis. Laboratory measurement of acid-base parameters should be performed frequently throughout the perioperative period because pH can change rapidly and significantly in response to changes in ventilation, volume status, circulation, and drug administration.

Acidosis affects the proportion of drug in the ionized and unionized states. Volume of distribution may also be affected in patients who have uncorrected hypovolemia.

Metabolic Alkalosis

Metabolic alkalosis is marked by an increase in plasma bicarbonate concentration and is usually compensated for by an increase in carbon dioxide tension. Common causes of metabolic alkalosis are listed in Table 20.13.

Metabolic alkalosis can be of renal or extrarenal origin and can be caused by either a net loss of hydrogen ions (e.g., loss of hydrochloric acid with vomiting) or a net gain of bicarbonate

TABLE 20.12 Causes of Metabolic Acidosis

Lactic acidosis
Diabetic ketoacidosis
Renal failure
Hepatic failure
Methanol and ethylene glycol intoxication
Aspirin intoxication
Increased skeletal muscle activity
Cyanide poisoning
Carbon monoxide poisoning

TABLE 20.13 Causes of Metabolic Alkalosis

Hypovolemia
Vomiting
Nasogastric suction
Diuretic therapy
Bicarbonate administration
Hyperaldosteronism
Chloride-wasting diarrhea

(e.g., caused by tubular defects of bicarbonate reabsorption). Abnormal losses of chloride with or without hydrogen ion (e.g., in cystic fibrosis or villous adenoma) also induce increased renal bicarbonate reabsorption in an attempt to maintain electroneutrality. Therefore metabolic alkaloses can be characterized as chloride responsive or chloride resistant. Another classification of metabolic alkalosis is volume-depletion alkalosis (resulting from vomiting, diarrhea, or chloride losses) and volume-overload alkalosis (resulting from primary or secondary mineralocorticoid excess).

Metabolic alkalosis can also occur secondary to renal compensation for chronic respiratory disease with hypercarbia. In these patients, bicarbonate levels may be quite high and associated with urinary losses of chloride along with obligatory losses of sodium and potassium. If the respiratory disorder is treated with mechanical ventilation and the carbon dioxide tension is reduced rapidly, a profound metabolic alkalosis may result.

Signs and Symptoms

Progressively more binding of calcium to albumin occurs as an alkalosis develops, so the signs and symptoms of alkalosis, especially those related to the neuromuscular and central nervous systems, may be very similar to those of hypocalcemia. Metabolic alkalosis may be accompanied by volume contraction, hypochloremia and hypokalemia, or volume overload and sodium retention, depending on the cause.

Diagnosis

As with metabolic acidosis, the diagnosis of metabolic alkalosis is dependent on a high index of suspicion and laboratory testing. Metabolic alkaloses secondary to chloride losses are associated with low urinary chloride levels (typically _ 10 mEq/L) and volume contraction. In contrast, metabolic alkaloses associated with mineralocorticoid excess are typically associated with volume overload and spot urine chloride values above 20 mEq/L.

Treatment

Volume-depletion metabolic alkalosis is treated by chloride replacement along with fluid resuscitation using saline, which is itself weakly acidic. If the alkalosis has been caused by gastric losses of hydrochloric acid, proton pump inhibitors can be given to stop perpetuation of the alkalosis. Metabolic alkalosis associated with loop diuretics can be improved by adding or substituting potassium-sparing diuretics. In the case of volume-overload metabolic alkalosis due to excess mineralocorticoid concentrations, administration of spironolactone plus potassium chloride may be useful if the source of mineralocorticoid secretion cannot be eliminated.

Management of Anesthesia

Management of anesthesia includes judicious volume replacement and adequate supplementation with chloride, potassium, and magnesium as needed. Invasive monitoring may be helpful in some patients. Care must be taken not to eliminate a compensatory metabolic alkalosis in patients with chronic lung disease and significant carbon dioxide retention, because successful weaning from mechanical ventilation will likely necessitate a return to the chronic respiratory acidosis and metabolic alkalosis the patient had at presentation.

KEY POINTS

- Total body water content is categorized as ICF and ECF, according to the location of the water relative to cell membranes. The distribution and concentration of electrolytes can differ greatly between fluid compartments. The electrophysiology of excitable cells is dependent on the intracellular and extracellular concentrations of sodium, potassium, and calcium.
- Water balance is predominantly mediated by osmolality sensors, neurons located in the anterior hypothalamus that stimulate thirst and cause pituitary release of vasopressin (antidiuretic hormone). Vasopressin is stored as granules in the posterior pituitary and acts through G protein–coupled receptors in the collecting ducts of the kidney, causing water retention that in turn corrects serum osmolality.
- As hyponatremia develops, it is usually associated with extracellular hypotonicity, which results in water movement into cells and can manifest as cerebral edema and increased intracranial pressure. Initial compensation is afforded by the movement of brain extracellular fluid into the cerebrospinal fluid. Later compensation includes the lowering of intracellular osmolality by the movement of potassium and organic solutes out of brain cells. This reduces water movement into the intracellular space. However, when these adaptive mechanisms fail or hyponatremia progresses, CNS manifestations of hyponatremia occur.
- The volume overload, hyponatremia, and hypoosmolality that may accompany transurethral resection of the prostate are known as TURP syndrome. This syndrome is more likely to occur when resection is prolonged (1 hour), when the irrigating fluid is suspended more than 40 cm above the operative field, and when the pressure in the bladder is allowed to increase above 15 cm H_2O. TURP syndrome manifests principally with cardiovascular signs of volume overload and neurologic signs of hyponatremia.
- Hypokalemia is diagnosed by testing the serum potassium concentration. The differential diagnosis requires determining whether the hypokalemia is acute and secondary to intracellular potassium shifts, such as might be seen with hyperventilation or alkalosis, or is chronic and associated with depletion of total body potassium stores.
- Immediate treatment of hyperkalemia is required if life-threatening dysrhythmias or ECG signs of severe hyperkalemia are present. This treatment is aimed at antagonizing the effects of a high potassium on the transmembrane potential and redistributing potassium intracellularly. Calcium chloride or calcium gluconate is administered to stabilize cellular

membranes. Hyperventilation, sodium bicarbonate administration, and insulin administration promote movement of potassium intracellularly.

- Binding of calcium to albumin is pH dependent, and acid-base disturbances can change the fraction and therefore the concentration of ionized calcium without changing total body calcium. Alkalosis reduces the ionized calcium concentration, so ionized calcium may be significantly reduced after bicarbonate administration or with hyperventilation.
- Signs and symptoms of hypermagnesemia begin to occur at serum levels of 4 to 5 mEq/L and include lethargy, nausea and vomiting, and facial flushing. At levels above 6 mEq/L, a loss of deep tendon reflexes and hypotension occur. Paralysis, apnea, and/or cardiac arrest are likely if the magnesium level exceeds 10 mEq/L.
- Major adverse consequences of severe systemic acidosis (pH ⊥7.2) can occur whether the acidosis is of respiratory, metabolic, or mixed origin. Acidosis decreases myocardial contractility, although clinical effects are minimal until the pH decreases below 7.2, which perhaps reflects the effects of catecholamine release in response to the acidosis. When the pH is less than 7.1, cardiac responsiveness to catecholamines decreases and compensatory inotropic effects are diminished. The detrimental effects of acidosis may be accentuated in those with underlying left ventricular dysfunction or myocardial ischemia and in those in whom sympathetic nervous system activity is impaired, such as by Γ-adrenergic blockade or general anesthesia.
- Major adverse consequences of severe systemic alkalosis (pH ⊥7.60) reflect impairment of cerebral and coronary blood flow due to arteriolar vasoconstriction. Associated decreases in serum ionized calcium concentration contribute to the neurologic abnormalities associated with systemic alkalosis. Alkalosis predisposes patients—especially those with coexisting heart disease—to severe, often refractory, ventricular dysrhythmias. Alkalosis also depresses ventilation.

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21

Renal Disease

Natalie F. Holt, Thomas R. Hickey

OUTLINE

INTRODUCTION

The kidney plays a key homeostatic role in the tight regulation of extracellular fluid volume, blood pressure, solute transport and electrolyte concentrations, pH, and excretion of drug metabolites. Knowledge of how the kidneys perform these important functions aids in understanding the clinical presentation, signs and symptoms, and treatment of renal diseases.

The kidneys are retroperitoneal organs located at the T12 to L4 levels, with the right slightly lower than the left. Nephrons are the structural units of the kidney and consist of a tuft of capillaries called a glomerulus, which filters tubular fluid, and the various portions of the tubule (i.e., proximal tubule, loop of Henle, distal tubule, and collecting duct) that form urine (Fig. 21.1). Parasympathetic innervation to the kidney is via the vagus nerve and to the ureters is via the S2 to S4 spinal segments. Sympathetic innervation is via preganglionic fibers from T8 to L1, and pain sensation is via afferent sympathetic fibers from T10 to L1. If a neuraxial blockade were chosen for kidney surgery, a sensory level from T8 to L4 would likely be required for anesthesia and postoperative analgesia.

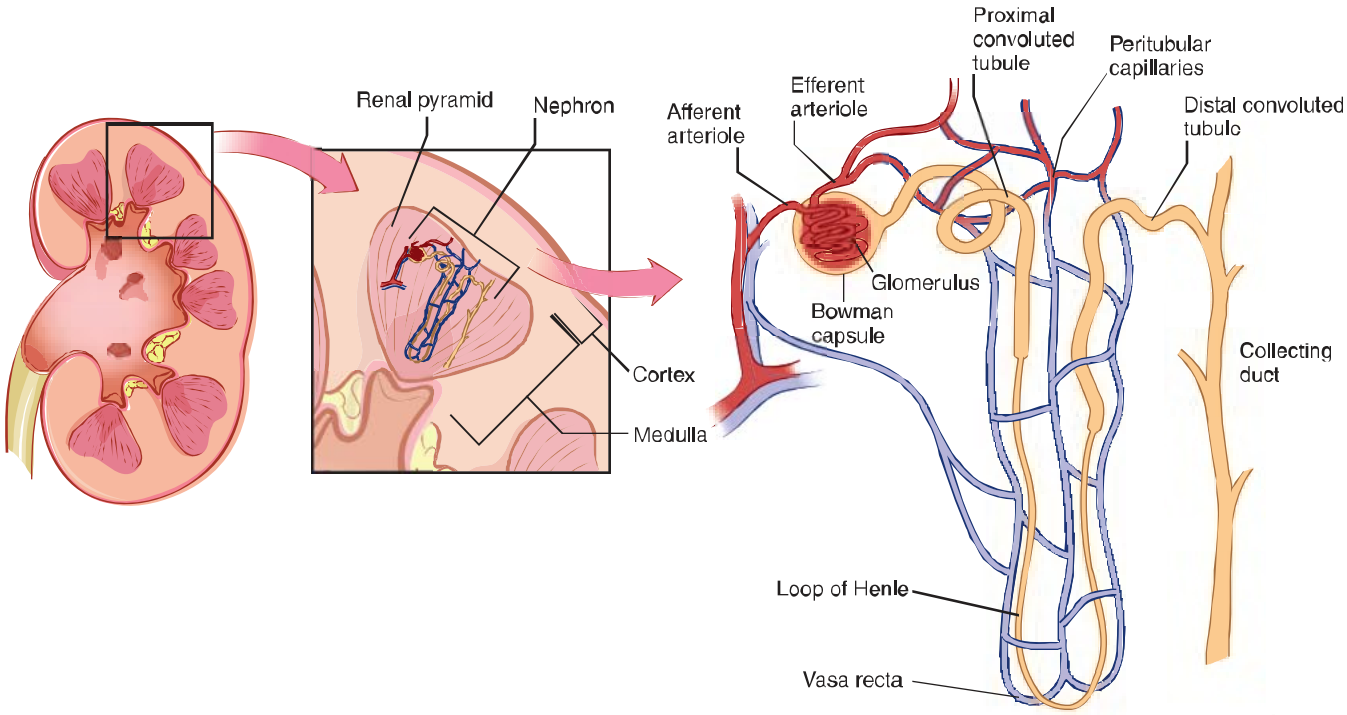

Fig. 21.1 Anatomy of the kidney and glomerulus. The kidneys receive about 20% of cardiac output; the majority of blood is distributed to the renal cortex. Each kidney consists of approximately 1 million nephrons, each of which has distinct anatomic parts: Bowman capsule, proximal tubule, loop of Henle, distal tubule, and collecting duct. A glomerulus, a tuft of capillaries, is surrounded by Bowman capsule and is supplied by an afferent arteriole and drained by a slightly smaller efferent arteriole. The juxtaglomerular apparatus is a specialized structure between the afferent arteriole and distal tubule that contributes to the control of renal perfusion and extrarenal hemodynamics. As plasma flows along the nephron, virtually all the fluid and solutes are reabsorbed by a number of active and passive transport systems. The main functions of the kidneys are water and sodium homeostasis, which are intimately linked and regulated by a number of feedback loops and hormonal controls. (From https://www.boundless.com/biology/textbooks/boundless-biology-textbook/osmotic-regulation-and-the-excretory-system-41/human-osmoregulatory-and-excretory-systems-229/kidney-structure-860-12107/.)

The kidneys receive about 20% of the cardiac output. Blood supply is via a single renal artery to each side. The afferent arteriole delivers blood to the nephron while the efferent arteriole, formed by glomerular capillaries, supplies the tubular system. Glomerular filtration is driven by hydrostatic pressure across the capillary wall and offset by oncotic pressure within the capillary. The glomeruli filter the plasma at a rate of 180 L/day, allowing all but protein and polysaccharides to pass into the tubule. The glomerular filtration rate (GFR) is a measure of glomerular function given in volume of plasma filtered per minute.

Renal blood flow autoregulation maintains a steady GFR over a wide range of blood pressures via changes in afferent and efferent arteriolar tone. A stretch in the afferent arteriole (as during periods of relative hypertension) causes its reflexive constriction while a relaxation in the afferent arteriole (as during periods of hypotension) causes its reflexive relaxation; these responses are known as the myogenic reflex. Tubuloglomerular feedback (TGF) is mediated by cells in the macula densa of the loop of Henle that sense solute concentration; high solute delivery triggers afferent arteriolar vasoconstriction while low solute delivery reduces the TGF. Lastly, low filtration states cause release of renin, which is converted to angiotensin II by angiotensin-converting enzyme (ACE). In this context, angiotensin II causes efferent arteriolar vasoconstriction, which increases filtration via increased glomerular hydrostatic pressure. It is also noteworthy that angiotensin II promotes release of antidiuretic hormone (ADH; see later), sodium reabsorption in the tubule, and aldosterone release from the adrenal gland. Aldosterone release leads to increased sodium absorption in the nephron. This system beginning with renin release is known as the renin-angiotensin-aldosterone system (RAAS).

Sodium absorption, beginning in the proximal tubule, is an active process with many other solutes coupled to its absorption. Water absorption is passive here, driven by osmotic gradients and peritubular capillary pressures, whereas in the distal tubule, water absorption is controlled by ADH (also known as vasopressin). ADH is secreted by the pituitary gland in response to increased serum osmolality and decreased atrial filling pressures, leading to increased collecting duct permeability.

Atrial natriuretic peptide (ANP), released in response to increased atrial stretch, acts to increase GFR, inhibit sodium resorption in the nephron, and inhibit the RAAS. Similarly, prostaglandins, which have an overall vasodilatory effect in the kidney, play an important role in maintaining renal blood flow (RBF) during periods of reduced renal perfusion. In settings of reduced renal perfusion caused by hypovolemia, heart failure, advanced age, or chronic kidney disease (CKD), nonsteroidal antiinflammatory

drug (NSAID)–mediated reduction in prostaglandins underlies the increased risk of acute kidney injury (AKI) associated with these drugs.

CLINICAL ASSESSMENT OF RENAL FUNCTION

There are a number of tests that are useful in evaluating renal function and diagnosing disease (Table 21.1).

Glomerular Filtration Rate

The GFR is considered the best measure of overall renal function, although it can be normal in some renal disease states (i.e., nephrotic syndrome). The GFR describes the plasma volume filtered per unit time. Conceptually, GFR can be thought of as follows:

$$GFR = K_f \times (\Delta P - \Delta \pi)$$

where K_f is the surface area for filtration, ΔP is the difference in hydrostatic forces across the membrane, and $\Delta \pi$ is the difference in osmotic pressures across the same membrane. Different renal impairments impact the different variables in this equation. For example, diseases of the glomerulus will decrease K_f while prerenal conditions such as hypovolemia will decrease ΔP.

GFR may be calculated from timed urine volumes plus urinary and plasma creatinine concentrations (creatinine clearance), or from the clearance of an exogenous substance such as inulin. A number of formulas exist that estimate the GFR from various serum and urine indices (Table 21.2). Normal values for GFR are 125 to 140 mL/min and vary with gender, body weight, and age. GFR decreases by approximately 8 mL/min per year after the age of 30. A GFR less than 60 mL/min for 3 months or longer is indicative of CKD.

TABLE 21.1 Tests Used to Evaluate Renal Function

Test	Normal Values
Glomerular Filtration Rate	
Blood urea nitrogen	10–20 mg/dL
Serum creatinine	0.6–1.3 mg/dL
Creatinine clearance	110–140 mL/min
Proteinuria (albumin)	<150 mg/day
Renal Tubular Function and/or Integrity	
Urine specific gravity	1.003–1.030
Urine osmolality	50–1400 mOsm/L
Urine sodium excretion	<40 mEq/L
Glucosuria	
Factors That Influence Interpretation	
Dehydration	
Variable protein intake	
Gastrointestinal bleeding	
Catabolism	
Advanced age	
Skeletal muscle mass	
Accurately timed urine volume measurement	

TABLE 21.2 Calculations Used to Measure or Estimate Glomerular Filtration Rate

Creatinine Clearance

Creatinine Clearance (mL/min) = $[(U_{Cr} \times V_{volume})] / [(P_{Cr} \times \text{time [min]})]$

Cockcroft-Gault Equation

GFR (mL/min) = $[(140 - \text{age}) \times \text{lean body weight (in kg)}]/[(P_{Cr} \times 72) \times 0.85 \text{ (for women)}]$

Modification of Diet in Renal Disease (MDRD)

GFR (mL/min/1.73 m^2) = $170 \times P_{Cr}^{-0.999} \times \text{Age}^{-0.176} \times P_{BUN}^{-0.170} \times P_{Albumin}^{0.318} \times 0.762$ (for women) $\times 1.180$ (for Blacks)

Urine and plasma concentrations of creatinine and BUN measured in mg/dL. Plasma albumin concentration measured in g/dL. Urine volume measured in mL.

BUN, Blood urea nitrogen; *Cr*, creatinine; *GFR*, glomerular filtration rate; *P*, plasma; *U*, urine.

Data from Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:33, table 1; Levey AS, et al. A more accurate method to estimate glomerular filtration equation from serum creatinine: a new prediction equation. *Ann Intern Med*. 1999;130(6):466, table 3, equation 7.

Serum Creatinine and Creatinine Clearance

Creatinine, an endogenous marker of renal filtration, is produced at a relatively constant rate by hepatic conversion of skeletal muscle creatinine. Creatinine is freely filtered by the kidney and is not reabsorbed. As a result, creatinine clearance is the most reliable measure of GFR. Unlike GFR, creatinine clearance does not require corrections based on age or the presence of a steady state.

Normal serum creatinine concentrations range from 0.6 to 1.1 mg/dL in women and 0.8 to 1.3 mg/dL in men, reflecting differences in skeletal muscle mass. A number of factors (i.e., accelerated creatinine production in the setting of a recent meat meal) can increase serum creatinine concentrations in the absence of a concomitant decrease in GFR. Conversely, a small increase in serum creatinine can reflect large decreases in GFR; in this context, knowledge of the baseline creatinine is critical. For example, an increase in creatinine concentration from a baseline 0.7 to 1.2 mg/dL in an elderly adult, while still "normal," reflects a near 50% decrease in GFR. Creatinine concentrations are normally stable until approximately 40% of renal function is lost. Serum creatinine values are also slow to reflect acute changes in renal function. For example, if AKI occurs and the GFR decreases from 100 to 10 mL/min, serum creatinine values may not plateau for 7 days.

Blood Urea Nitrogen

Blood urea nitrogen (BUN) concentrations also tend to vary inversely with the GFR. However, the pronounced influences of dietary intake, coexisting disease, and intravascular fluid volume on BUN concentrations make it potentially misleading as a test of renal function. For example, production of urea is increased by high-protein diets or gastrointestinal bleeding, resulting in increased BUN despite a normal GFR. Dehydration and increased catabolism, as occurs during a febrile illness, also

causes increased BUN despite a normal GFR. Despite this variability, chronic BUN concentrations higher than 50 mg/dL usually reflect a decreased GFR. An acute rise in BUN/creatinine ratio to 20:1 or higher can be seen in hypovolemia; this condition is often referred to as prerenal azotemia.

Urine Concentrating Ability

Renal tubular function is most often assessed by measuring urine concentrating ability. Renal tubular dysfunction is established by demonstrating that the kidneys do not produce appropriately concentrated urine in the presence of a physiologic stimulus for the release of ADH. In the absence of diuretic therapy, significant glycosuria, or proteinuria, a urine specific gravity higher than 1.018 suggests adequate urine-concentrating ability.

Proteinuria

The normal daily albumin excretion rate is less than 150 mg/day. Proteinuria is present in 5% to 10% of adults during screening examinations. Transient proteinuria may be associated with fever, congestive heart failure, seizure activity, pancreatitis, and exercise. Orthostatic proteinuria occurs in up to 5% of adolescents while in the upright position and resolves with recumbency; this typically is not associated with any deterioration in renal function. Persistent proteinuria generally connotes significant renal disease. Microalbuminuria is an early sign of diabetic nephropathy. Rates greater than 300 mg/day are considered severely increased and greater than 3500 mg/day are in the nephrotic range. Severe proteinuria may result in hypoalbuminemia, with associated decreases in plasma oncotic pressures and increases in unbound drug concentrations. The severity of albuminuria is used in the staging of CKD.

Fractional Excretion of Sodium

The fractional excretion of sodium (FENa) is a measure of the percentage of filtered sodium excreted in the urine (Table 21.3). It is most useful in the differentiation between prerenal and renal disease. A FENa less than 1% occurs when normally functioning renal tubules are conserving sodium and is suggestive of prerenal disease. A FENa greater than 2% reflects decreased ability of the renal tubules to conserve sodium and is consistent with tubular dysfunction.

Urinalysis

Examination of the urine is useful in the workup of renal and urologic diseases. Substances not ordinarily in a healthy urine can be detected, such as protein, glucose, hemoglobin, leukocytes, and toxins. The urine pH and specific gravity are determined, and sediment microscopy is used to identify the presence of cells, casts, microorganisms, and crystals. Hematuria may be caused by bleeding anywhere between the glomerulus and urethra. Microhematuria may be benign or may reflect glomerulonephritis, renal calculi, or cancer of the genitourinary tract. Sickle cell disease is a consideration in black patients who exhibit hematuria. Red blood cell casts are typical of acute glomerulonephritis. White blood cell (WBC) casts are commonly seen with pyelonephritis. Granular casts are characteristic of acute tubular necrosis (ATN).

TABLE 21.3 Calculation of Fractional Excretion of Sodium (FENa)

$$FENa\ (\%) = [(P_{Cr} \times U_{Na}) / (P_{Na} \times U_{Cr})] \times 100$$

Urine and plasma concentrations of creatinine and sodium measured in mg/dL. *Cr*, Creatinine; *Na*, sodium; *P*, plasma; *U*, urine.

ACUTE KIDNEY INJURY

AKI is characterized by deterioration of renal function over a period of hours to days, resulting in failure of the kidneys to excrete nitrogenous waste products and to maintain fluid and electrolyte homeostasis.

AKI has been estimated to affect nearly 20% of all hospitalized patients and up to 50% of patients admitted to intensive care units. Hypotension and hypovolemia are the most common causal factors. Nephrotoxins also contribute in a significant percentage of cases.

Diagnosis of Acute Kidney Injury

Presenting signs and symptoms of AKI range widely depending on the etiology. Patients may be asymptomatic, complain of generalized malaise, or be unresponsive in the setting of severe azotemia and acidosis. A hypovolemic patient with a prerenal injury may have recent weight loss and orthostatic vitals, whereas a cirrhotic patient with prerenal injury may present with dyspnea and appear volume overloaded on exam.

The diagnosis of AKI is usually made based on identification of one of the following: an increase in serum creatinine concentration of more than 0.3 mg/dL within 48 hours, an increase of at least 1.5 times the baseline creatinine within a 7-day period, or an abrupt decrease in urine output to less than 0.5 mL/kg/hr or 500 mL/day. A decrease in urine output does not necessarily accompany all cases of AKI. Depending on urine volume, AKI is divided into oliguric and nonoliguric subtypes. Anuria (i.e., urine output < 100 mL/day) rarely occurs in the context of AKI. Azotemia is a condition marked by abnormally high serum concentrations of nitrogen-containing compounds, such as BUN and creatinine, and is a hallmark of AKI regardless of its cause.

Etiology of Acute Kidney Injury

The etiology of AKI is classically divided into prerenal, intrarenal (or intrinsic), and postrenal causes (Table 21.4).

Prerenal Disease

Prerenal AKI occurs when there is insufficient renal perfusion. It is the most common form of AKI, accounting for nearly half of hospital-acquired cases of AKI. Prerenal azotemia is rapidly reversible if the underlying cause is corrected. Sustained prerenal disease is the most common factor that predisposes patients to ischemia-induced ATN. Elderly patients are uniquely susceptible to prerenal azotemia because of their predisposition to poor fluid intake, greater likelihood of polypharmacy (including potential nephrotoxins), and higher incidence of comorbidities (including renovascular disease). Among hospitalized

TABLE 21.4 Etiology of Acute Kidney Injury

Prerenal Azotemia
Hemorrhage
Gastrointestinal fluid loss
Trauma
Surgery
Burns
Cardiogenic shock
Sepsis
Hepatic failure
Aortic/renal artery clamping
Thromboembolism
Drugs impairing renal autoregulation (i.e., NSAIDs, ACE inhibitors, ARBs)

Renal Azotemia
Acute glomerulonephritis
Acute interstitial nephritis (drug related, infectious, malignancy, autoimmune)
Acute tubular necrosis
Ischemia
Nephrotoxic drugs (aminoglycosides, NSAIDs)
Solvents (carbon tetrachloride, ethylene glycol)
Heavy metals (mercury, cisplatin)
Radiographic contrast dyes
Myoglobinuria
Intratubular obstruction (crystals, paraproteinemia)

Postrenal Azotemia
Nephrolithiasis
Benign prostatic hyperplasia
Clot retention
Malignancy

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *NSAID*, nonsteroidal antiinflammatory drug.
Data from Levey AS, James MT. Acute kidney injury. *Ann Intern Med*. 2017;167(9): ITC69, figure 21–2.

TABLE 21.5 Characteristic Urinary Indices in Patients With Acute Oliguria Due to Prerenal or Renal Causes

Index	Prerenal Causes	Renal Causes
Urinary sodium concentration (mEq/L)	20	40
Urine osmolality (mOsm/kg)	⁻500	⁻350
Fractional excretion of sodium (%)	_1	_1
BUN to creatinine ratio	20	20
Proteinuria	Minimal	Mild to moderate
Sediment	Normal, occasional hyaline casts	Renal tubular epithelial cells, "muddy brown" granular casts

BUN, Blood urea nitrogen.
Data from Feehally J, Floege J, Tonelli M, et al., eds. *Comprehensive Clinical Nephrology*. New York, NY: Elsevier; 2019; Schrier RW, Wang W, Poole B, et al. Acute renal failure: definition, diagnosis, pathogenesis, and therapy. *J Clin Invest*. 2004;114(1):6, table 1.

patients, prerenal azotemia is often due to congestive heart failure, liver dysfunction, or septic shock. In the perioperative setting, anesthetic drugs are likely to reduce renal blood flow and perfusion pressure, particularly in the presence of hypovolemia and surgical blood loss.

Urinary indices are helpful in distinguishing prerenal from intrinsic AKI (Table 21.5). The use of urinary indices is based on the assumption that the ability of renal tubules to reabsorb sodium and water is maintained in the presence of prerenal causes of AKI, whereas these functions are impaired in the presence of tubulointerstitial disease or ATN. Blood and urine specimens for determination of urinary indices should be obtained before the administration of fluids, dopamine, mannitol, or other diuretic drugs.

Intrinsic Renal Disease

Intrinsic renal diseases that result in AKI are commonly categorized according to the primary site of injury (glomerulus, renal tubules, interstitium, renal vasculature). Glomerular diseases are often described as having either a nephritic or nephrotic pattern, though these can overlap. The classic nephritic pattern is seen in glomerulonephritis, where inflammation of the glomerulus leads to filtration of white and red blood cells into the tubule, resulting in an active urinary sediment, which consists of cellular elements often in the form of casts. Nephrotic syndrome is the classic nephrotic pattern, characterized by excessive proteinuria and an absence of cellular elements. Tubulointerstitial injury is most often due to ischemia or nephrotoxins (aminoglycosides, radiographic contrast agents). Injury may also occur during reperfusion due to an influx of inflammatory cells, cytokines, and oxygen free radicals. Up to three-quarters of cases of acute interstitial nephritis are attributable to medications, the majority of which are antibiotics and NSAIDs. Diseases of the renal vasculature that may cause AKI include vasculitides, atheroembolic disease, or renal vein thrombosis. Immunologic diseases such as scleroderma and thrombotic microangiopathies (i.e., hemolytic uremic syndrome) may also damage renal vessels and cause AKI.

Postrenal Disease

Postrenal or obstructive disease is the least common and most easily reversible mechanism for AKI. Postrenal injury occurs when urinary outflow tracts are obstructed, as with prostatic hypertrophy, ureteral stones, or cancer-causing extrinsic compression. It is important to diagnose postrenal causes of AKI promptly because the potential for recovery is inversely related to the duration of the obstruction. Renal ultrasonography is often useful for determining the presence of obstructive nephropathy. Percutaneous nephrostomy can relieve obstruction and rapidly improve renal function.

Risk Factors for Development of Acute Kidney Injury

Risk factors for the development of AKI include preexisting renal disease, advanced age, diabetes, sepsis, trauma, hypovolemia,

TABLE 21.6 Risk Factors for Perioperative Renal Failure

Advanced age	High-risk surgical procedures
Preexisting renal insufficiency	Renal vascularization
Congestive heart failure	Aortic cross-clamping
Diabetic nephropathy	Cardiopulmonary bypass
Hypertensive nephropathy	Urologic surgery
Liver failure	Transplantation
Pregnancy-induced hypertension	Trauma
Autoimmune disease	Nephrotoxins
(e.g., systemic lupus	Aminoglycoside antibiotics
erythematosus)	Radiocontrast dyes
Sepsis/shock	Nonsteroidal antiinflammatory drugs

Data from Sladen RN. Oliguria in the ICU: systemic approach to diagnosis and treatment. *Anesthesiol Clin North America.* 2000;18(4):740, table 21.1.

chronic liver disease, congestive heart failure (CHF), anemia, proteinuria, and burns (Table 21.6). Iatrogenic components that predispose to AKI include emergency surgery, major operative procedures (in particular those requiring cardiopulmonary bypass), inadequate fluid resuscitation, sustained hypotension, delayed treatment of sepsis, and administration of nephrotoxic drugs or dyes.

Complications Associated With Acute Kidney Injury

Acute, severe complications of AKI result from impaired fluid balance and electrolyte homeostasis. Retained fluid and solutes, together with inability to maintain pH, lead to volume overload, electrolyte abnormalities, and metabolic acidosis. AKI manifests in organ system dysfunction throughout the body. In addition, infections occur frequently in patients who develop AKI and are a leading cause of morbidity and mortality.

Neurologic complications of AKI include confusion, asterixis, somnolence, seizures, and polyneuropathy. These changes appear to be related to the buildup of protein and amino acids in the blood and fluid overload, and symptoms may be ameliorated by dialysis.

Cardiovascular and pulmonary complications include systemic hypertension, congestive heart failure, and pulmonary edema, reflecting salt and water retention. The presence of congestive heart failure or pulmonary edema suggests the need to decrease the intravascular fluid volume. Cardiac dysrhythmias may develop; peaked T waves and widened QRS complexes are indicative of hyperkalemia. Uremic pericarditis may also occur.

Hematologic complications include anemia, decreased vitamin D activation, and coagulopathy in the setting of uremia-induced platelet dysfunction. Hematocrit values between 20% and 30% are common as a result of hemodilution and decreased erythropoietin (EPO) production.

Metabolic derangements include hyperkalemia, hyperphosphatemia, hypocalcemia, hypermagnesemia, hypoalbuminemia, hyponatremia, and metabolic acidosis.

Gastrointestinal complications include anorexia, nausea, vomiting, and ileus. Gastroparesis may occur due to uremia. Upper gastrointestinal bleeding occurs in as many as one-third of patients who develop AKI and may contribute to anemia.

Infection commonly affects the respiratory and urinary tracts and sites where breaks in normal anatomic barriers have occurred owing to indwelling catheters. Impaired immune responses due to uremia may contribute to the increased likelihood of infections in patients with AKI.

Treatment of Acute Kidney Injury

Management of AKI is aimed at limiting further renal injury and correcting fluid, electrolyte, and acid-base derangements. Triage should be performed to assess the need for emergent renal replacement therapy (RRT). Underlying causes should be identified and terminated or reversed where possible. Specifically, hypovolemia, hypotension, and low cardiac output should be corrected, sepsis treated, and ongoing insults such as nephrotoxic drugs removed. A mean arterial pressure (MAP) of 65 mm Hg should be attained, but there is no evidence of better outcomes when supraphysiologic values of either systemic pressure or cardiac output are targeted.

Fluid resuscitation and vasopressor therapy are universally emphasized in the prevention and treatment of AKI. While there is significant practice variation on choice of crystalloid, balanced salt solutions such as lactated Ringer are increasingly used, particularly if a significant amount of fluid administration is anticipated. Traditionally, 0.9% normal saline was the preferred crystalloid for use in patients with renal dysfunction because it lacks potassium. However, significant resuscitation with normal saline increases the risk of hyperchloremic metabolic acidosis with resultant hyperkalemia and may predispose to AKI. Hydroxyethyl starch should be avoided, as it has been implicated as a possible cause of AKI.

In the treatment of AKI associated with sepsis, most recommendations favor the use of norepinephrine, titrating to maintain a MAP of 65 to 70 mm Hg or baseline blood pressure if known. Vasopressin is an alternative to traditional vasopressors in the treatment of septic shock and may be effective when other agents have failed. It may be of particular use in managing vasoplegia after cardiopulmonary bypass.

The use of dopamine to either treat or prevent AKI is not supported by the literature and in fact may have undesirable side effects, including tachycardia. Fenoldopam is a dopamine analogue with exclusively dopamine-1 agonist activity. Fenoldopam causes renal vasodilation at low doses and peripheral vasodilation at higher doses. Despite the theoretical renal benefit, the results of clinical trials using fenoldopam have been mixed, and it is not recommended in the setting of AKI.

Loop diuretics can be used in the hypervolemic, nonanuric patient with AKI; they can be continued if the patient is diuretic responsive. There is some evidence to suggest that the risk of posttransplantation ATN may be reduced in patients treated with mannitol plus hydration compared with hydration alone. The mechanism of action presumably relates to mannitol's ability to cause renal vasodilation through the production of renal prostaglandins. Mannitol is also commonly used in the treatment of pigment-induced nephropathies; however, clinical evidence of its benefit in this context is weak.

Prophylactic administration of N-acetylcysteine, an antioxidant that acts as a free radical scavenger, has been evaluated to protect against contrast-induced AKI. However, it is not recommended owing to conflicting data and the risk of serious complications such as anaphylactoid reactions. The same is true of the prophylactic administration of mannitol, statins, and sodium bicarbonate. However, alkalinization of urine with sodium bicarbonate is helpful in the treatment of pigment-induced nephropathies such as rhabdomyolysis, as it increases the solubility of myoglobin and prevents the formation of tubular precipitates.

Patients with AKI should receive adequate nutrition, ideally enterally. Protein and energy requirements increase in the context of sepsis and worsening underlying disease, and malnutrition can contribute to impaired immune system function. In diabetics, glucose should be kept under reasonable control to avoid exacerbation of the renal injury. Maintaining blood glucose below 180 mg/dL is a reasonable strategy. Restrictions on potassium, phosphorous, and sodium intake are usually necessary.

Renal replacement therapy remains the mainstay of treatment for severe AKI. The acronym AEIOU calls to mind indications for emergent RRT: severe metabolic acidosis, severe electrolyte abnormalities (in particular hyperkalemia), ingestion of dialyzable toxin (i.e., lithium, ethylene glycol), fluid overload (i.e., pulmonary edema), and signs or symptoms of severe uremia (i.e., seizures, hemodynamically significant pericardial effusion). RRT modalities include continuous RRT, intermittent hemodialysis, and peritoneal dialysis. The purpose of all of them is to remove excess fluid and solutes from the blood and optimize pH and electrolyte balance. The choice of RRT modality depends on the availability of resources and patient characteristics; there are no data supporting one method over another.

Prognosis for Patients With Acute Kidney Injury

AKI is a significant risk factor for both short- and long-term mortality. AKI in hospitalized patients confers an approximately 30% increased risk of death. For AKI in the setting of multiorgan failure, the mortality rate exceeds 50%. The most common causes of death are sepsis, cardiovascular dysfunction, and pulmonary complications. Patients who survive AKI have an increased risk of developing CKD.

Drug Dosing in Patients With Acute Kidney Injury

Renal impairment affects most organ systems and consequently the pharmacology of many drugs. The selection of drugs that do not rely on the kidneys for excretion is ideal but not always possible. Consultation with a pharmacist is recommended.

The first step in tailoring drug dosing for patients with renal impairment is to estimate the GFR. Doses rarely require modification until the GFR is less than 30 mL/min. If creatinine is stable, then the calculated estimate of GFR is a reasonable estimate of renal function. If creatinine is rapidly rising, however, calculated GFR is likely an overestimate. Conversely, if creatinine is falling quickly, the estimated GFR (eGFR) is probably less than the actual GFR.

Loading doses often require no adjustment, unless the estimated volume of distribution is increased, as in cases of fluid overload. Maintenance doses are usually decreased in proportion to the decrease in GFR, taking into account the percentage of drug that is renally cleared. In general, maintenance doses may be reduced by one of two methods: the interval method or the dose method. With the interval method, the patient receives the usual drug dose at longer dosing intervals. With the dose method, the patient receives a smaller drug dose at the usual dosing interval.

For medications with wide therapeutic ranges or long plasma half-lives, the interval between doses is generally increased. For medications with narrow therapeutic ranges or short plasma half-lives, reduced doses at normal intervals are advised. In reality, a combination of the two methods of dose adjustment is frequently used (Table 21.7).

Drugs with active or toxic metabolites are best avoided, as these metabolites can accumulate in patients with renal disease. Predictable nephrotoxins are also to be avoided. These include drugs that reduce renal perfusion (e.g., ACE inhibitors, angiotensin receptor blockers [ARBs], NSAIDs, diuretics) and those that are may act as renal tubular toxins (aminoglycosides, vancomycin, and contrast media).

TABLE 21.7 Analgesic Dose Adjustments in Patients With Renal Insufficiency

Drug	Adjustment Method	GFR > 50 mL/min	GFR 10–50 mL/min	GFR < 10 mL/min
Acetaminophen	↑ interval	q4h	q6h	q8h
Acetylsalicylic acid	↑ interval	q4h	q4–6h	Avoid
Alfentanil	↔ dose	100%	100%	100%
Codeine	↓ dose	100%	75%	50%
Fentanyl	↓ dose	100%	75%	50%
Ketorolac	↓ dose	100%	50%	25–50%
Meperidine	↓ dose	100%	Avoid	Avoid
Methadone	↓ dose	100%	100%	50–75%
Morphine	↓ dose	100%	75%	50%
Remifentanil	↔ dose	100%	100%	100%
Sufentanil	↔ dose	100%	100%	100%

↓, Decrease; ↑, increase; ↔, no change; *GFR*, glomerular filtration rate; *q*, every.

Data from Olyaei A, Bennett WM. Practical guidelines for drug dosing in patients with impaired kidney function. In: Schrier RW, ed. *Manual of Nephrology*. ed 8. Philadelphia, PA: Lippincott Williams & Wilkins; 2015.

Gastrointestinal absorption can be reduced in AKI due to gut edema, nausea and vomiting, and coadministration with phosphate binding drugs; however, this would rarely be of concern perioperatively because the vast majority of medications are given intravenously.

Anesthetic Management of Patients With Acute Kidney Injury

A thorough preoperative evaluation of the patient with AKI should include an electrocardiogram (ECG), serum chemistries, complete blood count, coagulation parameters, and urinary indices. Chest imaging is reasonable if there is respiratory insufficiency. Owing to the high morbidity and mortality, only lifesaving surgery should be undertaken in patients with AKI. The principles guiding the management of anesthesia are the same as those that guide supportive treatment of AKI, namely maintenance of an adequate systemic blood pressure and cardiac output and avoidance of further renal insults, including hypovolemia, hypoxia, and exposure to nephrotoxins.

Adequate peripheral venous access must be obtained, which often requires a second and large-bore IV. Invasive hemodynamic monitoring is advised to facilitate careful control of blood pressure and to accommodate frequent blood gas analyses and electrolyte measurements. Hyperkalemia in particular should be monitored for closely and treated aggressively, if identified.

Preoperative dialysis may be indicated in high-risk patients. If there is a suspicion of platelet dysfunction, desmopressin (DDAVP) can be administered preoperatively to temporarily increase concentrations of von Willebrand factor (vWF) and factor VIII and improve coagulation. Correction of anemia, targeting a hemoglobin of 10 g/dL, is also likely to reduce bleeding. This can be done with administration of iron, EPO, or transfusion depending on the etiology of the anemia and the urgency of the surgery. Estrogens and cryoprecipitate may also be of use in suspected uremic bleeding.

Maintenance (and restoration, if necessary) of intravascular fluid volume is essential to maintain renal perfusion. It is also important to maintain adequate systemic blood pressure and cardiac output and to avoid excessive peripheral vasoconstriction. Potentially nephrotoxic substances (i.e., NSAIDs, aminoglycosides, radiocontrast, proton pump inhibitors) and those that may contribute to prerenal injury (i.e., diuretics, ACE inhibitors, ARBs) should be prescribed cautiously, particularly during acute illness. For the particular case of anticipated contrast exposure, preventative measures include use of low-osmolar agents, reduced doses, and periprocedural volume expansion with isotonic fluids.

If a large volume resuscitation is required during a procedure, or if there are signs of hypervolemia, diuretics can be considered in the nonoliguric patient to reduce the risk of complications of volume overload. For patients who meet criteria, postoperative dialysis should be initiated as soon as the patient is hemodynamically stable.

Morphine (and codeine, which is metabolized to morphine), meperidine, and tramadol are best avoided in patients with reduced GFR due to the possible accumulation of the toxic metabolites morphine-6-glucuronide (neurotoxicity), normeperidine (seizures), and O-desmethyltramadol (seizures), respectively. Succinylcholine is typically avoided if potassium concentrations are greater than 5.5 mEq/L. If neuromuscular blockade is required, cisatracurium is a good choice due to its degradation by Hofmann elimination in the plasma. Antibiotics known to be nephrotoxic should be avoided or administered in reduced dose.

CHRONIC KIDNEY DISEASE

CKD is the progressive, irreversible deterioration of renal function resulting from a wide variety of diseases (Fig. 21.2). CKD is defined as an estimated GFR below 60 mL/min persisting for over 3 months. In most patients, regardless of the etiology, a decrease in the GFR to less than 25 mL/min eventually progresses to end-stage renal disease (ESRD) requiring dialysis or transplantation. Clinical manifestations of uremia generally appear when the GFR falls below 15 mL/min.

Just under 15% of American adults have CKD. Approximately half of the American population will develop CKD at some point in their lifetime. Rates of ESRD continue to rise, with a national prevalence of over 725,000 in 2016. In the United States, diabetes mellitus is the leading cause of ESRD followed closely by hypertension.

There are remarkable racial disparities in the incidence of ESRD. Compared to white patients, ESRD rates among black and Native American populations are 3.6 and 1.8 times greater, respectively. The rate of ESRD among Hispanics is 1.5 times higher than among non-Hispanics. Hypertensive nephropathy accounts for a relatively higher proportion of ESRD cases among black patients compared to other racial or ethnic groups. A combination of genetic variables and disparities in healthcare access is likely to underlie these differences.

Diagnosis

Signs and symptoms of CKD are often undetectable (Table 21.8). When they do appear, complaints are nonspecific, such as fatigue,

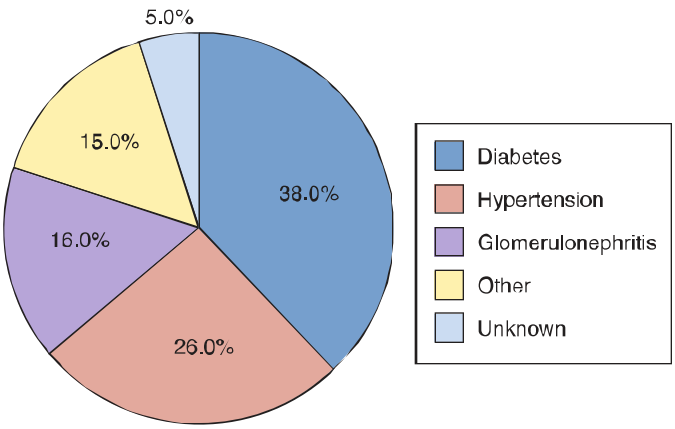

Fig. 21.2 Causes of end-stage kidney disease. The most common causes of end-stage kidney disease are hypertension and diabetes. Other causes include glomerulonephritis and cystic diseases of the kidney. (From US Renal Data System, 2016. https://www.cdc.gov/kidneydisease/publications-resources/2019-national-facts.html.)

TABLE 21.8 Manifestations of Chronic Kidney Disease

- Electrolyte imbalances
  - Hyperkalemia
  - Hypermagnesemia
  - Hyperphosphatemia
  - Hypocalcemia
- Metabolic acidosis
- Unpredictable intravascular fluid volume status
- Anemia
  - Increased cardiac output
  - Oxyhemoglobin dissociation curve shifted to the right
- Uremic coagulopathy
  - Increased bleeding time
  - Platelet dysfunction
- Neurologic changes
  - Autonomic dysfunction
  - Encephalopathy
  - Peripheral neuropathy
- Cardiovascular changes
  - Congestive heart failure
  - Dyslipidemia
  - Systemic hypertension
- Renal osteodystrophy
- Pruritus

TABLE 21.9 Classification of Chronic Kidney Disease Based on GFR and Albuminuria

GFR Stage	GFR	Stage
G1	≥90	1
G2	60–89	2
G3a	45–59	3
G3b	30–44	3
G4	15–29	4
G5	<15	5
Albuminuria Stage	**Albumin Excretion Rate (mg/day)**	
A1	<30	
A2	30–300	
A3	>300	

GFR, Glomerular filtration rate.
Data from KDIGO. Summary of recommendation statements. *Kidney Int.* 2013;3(Suppl):6; 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (CKD). https://kdigo.org/guidelines/ckd-evaluation-and-management.

malaise, and anorexia. Most patients will have the diagnosis made during routine testing. The workup is similar to that described for AKI. A careful history and laboratory evaluation, including serum creatinine and urinary sediment analysis, is helpful in establishing the diagnosis and etiology of renal dysfunction. Renal ultrasound is useful to rule out obstructive disease and screen for polycystic kidney disease. It is also helpful for assessing the renal vasculature and estimating the extent of parenchymal disease through evaluation of renal echogenicity and kidney size. Computed tomography (CT) scanning remains the gold standard for the diagnosis of nephrolithiasis. Renal biopsy may be required to establish the diagnosis.

Progression of Chronic Kidney Disease

Staging of CKD has been established by the international guideline group Kidney Disease: Improving Global Outcomes (KDIGO). Staging is based on eGFR (G-stage) and severity of albuminuria (A-stage) (Table 21.9). The cause of CKD is used in some staging paradigms. The degree of albuminuria may be evaluated by measuring daily albuminuria or using the albumin-to-creatinine ratio (ACR) in a spot urine sample. An ACR greater than 30 mg/g (3.4 mg/mmol) is considered abnormal. Established risk factors for rapid progression of CKD are hypertension, hyperglycemia, severe proteinuria, and black race.

Adaptation to Chronic Kidney Disease

The normally functioning kidneys precisely regulate the concentrations of solutes and water in the extracellular fluid despite large variations in daily dietary intake. Owing to substantial renal reserve function, patients with CKD often remain relatively asymptomatic until renal function is less than 10% of normal.

The kidneys exhibit various compensatory mechanisms to the loss of nephron volume that accompanies CKD. While effective in the short term, these mechanisms can contribute to long-term exacerbation of kidney injury. For example, there is accelerated filtration in the normally functioning nephrons—a process known as hyperfiltration. This occurs as a result of glomerular hypertension and increased glomerular permeability. Filtered macromolecules may result in inflammation and further injury, including glomerulosclerosis. Activation of the renin-angiotensin-aldosterone axis can contribute to chronic tubulointerstitial ischemia and resulting injury. Treatments seek to intervene in this harmful chain of events.

Adaptation to progressive functional impairment can be divided into several stages. The first adaptation involves an increase in substances such as creatinine and urea, which are largely dependent on glomerular filtration for urinary excretion. As the GFR decreases, the plasma concentrations of these substances increase, but the increase is not directly proportional to the degree of GFR impairment. For example, serum creatinine concentrations frequently remain within normal limits despite a 50% decrease in GFR. Beyond a certain point, however, when the renal reserve has been exhausted, even minimal further decreases in the GFR can result in significant increases in the serum creatinine and urea concentrations.

The second stage of adaptation is seen with solutes such as potassium. Serum potassium concentrations are maintained within normal limits until GFR approaches 10% of normal, at which point hyperkalemia manifests. As nephrons are lost, the remaining nephrons increase their secretion of potassium through increased blood flow and increased sodium delivery to the collecting tubules. In addition, because aldosterone secretion increases in patients with renal failure, there is a greater loss of potassium through the gastrointestinal tract. This system of enhanced gastrointestinal secretion is an effective compensatory mechanism in the presence of normal dietary intake of

potassium but can be easily overwhelmed by an acute exogenous potassium load (i.e., packed RBC administration during the perioperative period) or acute endogenous potassium load (i.e., hemolysis or tissue trauma such as that associated with surgery).

The third stage of adaptation is seen in sodium homeostasis and regulation of the extracellular fluid compartment volume. In contrast to the levels of other solutes, sodium balance remains intact despite progressive deterioration in renal function and variations in dietary intake. Nevertheless, the system can be overwhelmed by abruptly increased sodium intake (resulting in volume overload) or decreased sodium intake (resulting in volume depletion).

Complications of Chronic Kidney Disease Affect Multiple Organ System

Cardiovascular

CKD is a powerful risk factor for cardiovascular disease, both because of the CKD process itself and because of underlying cardiovascular risk factors that are often present in this patient group, including advanced age, hypertension, smoking, dyslipidemia, and diabetes mellitus. Indeed, mortality from cardiac causes is at least 10 times higher in the CKD versus non-CKD patient.

Nontraditional risk factors also play a role in the increased cardiovascular disease burden. These factors stem from the disease process itself and include the uremic and inflammatory milieu, sympathetic nervous system activation, poor nutrition, oxidative stress, elevated serum calcium with vascular calcification, and endothelial dysfunction.

Systemic hypertension contributes to left ventricular hypertrophy, congestive heart failure, coronary artery disease, and cerebrovascular disease. Uncontrolled systemic hypertension also speeds the progression of renal disease. The pathogenesis of systemic hypertension is multifactorial. Intravascular volume expansion due to retention of sodium and water in the setting of both sympathetic and RAAS activation plays a key role. Dyslipidemias and varying degrees of insulin resistance are common at all stages of CKD and increase the risk of cardiovascular morbidity and mortality. Approximately 40% of dialysis patients are diabetic. Patients with CKD also have greater incidence of peripheral arterial disease, stroke, atrial fibrillation, cardiac arrest, aortic stenosis, and obstructive sleep apnea than similar patients with normal renal function.

Acute myocardial infarction (AMI) in patients with CKD predicts a worse outcome than in a population without CKD, with 2-year mortality over 70% in dialysis patients. Unfortunately, acute coronary syndrome is often underrecognized and undertreated in ESRD patients. One possible explanation is that this population will less often experience typical chest pain and ST-segment elevation.

Cardiac tamponade and hemodynamic instability associated with uremic pericarditis are indications for prompt drainage of the effusion, either via percutaneous pericardial catheter or pericardial window. Hypotension unresponsive to intravascular fluid volume replacement in a patient with ESRD should prompt an immediate workup for cardiac tamponade.

Anemia

Anemia frequently accompanies CKD and is presumed to be responsible for many of the symptoms (fatigue, weakness, decreased exercise tolerance) characteristic of what was historically described as the "uremic syndrome." The anemia of CKD is usually normochromic and normocytic and is primarily due to decreased renal EPO production. Gastrointestinal bleeding, serial phlebotomy, replacement of bone marrow with fibrous tissue in renal osteodystrophy, and chronic inflammation may also contribute to anemia. Chronic anemia results in cardiovascular sequelae, including chronically increased cardiac output, left ventricular hypertrophy, left ventricular dilation, and, if severe, myocardial ischemia.

Uremic Bleeding

Patients with CKD have an increased tendency to bleed despite the presence of a normal platelet count, prothrombin time, and plasma thromboplastin time. The bleeding time, while rarely performed, is the screening test that best correlates with bleeding risk. Hemorrhagic episodes (gastrointestinal bleeding, epistaxis, hemorrhagic pericarditis, subdural hematoma) are significant sources of morbidity in patients with CKD and contribute to persistent anemia.

Renal Osteodystrophy

Changes in bone structure and mineralization are nearly universal in patients with CKD. The most important factors are secondary hyperparathyroidism (HPT) and decreased vitamin D production by the kidneys. Decreased vitamin D production impairs intestinal absorption of calcium. Hypocalcemia stimulates parathyroid hormone (PTH) secretion, which increases bone resorption to restore serum calcium concentrations. As the GFR decreases, there is a parallel decrease in phosphate clearance and an increase in the serum phosphate concentration. Increased serum phosphate results in a reciprocal decrease in serum calcium concentration, exacerbating the HPT and resulting in calcium phosphate crystal deposits that can exacerbate joint pain. Radiographs demonstrate evidence of bone demineralization. Clinically, renal osteodystrophy may manifest as joint pain, weakness, fractures, and kyphoscoliosis.

Neurologic

Neurologic changes may be early manifestations of progressive renal insufficiency. Symptoms range from mild (impaired abstract thinking, insomnia, irritability) to severe (seizures, obtundation, uremic encephalopathy, coma) as renal disease progresses. A disabling complication of ESRD is the development of a distal, symmetric mixed motor and sensory polyneuropathy, marked by paresthesias, hyperesthesias, or distal lower extremity weakness. The arms may also be affected. Superimposed diabetic neuropathy may be present, including autonomic neuropathy. The extent to which hemodialysis improves uremic polyneuropathy depends on the severity of symptoms at baseline.

Immunologic

Based on statistics from the 2016 US Renal Data System, infection is the second leading cause of mortality in ESRD patients

at 8%, second only to cardiovascular disease. Immune system dysfunction and indwelling vascular access account for some of this increased risk. Both pulmonary and urinary tract infections are dramatically increased in patients with ESRD. In patients between the ages of 18 and 54 years, an eGFR less than 30 mL/min results in a 15-fold increased risk of hospitalization with pneumonia and a more than 20-fold increased risk of death from pneumonia compared to an eGFR of 60 to 104 mL/min.

Prevention and Treatment of Complications of Chronic Kidney Disease

Management of patients with CKD includes aggressive treatment of the underlying cause, pharmacologic therapy to delay disease progression and prevent complications, as well as preparation for renal replacement therapy as ESRD ensues.

Cardiovascular

Many of the prevention strategies in CKD are identical to those employed in patients with normal renal function. For example, exercise, smoking cessation, and balanced diet with maintenance of a normal body weight are recommended.

All patients with CKD should be screened with a lipid panel. Hypertriglyceridemia is the most common lipid abnormality in patients with CKD but is usually managed with dietary modifications. Statins are often recommended as primary prevention against cardiovascular disease when the GFR drops below 60 mL/min/1.73 m^2, especially when other cardiovascular risk factors are present.

Reductions in both systemic and glomerular hypertension are important in slowing the progression of CKD. A target blood pressure less than 130/80 mm Hg is commonly recommended, especially in patients with proteinuria. ACE inhibitors or ARBs are typically first-line antihypertensives, particularly in proteinuric and diabetic patients. Both of these drug categories have been demonstrated to have renoprotective effects, including reductions in proteinuria and slowing of the progression of glomerulosclerosis. Nondihydropyridine calcium channel (e.g., diltiazem, verapamil) and mineralocorticoid receptor blockers (e.g., spironolactone) also have renoprotective effects and may be added as second-line agents if blood pressure goals are not met with monotherapy.

Effective glycemic control in patients with diabetes is critical. Reasonable HbA_{1c} targets are below 7.0% in mild CKD and below 8.0% in moderate and advanced CKD, given the increased harm of severe hypoglycemia in these sicker, frailer patients. Relatively novel agents such as sodium-glucose cotransporter 2 (SGLT2) inhibitors may play an increasing role in diabetic patient management given their apparent effectiveness in reducing cardiovascular morbidity and mortality and progression of nephropathy.

Baseline ECG and echocardiogram are useful in CKD patients, particularly in those initiating dialysis. Chemical stress testing may be preferred to exercise stress testing, as patients in renal failure are often unable to exercise adequately. While there is ample evidence that coronary artery disease and acute coronary syndrome are underrecognized and undertreated in the CKD population, best practices suggest that they should be worked up and treated in the same manner as patients without CKD.

Anemia

Patients with CKD who exhibit anemia should be screened for the usual causes, including iron, folate, and vitamin B_{12} deficiency and occult bleeding. Treatment of the anemia of CKD is with recombinant human EPO or darbepoetin. Intermittent injections of parenteral iron are recommended to maximize the response to EPO. Blood transfusions are avoided due to complications, including volume overload, transfusion reactions, and the risk of human leukocyte antigen (HLA) alloimmunization jeopardizing future kidney transplantation. A hemoglobin target between 10 and 11 g/dL is reasonable. The acute development or exacerbation of systemic hypertension, possibly with seizure, is a risk of EPO administration. Looking ahead, novel hypoxia-inducible factor inhibitors such as roxadustat may see increasing use.

Nutrition

A number of studies in both diabetic and nondiabetic patients with CKD have demonstrated that modest protein restriction reduces the progression of renal disease. However, an overly restrictive diet places patients at risk for malnutrition. Reducing daily protein intake to approximately 0.7 mg/kg is advised.

Dietary sodium restriction has been shown to lower urinary protein excretion, especially in patients who are being treated with ACE inhibitors. Salt intake is typically limited to approximately 2 to 3 g sodium daily.

Renal Osteodystrophy

Treatment of secondary hyperparathyroidism centers on restricting dietary phosphate intake (largely limiting protein and dairy), administering phosphate binders, and administering vitamin D supplements. If medical therapies fail to control hypocalcemia due to secondary HPT, subtotal parathyroidectomy is often recommended.

Uremic Bleeding

DDAVP can be administered to temporarily increase concentrations of vWF and factor VIII and improve coagulation. The maximal effect is present within 2 to 4 hours and lasts for about 6 to 8 hours. Tachyphylaxis appears to develop with repeat doses and may be related to depletion of endothelial stores of vWF (Table 21.10). Correction of anemia, targeting a hemoglobin of 10 g/dL, is also likely to reduce bleeding.

Conjugated estrogens have also been shown to improve bleeding times in patients with uremia. The time to onset of action is about 6 hours, but the effects last 14 to 21 days. Cryoprecipitate may also be of use in suspected life-threatening uremic bleeding; improvement should be seen within 1 hour.

Renal Replacement Therapy

Referral for RRT is usually advised when the GFR reaches 15 to 20 mL/min or less and therapy initiated at GFR of 10 mL/min

TABLE 21.10 Treatment of Uremic Bleeding

Drug	Dose	Onset of Effect	Duration of Effect
Cryoprecipitate	10 units IV over 30 min	~1 hr	4–24 hr
DDAVP (desmopressin)	0.3 μg/kg IV or SC or 3 μg/kg intranasally	~1 hr	4–8 hr
Conjugated estrogen	0.6 mg/kg/day IV for 5 days or 2.5–25 mg PO daily	6 hr	14 days

IV, Intravenous; *PO,* by mouth; *SC,* subcutaneous.

TABLE 21.11 Findings Suggestive of Inadequate Hemodialysis

Clinical

Anorexia, nausea, vomiting
Poor nutritional status
Depressed sensorium
Pericarditis
Ascites
Minimal weight gain or weight loss between treatments
Fluid retention and systemic hypertension

Chemical

Decrease in blood urea nitrogen concentration during hemodialysis <65%
Albumin concentration <4 g/dL
Predialysis blood urea nitrogen concentration >150 mg/dL (a sign of malnutrition)
Predialysis serum creatinine concentration <5 mg/dL (a sign of malnutrition)
Persistent anemia (hematocrit <30%) despite erythropoietin therapy

Data from Ifudu O. Care of patients undergoing hemodialysis. *N Engl J Med.* 1998;339(15):1054, table 1.

or less. There is clear evidence that the dialysis dose is significantly correlated with survival. Since clinical signs and symptoms are not reliable indicators of dialysis adequacy, the delivered dose should be measured and monitored routinely (Table 21.11). Dialysis dose can be calculated from a number of different formulas or models; all of them rely on urea clearance, which is calculated using the difference in predialysis and postdialysis plasma BUN. Urea is used to calculate dialysis dose because it is a small, readily dialyzed solute that rapidly equilibrates after dialysis.

Dialysis is the indicated treatment of patients who are hypertensive because of hypervolemia despite salt restriction and appropriate diuretic therapy, and in those who develop uremic pericarditis. In these patients, dialysis is likely to improve hypertension control and reduce left ventricular mass.

Hemodialysis

Hemodialysis involves the diffusion of solutes between the blood and dialysis solution. This results in the removal of metabolic waste products and excess fluid volume, as well as the replenishment of body buffers. During the procedure, blood is heparinized and passed through a plastic dialyzer, with dialysate flowing in countercurrent across a semipermeable membrane (Fig. 21.3). The dose of dialysis, type of dialysis membrane, and solute clearance are the most important modifiable factors. A typical dialysis session lasts for about 4 hours and typically targets about a 65% reduction in serum BUN. The annual adjusted mortality for patients on dialysis as of 2016 was approximately 16%, which is decreased nearly 30% from 2001. The majority of this mortality is attributable to cardiovascular

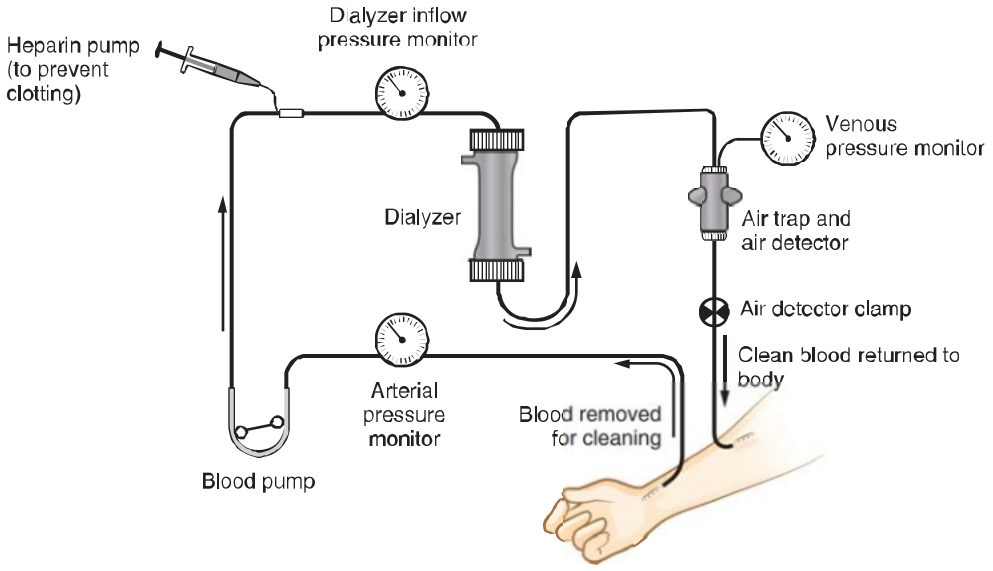

Fig. 21.3 Hemodialysis circuit. Hemodialysis involves the diffusion of solutes across a semipermeable membrane between the blood and a dialysis solution. This results in removal of metabolic waste products and excess fluid volume, as well as replenishment of body buffers. During the procedure, blood is heparinized and passed through a plastic dialyzer. Filtered blood is then returned to circulation after passing through an air detection trap. (From http://www.niddk.nih.gov/health-information/health-topics/kidney-disease/hemodialysis/Pages/facts.aspx.)

disease, with arrhythmia and/or cardiac arrest accounting for 40% of known causes.

Peritoneal Dialysis

Peritoneal dialysis (PD) is the mode of dialysis delivery in less than 10% of patients in dialysis patients in the United States. It requires placing an anchored plastic catheter in the peritoneal cavity for infusion of a dialysate that remains in place for several hours. During that time, diffusive solute transport occurs across the peritoneal membrane until fresh fluid is exchanged for the old fluid. Automated PD, in which a mechanized cycler infuses and drains peritoneal dialysate at night, is used by many patients.

PD may be desirable for patients with congestive heart failure or unstable angina who may not tolerate the rapid fluid shifts or fluctuations in systemic blood pressure that often accompany hemodialysis. PD is also indicated for patients with extensive vascular disease that prevents the placement of vascular access for hemodialysis. In patients with diabetes, insulin can be infused with the dialysate.

There are very few absolute contraindications to PD. Diffuse peritoneal scarring, as from prior surgeries, may interfere with its effective use. Peritonitis is the most common serious complication of peritoneal dialysis. Diagnosis is made based on symptoms (abdominal pain), signs (cloudy effluent peritoneal fluid), and positive dialysate culture. Treatment is with appropriate antibiotics. Survival rates and annual costs are similar with PD and hemodialysis, but hospitalization rates are higher among patients treated with PD.

Drug Clearance in Patients Undergoing Dialysis

Patients who are undergoing dialysis require special consideration with respect to drug dosing and administration schedules. Supplemental dosing may be needed with drugs that are cleared by dialysis. When possible, drug doses are best timed for administration after completion of a dialysis session.

Drug properties that influence clearance by dialysis include protein binding, water solubility, and molecular weight. In this regard, low-molecular-weight (< 500 Da), water-soluble, nonprotein-bound drugs are readily cleared by dialysis. Continuous renal replacement therapies, such as continuous venovenous hemofiltration and continuous arteriovenous hemofiltration, efficiently remove drugs unless they are bound to protein.

Vascular Access

A surgically created vascular access site is necessary for effective chronic hemodialysis. Arteriovenous (AV) fistulas are generally preferred to AV grafts because of their overall lower morbidity and mortality risks. The preferred locations for AV grafts are distal (e.g., radial-cephalic) rather than proximal (e.g., brachial-basilic) (Fig. 21.4). The most common access-related complication is intimal hyperplasia, which results in stenosis proximal to the venous anastomosis. Other complications related to access include thrombosis, infection, aneurysm formation, and limb ischemia. When dialysis is urgently required, vascular access is obtained with a double-lumen dialysis catheter, most often using the jugular or femoral vein. Novel tissue-engineering techniques offer the potential of vascular grafts with functional intimal, media, and adventitial layers.

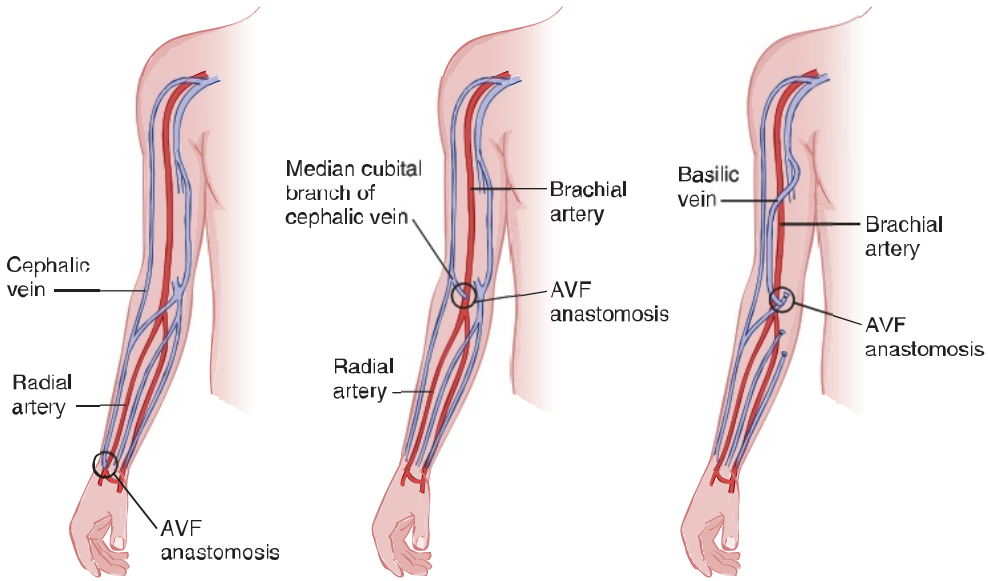

Fig. 21.4 Anatomy of common arteriovenous fistulas (AVFs). Native vessels are preferred for use when vascular access is required for hemodialysis. Both the artery and vein must have lumens of adequate diameter for the procedure to be successful. The radial artery and cephalic vein are the preferred access points when adequate. Alternative access points include the brachial artery and basilic vein. (From Pereira B, Sayegh M, Blake P (eds). *Chronic Kidney Disease, Dialysis, and Transplantation*. ed 2. Philadelphia, PA: Saunders; 2005:344.)

Complications Associated With Hemodialysis

Intradialytic complications. Hypotension is the most common adverse event during hemodialysis, occurring in approximately 25% of treatments. Hypotension during dialysis most likely reflects reduced intravascular volume due to excess fluid removal. Hypotensive episodes may also be due to myocardial stunning and/or ischemia, cardiac dysrhythmias, pericardial tamponade, air embolus, antihypertensive medications, autonomic neuropathy, sepsis, or technical malfunction (i.e., incorrect dialysate composition). Most hypotensive episodes are successfully treated by slowing or suspending ultrafiltration, repositioning the patient to a legs-up or Trendelenburg position, and/or administering small boluses of intravenous saline.

Blood exposure to numerous foreign substances throughout the dialysis process can precipitate dialysis reactions, including anaphylaxis and anaphylactoid reaction. Concomitant ACE inhibitor use predisposes to these reactions.

Dialysis disequilibrium syndrome is marked by nausea, headaches, and fatigue, but may progress to seizures or coma. The condition is perhaps due to rapid changes in pH and osmolarity in the central nervous system. Management includes reducing the rate of dialysate and blood flow, using smaller surface area dialyzers, and supportive care as needed. Muscle cramps and restless leg syndrome are also frequent complaints in the dialysis patient.

Malnutrition and Metabolic

During progressive renal failure, catabolism and anorexia lead to loss of lean body mass, but concomitant fluid retention can mask weight loss. Protein-energy wasting is the current terminology describing this progressive loss in body protein mass and energy reserves; when present, it is a poor prognosticator. Its cause is multifactorial, including decreased oral intake, hemodialysis-induced catabolism, and hormonal imbalances. Routine assessment of nutritional status by exam and biomarkers (albumin, prealbumin) is advised. Management includes dietary consultation and nutritional supplementation geared toward increasing daily protein and calorie intake.

Patients with ESRD have decreased total body potassium stores and a tolerance of hyperkalemia. The expected cardiac and neuromuscular responses to hyperkalemia are less pronounced in patients on hemodialysis than in those with normal renal function. Clearance of potassium by hemodialysis is efficient, and because most potassium is intracellular, it is likely that hypokalemia will be suggested by a blood sample obtained soon after completion of hemodialysis and before transcellular equilibration has occurred. Some restriction in sodium and fluid intake is likely beneficial to prevent volume overload. Normal weight gain between dialysis treatments is 3% to 4% of total body mass.

Decreased catabolism of insulin in many patients on hemodialysis may result in decreased insulin requirements compared with predialysis requirements. The presentation of diabetic ketoacidosis in patients on dialysis is rare; when it does occur, its presentation may be atypical.

Infection

As in nondialysis-dependent CKD, infection is the second leading cause of death in dialysis patients. Contributing factors include impaired phagocytosis, neutrophil chemotaxis, and antibody responses, as well as malnutrition. All patients on hemodialysis should be vaccinated against tetanus, pneumococcus, hepatitis B, varicella zoster, and influenza. However, these patients will have an impaired antibody response to vaccines, and the diagnosis of infection may be difficult because many patients do not mount typical symptoms such as fever.

Similarly, hepatitis B or C virus infection in patients on hemodialysis is often asymptomatic, and liver aminotransferase concentrations may not be increased. A substantial proportion of patients on hemodialysis have antibodies to hepatitis C. Of note, dose adjustments of drugs used to treat human immunodeficiency virus infection are not required during hemodialysis. Tuberculosis in patients on hemodialysis is usually extrapulmonary and often presents with atypical symptoms that mimic those of inadequate dialysis. Because anergy in response to skin testing is common, unexplained weight loss and anorexia, with or without persistent fever, should prompt further testing to rule out tuberculosis.

ANESTHETIC MANAGEMENT OF PATIENTS WITH CHRONIC KIDNEY DISEASE

Management of anesthesia in patients with CKD requires an understanding of the pathologic changes that accompany renal disease, coexisting medical conditions, and the impact of reduced renal function on drug pharmacology (Table 21.12). Assessment of the appropriateness of the contemplated surgery in this high-risk population should be undertaken in concert with the surgery team. Optimization of modifiable risk factors and the development of an anesthetic management plan aimed at minimizing further kidney injury are imperative. The general approach is akin to that described previously for the AKI patient.

Preoperative Evaluation

Common comorbidities in dialysis patients include angina (17%), history of MI (12%), history of transient ischemic attack (TIA) or stroke (11%), smoking (15%), diabetes (9%), and malignancy (13%). While all CKD patients are at increased risk, those who already have impaired oxygen delivery are at the highest risk; in the absence of sophisticated exercise testing, employing a preoperative assessment that can estimate functional capacity will give some insight into this parameter. Evaluation of the Revised Cardiac Risk Index (RCRI) should also be conducted according to American College of Cardiology/American Heart Association guidelines. A RCRI greater than or equal to 2 in the setting of metabolic equivalents (METs) less than 4 should prompt consideration of additional cardiopulmonary workup.

Evaluation of the trend in eGFR is useful in determining whether renal function is stable. Volume status may be estimated by comparing trends in body weight, particularly in dialysis patients where dry weight should be the target preoperatively.

TABLE 21.12 Drugs Used in Anesthesia Practice That Significantly Depend on Renal Elimination

Class	Drugs
Induction agents	Phenobarbital
	Thiopental
Muscle relaxants	Pancuronium
Anticholinergics	Atropine
	Glycopyrrolate
Cholinesterase inhibitors	Edrophonium
	Neostigmine
Cardiovascular drugs	Digoxin
	Inotropes
	Hydralazine
	Milrinone
Antimicrobials	Aminoglycosides
	Cephalosporins
	Penicillin
	Sulfonamides
	Vancomycin
Analgesics	Codeine
	Meperidine
	Morphine

Data from Malhotra V, Sudheendra V, O'Hara J, et al. Anesthesia and the renal and genitourinary systems. In: Miller RD, Cohen NH, Eriksson LI, et al., eds. *Miller's Anesthesia*. ed 8. Philadelphia, PA: Saunders Elsevier; 2015, table 72–7.

In general, patients maintained on dialysis should be dialyzed within the 24 hours preceding elective surgery.

Blood pressure should be well controlled prior to elective surgery. Antihypertensive therapy should be continued; however, ACE inhibitors and ARBs are increasingly withheld on the day of surgery to reduce the risk of hypotension and associated end-organ injury. This hypotension may be especially pronounced if neuraxial anesthesia is administered or blood loss is significant. As diabetes is often seen in these patients, glucose management is of concern; targeting glucose levels less than 180 mg/dL is reasonable. A common recommendation is that the serum potassium concentration should not exceed 5.5 mEq/L on the day of surgery; this recommendation should be tailored to the individual patient and his or her baseline potassium.

Preoperative intervention (i.e., iron, EPO) should be strongly considered for untreated anemia. Similarly, if there is very poor nutritional or functional status, there may be a role for a prehabilitation program, which typically involves a combination of physical and lifestyle modifications to improve recovery after surgery. Preoperative coagulopathy should be identified and treated as appropriate, usually with DDAVP. Gastric aspiration prophylaxis should be considered, especially in diabetic patients. However, H_2-receptor blockers are renally excreted and therefore require dose adjustment.

Monitoring

Intravascular access and invasive blood pressure monitoring are tailored to the individual patient comorbidities and invasiveness of the planned procedure. Arterial waveform analysis can predict fluid responsiveness in the paralyzed, mechanically ventilated patient in sinus rhythm. For high-risk patients, central and/or pulmonary arterial catheters can be of value in estimating intravascular volume and cardiac output, respectively. Transesophageal echocardiography is an alternative method for monitoring hemodynamic status.

Vascular access can be complicated by the need to avoid the extremity in which an AV fistula is present. In addition, if possible, venipuncture should be avoided in the nondominant arm, as well as in the upper part of the dominant arm, to preserve blood vessels for future dialysis access. Similarly, radial and ulnar artery cannulation should be avoided, as they are often used in AV fistula creation. The same may be said of the brachial and even the axillary arteries. Use of the femoral arteries carries the risk of line infection, particularly since these patients are already immunocompromised. These considerations of course become less relevant when there is hemodynamic instability or in the case of urgent or emergent surgery. Remaining options include the dorsalis pedis or posterior tibial arteries, which may be inconvenient because of positioning or difficult to access because of edema and tissue induration. Whichever site is chosen, it is important to note that neither the arterial pressure nor arterial blood gases will be accurate if the cannula is placed in the same extremity as a functioning or partially patent AV fistula.

Although discouraged, temporary dialysis catheters may be accessed for the administration of fluids or drugs if alternative intravenous access proves too difficult. However, strict aseptic technique must be followed when accessing the line. In addition, heparin must be aspirated before connecting to an intravenous line or pressure transducer, and heparin must be reintroduced when access is discontinued.

Induction of Anesthesia

Many patients with ESRD respond to induction of anesthesia as if they were hypovolemic. The likelihood of hypotension is increased when the patient is uremic or is on antihypertensive therapy. Induction drugs should be titrated to effect given their often exaggerated central nervous system and hemodynamic effects in this population. In particular, thiopental has an increased volume of distribution and reduced protein binding in patients with CKD; therefore a reduced dose is advised.

If indicated, rapid-sequence induction with succinylcholine may be performed if the potassium concentration is less than 5.5 mg/dL. Potassium release following administration of succinylcholine is not exaggerated in patients with CKD. Alternatively, a nondepolarizing muscle relaxant with a short onset of action such as rocuronium may be selected, though its reduced clearance will result in a significantly prolonged effect.

Attenuated sympathetic nervous system activity impairs compensatory peripheral vasoconstriction; thus small decreases in blood volume, institution of positive-pressure ventilation, abrupt changes in body position, or drug-induced myocardial depression can result in an exaggerated decrease in systemic blood pressure.

Maintenance of Anesthesia

When general anesthesia is employed, a balanced anesthetic technique using a volatile agent, muscle relaxant, and opioids is

most often selected. Elimination of volatile anesthetics is not dependent on renal function. Sevoflurane may be avoided because of concerns related to fluoride nephrotoxicity or production of compound A, although there is no evidence that patients with coexisting renal disease are at increased risk of renal dysfunction following its administration. Total intravenous anesthesia is also an option. Processed electroencephalographic (EEG) monitoring may allow "right sizing" the anesthetic dose to the patient's requirements, thereby avoiding unnecessary negative inotropy, vasodilation, and the need for excess fluids and/or vasopressors. Cerebral oximetry may be useful in high-risk patients to detect actionable decreases in regional cerebral oxygen saturation.

Hemodynamic lability is expected. When possible, short-acting agents to raise and lower blood pressure and heart rate should be immediately available. Potent volatile anesthetics may be useful for controlling intraoperative systemic hypertension and decreasing the doses of muscle relaxants needed for adequate surgical relaxation; however, volatile anesthetics can also depress cardiac output. A defibrillator with pacing capability must be immediately available; defibrillator pads may be placed prior to the start of surgery in patients at high risk for developing life-threatening arrhythmias.

Neuromuscular blockade should be avoided if possible. Renal disease is expected to slow excretion of vecuronium and rocuronium, whereas clearance of mivacurium, atracurium, and cisatracurium from plasma is independent of renal function. Renal failure may delay clearance of laudanosine, the principal metabolite of atracurium and cisatracurium. Laudanosine lacks effects at the neuromuscular junction, but at high plasma concentrations it may stimulate the central nervous system. Regardless of the drug selected, it is prudent to decrease the initial dose and administer subsequent doses based on the responses observed using a peripheral nerve stimulator.

Renal excretion accounts for approximately 50% of the clearance of neostigmine and approximately 75% of the elimination of edrophonium and pyridostigmine. Therefore the risk of recurarization following reversal of muscle relaxant is low, as the half-lives of these agents are likely to be prolonged to a greater extent than the half-lives of the nondepolarizing muscle relaxants. Sugammadex appears safe and effective in CKD with creatinine clearance greater than 30 mL/min; the data are insufficient to recommend its use in patients with more significant renal impairment.

Opioids are useful in that they lack significant cardiodepressant effects and reduce the need for volatile anesthetics. Both morphine and meperidine undergo metabolism to potentially neurotoxic compounds (morphine-3-glucoronide and normeperidine, respectively) that rely on renal clearance. Morphine-6-glucoronide, a morphine metabolite more potent that its parent compound, may also accumulate in patients with CKD and result in profound respiratory depression. Hydromorphone also has an active metabolite, hydromorphone-3-glucoronide, that may accumulate in patients with CKD; however, hydromorphone may be used safely with proper monitoring and judicious dosing. Alfentanil, fentanyl, remifentanil, and sufentanil lack active metabolites. However, the elimination half-life of fentanyl may be prolonged in patients with CKD. Remifentanil can be safely used in patients with CKD, including those on dialysis.

Fluid Management and Urine Output

Most patients with CKD come to the operating room with a contracted extracellular fluid volume. Patients with severe renal dysfunction but not requiring hemodialysis and those without renal disease undergoing operations associated with a high incidence of postoperative renal failure may benefit from preoperative hydration to the point of euvolemia with balanced salt solutions. A bolus of balanced salt solution to restore circulating volume (500 mL IV) should increase urine output in the presence of hypovolemia. However, the benefits of fluid resuscitation must be weighed against the risk of pulmonary edema. Normal saline is often used in this population as it lacks potassium. However, significant resuscitation with normal saline increases the risk of hyperchloremic metabolic acidosis with resultant hyperkalemia. Therefore a balanced salt solution is probably a better choice.

For the nonanuric patient, urine output is reassuring when present but has been shown to be a poor predictor of postoperative creatinine change. Stimulation of urine output with osmotic (mannitol) or tubular (furosemide) diuretics in the absence of adequate intravascular fluid volume replacement is not advised. Indeed, the most likely etiology of oliguria is an inadequate circulating fluid volume, and administration of diuretics in this setting may further compromise renal function.

Patients dependent on hemodialysis require special attention with respect to perioperative fluid management. An absence of renal function narrows the margin of safety between insufficient and excessive fluid administration. Noninvasive operations require replacement of only insensible water losses. The small amount of urine output can be replaced with 0.45% sodium chloride. Thoracic or abdominal surgery can be associated with loss of significant intravascular fluid volume to the interstitial spaces. This loss is best replaced with balanced salt solutions or colloid. Blood transfusions are indicated if the oxygen-carrying capacity must be increased or if blood loss is excessive.

Anesthesia for Vascular Access

Brachial plexus block is useful for placing vascular access for chronic hemodialysis. The addition of an intercostobrachial field block to a supra- or infraclavicular block should provide adequate surgical anesthesia to the entire arm. In addition to providing surgical anesthesia and analgesia, the local anesthetic administered during regional nerve blockade produces vasodilation that facilitates the surgical procedure and improves surgical outcome. The presence of uremic neuropathies should be queried and documented appropriately before regional anesthesia is performed. Coexisting metabolic acidosis may decrease the seizure threshold if local anesthetic is systemically absorbed.

Neuraxial anesthesia may be considered in patients with CKD. A sympathetic block of T4 to T10 levels may theoretically improve renal perfusion by attenuating catecholamine-induced renal vasoconstriction and suppressing the surgical stress

response. However, platelet dysfunction and the effects of residual heparin in patients on hemodialysis must also be considered. In addition, adequate intravascular fluid volume must be maintained to minimize hypotension. Transversus abdominis plane blocks have also been demonstrated to improve postoperative pain and reduce postoperative opioid requirements after abdominal surgeries, including nephrectomy and kidney transplant.

Patient Positioning

Attention to patient positioning on the operating room table is important. Poor nutritional status renders the skin of patients with CKD particularly prone to bruising and sloughing, and extra padding is required to protect vulnerable nerves around the elbow, knees, and ankles. Fistulas must be protected at all cost and be well padded to prevent pressure injury. Blood pressure cuffs should not be applied to the arm with the fistula. If possible, the arm with the fistula should not be tucked but positioned so that the fistula thrill can be checked at intervals throughout the surgery.

Perioperative Hemodialysis

Patients with ESRD should undergo adequate dialysis within 24 hours of elective surgery to optimize volume and metabolic statuses. Ideally, the patient is at or near dry weight at the time of surgery. Depending on the planned surgery, it may be advisable to recommend that the use of heparin be avoided or minimized during preoperative hemodialysis. Patients on peritoneal dialysis who are undergoing abdominal surgery generally undergo hemodialysis in the immediate postoperative period. Urgent hemodialysis is not required after radiocontrast dye exposure in patients with dialysis, including for the empiric prevention of volume overload.

Postoperative Management

Patients with CKD are at increased risk for perioperative MI; therefore consideration should be given to continuous ECG monitoring in the postoperative period. High-risk patients should be monitored in an intensive care unit. Close attention to fluid status and electrolyte balance is mandatory. Hemodialysis is often held for approximately 24 hours postoperatively, at which point the risk of significant fluid shifts and/or bleeding is reduced. Multimodal analgesia should be employed to the extent possible if postoperative pain is expected. Delayed emergence should prompt consideration of abnormal drug pharmacology, including the risk of an exaggerated response to opioids.

RENAL TRANSPLANTATION

Candidates for renal transplantation are selected from patients with ESRD who are on established programs of long-term RRT. Those who receive a transplant outlive their counterparts who remain on the transplant list by approximately 4 years. Death among transplant patients is most often due to cardiovascular disease or infection.

Living donor kidneys are preferred to deceased-donor kidneys; however, in a typical year, approximately twice the number of kidney transplants performed in the United States come from deceased donors. A kidney from a cadaver donor can be preserved by perfusion at low temperatures for up to 48 hours, making its transplantation a semielective surgical procedure. Attempts are made to match HLAs and ABO blood groups between donor and recipient. Paradoxically, the presence of certain common shared HLAs in the blood administered to a potential transplant recipient has been observed to induce tolerance to donor antigens and thus improve graft survival. The donor kidney is placed in the lower abdomen and receives its vascular supply from the iliac vessels. The ureter is anastomosed directly to the bladder.

Management of Anesthesia

Perioperative considerations for renal transplantation are similar to those for any surgery in a patient with ESRD. Preoperatively, most patients are administered an antimetabolite such as mycophenolate and a steroid, in addition to an induction dose of antithymocyte globulin (thymoglobulin). Methylprednisolone at 7 mg/kg (maximum dose of 500 mg) is typically administered intravenously in the operating room, followed by a tapering dose of oral prednisone. Maintenance therapy with a calcineurin inhibitor such as tacrolimus usually begins on postoperative day 1. Premedication with acetaminophen, corticosteroids, and/or antihistamines decreases the side effects related to thymoglobulin administration, including chills, headache, and abdominal pain.

Although both neuraxial and general anesthesia have been successfully used for renal transplantation, general anesthesia is more common. Blockade of the peripheral sympathetic nervous system, as produced by neuraxial anesthesia, can complicate control of systemic blood pressure, especially considering the unpredictable intravascular fluid volume status of these patients. The use of regional anesthesia, particularly epidural anesthesia, is controversial in the presence of abnormal coagulation. General anesthesia provides a secure airway and facilitates controlled ventilation, as respiratory mechanics may be compromised by surgical retraction in the area of the diaphragm. Renal function after kidney transplantation is not predictably influenced by choice of volatile anesthetic. The use of atracurium or cisatracurium or neuromuscular muscular is desirable, as their plasma clearance is organ independent. However, a newly transplanted kidney should be able to clear neuromuscular blockers and the anticholinesterase drugs used for their reversal at a rate comparable to normal patients.

Traditional fluid management called for aggressive crystalloid infusion targeting blood pressures and central venous pressures to guide reperfusion of the transplanted organ; systolic blood pressure of 140 mm Hg, mean arterial pressures above 80 mm Hg, and central venous pressure of approximately 10 were typical goals. Recent trends have been toward more goal-directed fluid therapy. Low-dose dopamine has traditionally been used for blood pressure support in patients with renal failure and stills appears in some institutional kidney transplant protocols; however, most studies do not support its use. Dobutamine is a more appropriate inotrope. While pressors may theoretically impair graft function, they

have a role in the patient not responding to fluid therapy; in these cases, norepinephrine is the best choice. Arterial lines are used only if indicated due to the presence of other comorbid conditions or to guide fluid management.

Mannitol is often administered to facilitate urine formation by the newly transplanted kidney and reduce the risk of ATN. Mannitol is an osmotic diuretic that facilitates urine output by decreasing excess tissue and intravascular fluid. In addition, mannitol increases renal blood flow through the local release of prostaglandins.

When clamps on the renal vessels are released after the surgical anastomoses have been created, renal preservative solution from the transplanted kidney and venous drainage from the legs are released into the circulation. Cardiac arrest has been described after completion of the arterial anastomosis to the transplanted kidney and release of the vascular clamp. This event is most likely due to sudden hyperkalemia. Unclamping may also be followed by hypotension due to the abrupt addition of up to 300 mL to the capacity of the intravascular fluid space and the release of vasodilating chemicals from previously ischemic tissues.

Postoperative Complications

The newly transplanted kidney may suffer acute immunologic rejection, which manifests in the vasculature of the transplanted kidney. It can be so rapid that inadequate circulation is evident almost immediately after the blood supply to the kidney is established. The only treatment for this acute rejection reaction is removal of the transplanted kidney, especially if the rejection process is accompanied by disseminated intravascular coagulation. Immunosuppressive therapy is continued postoperatively, typically with a combination of calcineurin inhibitors, corticosteroids, and antiproliferative agents. A hematoma also may arise in the graft postoperatively, causing vascular or ureteral obstruction.

Delayed signs of graft rejection include fever, local tenderness, and deterioration of urine output. Treatment with high doses of corticosteroids and antilymphocyte globulin may be helpful. The ATN that may occur in the transplanted kidney secondary to prolonged ischemia usually responds to hemodialysis. Cyclosporine toxicity may also cause AKI. Ultrasonography and needle biopsy are performed to differentiate between the possible causes of kidney malfunction.

Opportunistic infections owing to long-term immunosuppression are common after renal transplantation. Long-term survival is particularly poor in patients who are hepatitis B surface antigen positive. The frequency of cancer is 30 to 100 times higher in transplant recipients than in the general population, presumably the result of immunosuppression. Large-cell lymphoma is a well-recognized complication of transplantation, occurring almost exclusively in patients with evidence of Epstein-Barr virus infection.

Anesthetic Considerations in Renal Transplant Recipients Presenting for Surgery

Renal transplant recipients are often elderly and have multiple coexisting diseases. Nondiabetic patients often develop diabetes after transplant. Immunosuppressive medications place them at risk of worsening cardiovascular disease, malignancy, and infection. Given such comorbidities, these patients deserve special scrutiny prior to elective surgery.

They should be confirmed to be in their usual state of health by history and physical exam prior to surgery. Serum creatinine concentrations are likely to be normal in the presence of normally functioning grafts. Nevertheless, the GFR and renal blood flow are likely to be lower than those of healthy individuals. Drugs that are potentially nephrotoxic or dependent on renal clearance should be avoided. Diuretics should be administered only after careful evaluation of the patient's intravascular volume status. Conditions such as hypovolemia that may decrease renal blood flow should be minimized. The presence of declining GFR, azotemia, proteinuria, or systemic hypertension may indicate chronic rejection of the kidney transplant. Chronic corticosteroid use may cause adrenal insufficiency.

CONDITIONS AFFECTING RENAL FUNCTION

A number of pathologic processes can primarily involve the kidneys or occur in conjunction with dysfunction in other organ systems. Knowledge of the pathology and characteristics of these diseases is important for the perioperative management of patients with these conditions.

Glomerular Diseases

The classic patterns of glomerular disease are nephritic or nephrotic. In nephritic conditions, inflammation of the glomerulus leads to filtration of white and red blood cells into the tubule, resulting in a so-called active sediment. By contrast, nephrotic conditions are characterized by excessive proteinuria and an absence of cellular elements. A brief overview and several of the commonest diseases are included herein.

Nephrotic Syndrome

Nephrotic syndrome is defined by urinary protein excretion exceeding 3.5 g/day and the presence of peripheral edema. Common diseases presenting as nephrotic syndrome in adults include diabetic nephropathy, membranous nephropathy, focal segmental glomerulosclerosis, and amyloid disease. Membranous nephropathy, which is a common etiology in adults, can result from drugs (including NSAIDs), infections such as hepatitis B and C, and malignancies. In children, minimal change disease is by far the most common etiology of nephrotic syndrome.

Patients with nephrotic syndrome may experience hypovolemia with associated orthostatic hypotension, tachycardia, peripheral vasoconstriction, and occasionally even AKI in response to the administration of diuretics. The risk of AKI is increased in elderly patients and those who receive NSAIDs. Infusion of albumin will improve these acute clinical signs of hypovolemia. Hyperlipidemia accompanies nephrotic syndrome and may be associated with an increased risk of vascular disease.

Thromboembolic complications such as renal vein thrombosis, pulmonary embolism, and deep venous thromboses are

major risks in patients with nephrotic syndrome, particularly those who have membranous nephropathy or whose albumin concentration is less than 2 g/dL. Arterial thromboses are less common than venous thromboses, although there is an approximately five times increased risk of coronary death in patients with chronic nephrotic conditions. Prophylactic administration of heparin or oral anticoagulants may be considered in high-risk patients.

Hypoalbuminemia decreases the available binding sites for many drugs and increases the concentration of unbound drug, which is often the concentration that drives drug effect. This scenario can create challenges in drug dosing and administration. While an increased free drug fraction may increase drug effect, it may also accelerate drug clearance. Dramatic hypogammaglobulinemia, malnutrition, and concomitant treatment with immunosuppressive drugs make patients susceptible to infection.

Generalized edema is a function of an increase in total body sodium content. Dietary sodium restriction and diuretics are used to slowly decrease edema, as abrupt natriuresis may cause hypovolemia and AKI. In addition, abrupt hemoconcentration increases the risk of thromboembolic complications.

Glomerulonephritis

Acute glomerulonephritis is usually due to deposition of antigen-antibody complexes in the glomeruli. The source of antigens may be exogenous (poststreptococcal infection) or endogenous (lupus nephritis). Other diseases presenting with this nephritic pattern include IgA nephropathy and endocarditis. Clinical manifestations of glomerular disease include hematuria, hypertension, edema, and increased serum creatinine concentration. Red blood cell casts are also highly suggestive of renal dysfunction due to a glomerular process. Proteinuria may be present, reflecting an increase in glomerular permeability, but it is not nearly as profound as in nephrotic conditions. Prompt diagnosis is important, as immunosuppressive drugs may help prevent permanent kidney injury.

Goodpasture Syndrome

Goodpasture syndrome is a rare autoimmune disease that manifests as rapidly progressing glomerulonephritis in combination with pulmonary hemorrhage. It occurs most often in young males. Antiglomerular basement membrane antibodies account for renal dysfunction and apparently react with similar antigens in the lungs, producing alveolitis and hemoptysis. Hemoptysis is present in about 50% of patients and precedes clinical evidence of renal disease. Early intervention with plasmapheresis and immunosuppression (corticosteroids, cyclophosphamide) reduces the likelihood of progression to ESRD.

Interstitial Nephritis

Acute interstitial nephritis involves a kidney injury characterized by an inflammatory interstitial filtrate, with variable presenting symptoms and pyuria, hematuria, and WBC casts. It is associated with drugs (predominately antibiotics) in upwards of three-quarters of cases. Other causes include autoimmune diseases (systemic lupus erythematosus), infiltrative diseases (sarcoidosis), and infection. Renal injury due to acute interstitial nephritis is often reversible after withdrawal of the offending agent or treatment of the underlying condition. Corticosteroid therapy may be beneficial.

Hereditary Nephritis

Hereditary nephritis (Alport syndrome) is often accompanied by hearing loss and ocular abnormalities. The disorder is more common in males than in females. In women the disease is usually mild, but in men the symptoms are more severe and progressive. Drug therapy has not proven successful, although lowering the intraglomerular pressure with ACE inhibitors or ARBs may slow the progression of renal injury. Hypertension and renal failure are expected, with renal failure typically occurring between the second and fifth decades.

Polycystic Kidney Disease

Polycystic kidney disease is a common genetic disorder most often inherited as an autosomal dominant trait and present in approximately 1 in 500 births. The condition is marked by the development of multiple cysts in the kidneys as well as other organs such as the liver and pancreas. Cerebral aneurysms and cardiac valve abnormalities may also be present. Mild systemic hypertension, hematuria, kidney stones, and urinary tract infections are common. The disease typically progresses slowly until renal failure occurs during middle age. Hemodialysis or renal transplantation is eventually necessary in most patients.

Bartter and Gitelman Syndromes

Bartter and Gitelman syndromes are inherited renal salt-wasting disorders caused by defects in sodium, chloride, and potassium channels in the thick ascending limb of the distal convoluted tubule. Juxtaglomerular hyperplasia, hyperaldosteronism, and hypokalemic acidosis are pathognomic of these disorders. Treatment includes salt supplementation (sodium, potassium, magnesium), careful administration of NSAIDs (which mitigate the dramatic prostaglandin increases seen in Bartter syndrome), potassium-sparing diuretic (i.e., spironolactone), and ACE inhibitors. These syndromes alone do not lead to renal failure. However, if patients for other reasons develop ESRD, transplantation of a kidney from a healthy donor results in normal renal solute handling.

Renal Tubular Acidosis

Renal tubular acidosis (RTA) is a syndrome that causes metabolic acidosis due to inappropriate acidification of the urine. Several subtypes of the disorder are recognized. Type 1 RTA is caused by impaired acid secretion in the distal tubule. Type 2 RTA is due to impaired proximal bicarbonate resorption. Generalized type 2 tubular dysfunction leads to Fanconi syndrome, which is described next. Type 4 RTA occurs when plasma aldosterone levels are inappropriately low or the kidney fails to respond to aldosterone normally. It causes a metabolic acidosis but is distinct from the other types in that it is associated with hyperkalemia rather than hypokalemia. Type 4 RTA is often seen in patients with CKD.

Fanconi Syndrome

Fanconi syndrome results from inherited or acquired disturbances of proximal renal tubular function. There is renal loss of substances normally conserved by the proximal renal tubules, including potassium, bicarbonate, phosphate, amino acids, glucose, and water. Symptoms include polyuria, polydipsia, metabolic acidosis, and skeletal muscle weakness. Dwarfism and osteomalacia, reflecting loss of phosphate, are also common, and patients may present with vitamin D–resistant rickets. Management of anesthesia includes attention to fluid and electrolyte abnormalities and the recognition that left ventricular cardiac failure secondary to uremia is often present in advanced stages of the disease.

Nephrolithiasis

Although the pathogenesis of nephrolithiasis is complex and not completely understood, several predisposing factors are recognized for the five major types of renal stones that occur (Table 21.13). Most stones are composed of calcium oxalate, resulting from excess calcium excretion by the kidneys. In these patients, causes of hypercalcemia (hyperparathyroidism, sarcoidosis, cancer) must be considered. Urinary tract infections with urea-splitting organisms that produce ammonia favor the formation of magnesium ammonium phosphate stones. Formation of uric acid stones is favored by a persistently acidic urine (pH 6.0) that decreases the solubility of uric acid. Approximately 50% of patients with uric acid stones have gout.

Stones in the renal pelvis are typically painless unless they are complicated by infection or obstruction. By contrast, renal stones passing down the ureter can produce intense flank pain, often radiating to the groin, associated with nausea and vomiting, and mimicking an acute surgical abdomen. Hematuria is common during ureteral passage of stones; ureteral obstruction may precipitate renal failure.

Treatment of renal stones depends on identifying the composition of the stone and correcting predisposing factors, such as hyperparathyroidism, urinary tract infection, or gout. High fluid intake sufficient to maintain a daily urine output of 2 to 3 L is often part of the therapy. Extracorporeal shockwave lithotripsy (ESWL) is a noninvasive treatment for renal stones that uses focused, high-intensity acoustic impulses to break up stones into pieces small enough to be excreted in the urine. It can be performed under sedation, general or neuraxial anesthesia. Cardiac dysrhythmias may occur during ESWL, presumably the result of premature stimulation of the atria from the electrical discharge that precedes each shockwave. Lithotripters are equipped with ECG gating that helps limit the risk of ventricular fibrillation caused by the "R-on-T" phenomenon. For stones not amenable to ESWL or ureteroscopic removal, percutaneous nephrolithotomy can be performed. The percutaneous approach can be performed under local, neuraxial, or general anesthesia and is carried out in the prone position. Stones too large for intact extraction can be fragmented by laser, pneumatic, and/or ultrasonic methods.

Uric Acid Nephropathy

Acute uric acid nephropathy occurs when uric acid crystals precipitate in the renal collecting tubules or ureters. This precipitation occurs when uric acid concentrations reach a saturation point in acidic urine. The condition is particularly likely to occur when uric acid production is greatly increased, as in patients with myeloproliferative disorders being treated with chemotherapeutic drugs. These patients are particularly vulnerable to uric acid nephropathy when they become dehydrated or acidotic because of decreased caloric intake. Untreated, the condition can result in acute oliguric renal failure.

Renal Hypertension

Renal disease is the most common cause of secondary systemic hypertension. Accelerated or malignant hypertension is likely to be associated with renal disease. Furthermore, the appearance of systemic hypertension in young patients suggests the diagnosis of renal rather than essential hypertension. Hypertension due to renal dysfunction reflects parenchymal disease of the kidneys or renovascular disease.

Chronic pyelonephritis and glomerulonephritis are parenchymal diseases often associated with systemic hypertension, particularly in younger patients. Less common forms of renal parenchymal disease that can cause systemic hypertension include diabetic nephropathy, cystic disease of the kidneys, and renal amyloidosis.

Renovascular disease is caused by narrowing of the renal arteries caused by either fibromuscular dysplasia or atheroma. The sudden onset of a marked increase in systemic blood pressure or the presence of hypertension before the age of 30 years should arouse suspicion of renovascular disease. A bruit may

TABLE 21.13 Composition and Characteristics of Renal Stones

Type of Stone	Prevalence (%)	Radiographic Appearance	Etiology
Calcium oxalate	75	Opaque	Primary hyperparathyroidism Idiopathic hypercalciuria Hyperoxaluria
Magnesium ammonium phosphate (struvite)	1	Opaque	Alkaline urine (usually due to chronic bacterial infection)
Calcium phosphate	15	Opaque	Renal tubular acidosis Alkaline urine
Uric acid	8	Translucent	Acid urine Gout Hyperuricosuria
Cystine	1	Opaque	Cystinuria

be audible on auscultation of the abdomen over the kidneys. Systemic hypertension due to renovascular disease does not respond well to treatment with antihypertensive drugs.

The mechanism that produces systemic hypertension in the presence of renal parenchymal or renovascular disease is not established. Stimulation of the RAAS is a possible, but unproven, mechanism. Regardless of the mechanism, treatment of hypertension associated with renal parenchymal disease is usually with antihypertensive drugs, including Γ-adrenergic antagonists, which inhibit the release of renin from the kidneys. Treatment of renovascular hypertension is with renal artery endarterectomy or nephrectomy.

Hepatorenal Syndrome

Acute oliguria in patients with decompensated cirrhosis of the liver is called hepatorenal syndrome. Cirrhosis of the liver is associated with decreased GFR and renal blood flow preceding overt renal dysfunction by several weeks. Renal failure in these patients reflects reduction in effective circulating volume partly as a result of diuretic treatment and partly due to splanchnic arteriolar dilatation. The typical patient is severely jaundiced and moribund; ascites, hypoalbuminemia, and hypoprothrombinemia are present. Treatment is directed at restoring renal perfusion; in critically ill patients, norepinephrine and albumin are often administered to achieve this goal. In noncritically ill patients, a trial of vasopressin analogues such as ornipressin and terlipressin, which cause splanchnic vasoconstriction, may help to increase renal perfusion and GFR. A peritoneal-to-venous shunt for the treatment of ascites may also be associated with improved renal function.

Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate due to excessive growth of both the glandular and stromal elements of the gland. Symptoms occur as a result of compression of the urethral canal and disruption of the normal flow of urine. BPH is common worldwide in men older than 40 years of age.

Γ-adrenergic antagonists (terazosin, doxazosin, tamsulosin) are administered to block adrenergic receptors in hyperplastic prostatic tissue, the prostatic capsule, and the bladder neck, thereby decreasing smooth muscle tone and resistance to urinary flow. These drugs also have antihypertensive effects and may cause orthostatic hypotension in some patients. Prostatic tissue growth is androgen sensitive, such that androgen deprivation decreases the size of the prostate and thereby the resistance to outflow through the prostatic urethra. 5_-reductase inhibitors such as finasteride are moderately effective for symptomatic treatment of BPH via this mechanism. Side effects are minimal.

The most commonly used minimally invasive treatments of BPH are transurethral microwave thermotherapy (TUMT) and transurethral needle ablation (TUNA). These procedures rely on the generation of heat to cause tissue necrosis and shrinkage of the prostate.

Most surgical treatments are transurethral and use one of several methods to remove prostatic tissue. While transurethral resection of the prostate (TURP) with cautery has been considered the gold standard for many years, other modalities such as photoselective vaporization and laser enucleation are gaining favor. These alternatives tend to have less blood loss, reduced irrigant requirements, shorter lengths of hospital stay, and less need for indwelling urinary catheters postprocedure.

TURP Syndrome

During TURP, large volumes of a nonconductive irrigation solution (glycine, sorbitol, mannitol) may be used to provide surgical visualization, remove blood and resected tissue, and avoid thermal injury. The procedure is accompanied by absorption of irrigating fluid via direct intravascular access through the prostatic venous plexus or more slowly through absorption from the retroperitoneal and perivesical spaces. TURP syndrome is characterized by an acute hyponatremia and hypoosmolar state induced by excess fluid absorption (Table 21.14).

Rapid intravascular fluid volume expansion due to systemic absorption of irrigating fluids (absorption rates may reach 200 mL/min) can cause systemic hypertension and reflex bradycardia. Patients with poor left ventricular function may develop pulmonary edema owing to acute circulatory volume overload. Solute changes may alter neurologic function independent of volume-related effects.

Although monitoring serum sodium concentrations during TURP is effective for assessing intravascular fluid absorption, there may be benefits from monitoring serum osmolality as well. Hypoosmolality appears to be the principal factor that contributes to the neurologic changes typical of TURP syndrome, which range from headache to coma. This is predictable because the blood-brain barrier is essentially impermeable to sodium but freely permeable to water. Cerebral edema caused by acute hypoosmolality can result in increased intracranial pressure with resultant bradycardia and hypertension.

Acute hyponatremia due to intravascular absorption of sodium-free irrigating fluids may cause confusion, agitation, visual disturbances, pulmonary edema, cardiovascular collapse, and seizures. Changes on the ECG may accompany progressive decreases in serum sodium concentrations.

Diuretics administered to treat hypervolemia during TURP may accentuate hyponatremia and hypoosmolality. Also, serum sodium concentration and osmolality may continue to decrease following TURP because of continued absorption.

Factors that influence the amount of irrigating solution absorbed include the intravesicular pressure, which is determined by the height of the irrigation bag above the prostatic sinuses (limit height to 40 cm H_2O above the prostate) and the number of prostatic sinuses opened (limit resection time to 1 hour and leave a rim of tissue on the capsule). If intravesical pressures are maintained below 15 cm H_2O, absorption of irrigating fluids is minimal. Fluid deficits should be monitored throughout the procedure; some centers advise stopping the procedure when gender-specific deficits are reached (i.e., 2 L in males). If bipolar cautery is employed, then conductive irrigants (i.e., normal saline) can be used.

TABLE 21.14 Signs and Symptoms of Transurethral Resection of the Prostate (TURP) Syndrome

System	Signs and Symptoms	Cause
Cardiovascular	Hypertension, reflex bradycardia, pulmonary edema, cardiovascular collapse, ECG changes (wide QRS, elevated ST segment, ventricular arrhythmias)	Rapid fluid absorption, reflex bradycardia (secondary to hypertension or increased ICP), third-spacing secondary to hyponatremia and hypoosmolality
Respiratory	Tachypnea, hypoxemia, Cheyne-Stokes breathing	Pulmonary edema
Neurologic	Nausea, restlessness, visual disturbances, confusion, somnolence, seizure, coma, death	Hyponatremia and hypoosmolality causing cerebral edema and increased ICP, hyperglycinemia (inhibitory neurotransmitter, potentiates NMDA receptor activity), hyperammonemia
Hematologic	Disseminated intravascular coagulation, hemolysis	Hyponatremia and hypoosmolality
Renal	Renal failure	Hypotension, hyperoxaluria (metabolite of glycine)
Metabolic	Acidosis	Deamination of glycine to glyoxylic acid and ammonia

ECG, Electrocardiogram; *ICP*, intracranial pressure; *NMDA*, N-methyl-D-aminotransferase.

Supportive care remains the most important therapeutic approach for managing cardiovascular, central nervous system, and renal complications of TURP syndrome. If there is clinical suspicion for TURP syndrome, plasma sodium and osmolality should be measured. Symptomatic hyponatremic, hypoosmolar patients should be treated in a monitored setting with hypertonic saline. While the risk of osmotic demyelination should be low given the acute (rather than chronic) nature of the hyponatremia, treatment should be given carefully and incrementally with regular lab measurements.

Neuraxial techniques have the advantage of providing continuous neurologic monitoring. However, this typically elderly population presents challenges to neuraxial techniques such as degenerative spine disease and, commonly, anticoagulation. Moreover, spinal anesthesia is associated with hypotension, nausea, and vomiting that mimics common symptoms of TURP syndrome.

KEY POINTS

- The kidneys are involved in water conservation, electrolyte homeostasis, acid-base balance, and multiple neurohumoral and hormonal functions. Some or all of these functions are affected by renal disease. GFR is the best measure of overall renal function.
- Risk factors for perioperative AKI include advanced age, preexisting CKD, sepsis, diabetes, hypovolemia, anemia, chronic liver disease, and CHF. High-risk surgical procedures include trauma and major surgery (particularly those requiring aortic cross-clamping and/or cardiopulmonary bypass). Prevention of AKI hinges on maintaining adequate renal perfusion and avoiding nephrotoxins.
- The etiology of AKI is classically divided into prerenal, intrarenal (or intrinsic), and postrenal. In the majority of cases, treatment is supportive, aimed at limiting further injury by maintaining hemodynamic stability and adequate intravascular fluid volume.
- CKD is a common, often silent disease, which is also a significant risk factor for cardiovascular morbidity and mortality. The severity of CKD is staged based on cause, GFR, and degree of proteinuria.
- Most RRT in the United States is performed via hemodialysis. Emergent indications for RRT include severe acidosis or electrolyte abnormalities, toxic ingestion, fluid overload, and/or symptomatic uremia. RRT is typically initiated at GFR of 10 mL/min or less.
- Preoperative evaluation of patients with both AKI and CKD should take into consideration not only baseline renal function but also highly prevalent comorbid conditions, including cardiovascular disease and diabetes.
- National guidelines advise careful management of cardiovascular risk factors in patients with CKD. ACE inhibitors or ARBs are first-line therapies targeting blood pressure below 130/80 mm Hg, while statins and antihyperglycemic medications are key in managing dyslipidemias and diabetes. Malnutrition and anemia are increasingly common as CKD progresses and should be treated.
- Provision of anesthesia in CKD patients focuses on meticulous fluid, electrolyte, and acid-base management and attention to appropriate drug dosing. Vessels of the nondominant arm should be preserved in anticipation of their potential use for vascular access for hemodialysis.
- The overriding goal in renal transplantation is adequate perfusion of transplanted kidney. Hypotension and cardiac dysrhythmias may develop when vascular clamps are released.

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22

Endocrine Disease

Leila Zuo, Dawn Dillman

OUTLINE

DIABETES MELLITUS

Normal glucose physiology requires a balance between glucose utilization and endogenous production or dietary delivery (Fig. 22.1). The liver is the primary source of endogenous glucose production via glycogenolysis and gluconeogenesis. Approximately 70% to 80% of glucose released by the liver is metabolized by insulin-insensitive tissues such as the brain, gastrointestinal tract, and red blood cells. Following a meal, plasma glucose level increases, which stimulates an increase in plasma insulin secretion that promotes glucose utilization. Late in the postprandial period, approximately 2 to 4 hours after eating, when glucose utilization exceeds glucose production, a transition from exogenous glucose delivery to endogenous production becomes necessary to maintain a normal plasma glucose level. During this time, diminished insulin secretion is fundamental to the maintenance of a normal plasma glucose concentration. Hyperglycemia-producing hormones such as glucagon, epinephrine, growth hormone, and cortisol comprise the glucose counterregulatory system and support glucose production. Glucagon plays a primary role by stimulating glycogenolysis and gluconeogenesis, and inhibiting glycolysis.

Diabetes mellitus is the most common endocrine disease and affects 1 in 10 adults. Diabetes mellitus results from an inadequate supply of insulin and/or an inadequate tissue response to insulin. This leads to increased circulating glucose levels with eventual microvascular and macrovascular complications. Type 1a diabetes is caused by a T-cell–mediated autoimmune destruction of cells within pancreatic islets resulting in complete absence or minimal circulating levels of insulin. Type 1b diabetes is a rare disease of absolute insulin deficiency that is not immune mediated. Type 2 diabetes is also not immune mediated and results from defects in insulin receptors and postreceptor intracellular signaling pathways.

Signs and Symptoms

Type 1 Diabetes

Between 5% and 10% of all cases of diabetes are type 1. There are 1.4 million individuals with type 1 diabetes and using insulin in the United States. The disorder is usually diagnosed before the age of 40 and is one of the most common chronic childhood illnesses.

The exact cause of the autoimmune process in type 1a diabetes is unknown, although environmental triggers such as viruses (especially enteroviruses), dietary proteins, or drugs or chemicals may initiate the autoimmune process in genetically susceptible hosts. A long preclinical period (9–13 years) characterized by production of antibodies to -cell antigens with loss of -cell function precedes the onset of clinical diabetes in the majority of patients. At least 80% to 90% of -cell function must be lost before hyperglycemia occurs. The autoimmune attack initially presents as islet inflammation (insulitis), with immune cells infiltrating the pancreatic islets. Circulating antibodies signify islet cell injury.

The presentation of clinical disease is often sudden and severe secondary to loss of a critical mass of cells. Patients demonstrate hyperglycemia over several days to weeks associated with fatigue, weight loss, polyuria, polydipsia, blurring of vision, and signs of intravascular volume depletion. The presence of ketoacidosis indicates severe insulin deficiency and unrestrained lipolysis.

Type 2 Diabetes

Type 2 diabetes is responsible for over 90% of all cases of diabetes mellitus in the world. In 2000, there were approximately 151 million individuals with type 2 diabetes globally, with about 463 million people living with diabetes in 2019. By 2030, there will be an estimated 578 million adults with diabetes. Patients with type 2 diabetes are typically in the middle to older age group and are overweight, although there has been a significant increase in younger patients and even children with type 2 diabetes over the past decade. Type 2 diabetes continues to be underrecognized and underdiagnosed because of its subtle presentation. It is estimated that most individuals with type 2 diabetes had the disease for approximately 4 to 7 years before the disorder was diagnosed.

Type 2 diabetes is characterized by relative -cell insufficiency and insulin resistance. In the initial stages of the disease, an insensitivity to insulin on the part of peripheral tissues leads to an increase in pancreatic insulin secretion to maintain normal

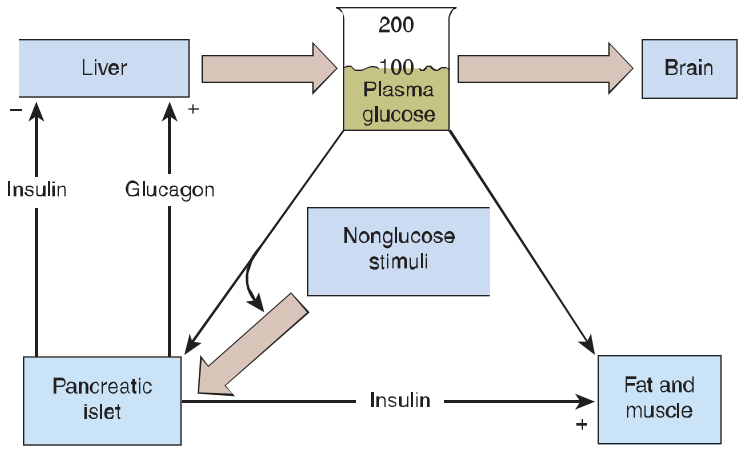

Fig. 22.1 The pancreatic islets act as glucose sensors to balance hepatic glucose release to insulin-insensitive tissues (brain) and insulin-sensitive tissues (fat, muscle). Insulin inhibits glucose release by the liver and stimulates glucose utilization by insulin-sensitive tissues. With hyperglycemia, insulin secretion increases. With hypoglycemia, the reverse occurs. (Adapted from Porte Jr. D. Beta-cells in type II diabetes mellitus. *Diabetes*. 1991;40:166–180).

plasma glucose levels. As the disease progresses and pancreatic cell function decreases, insulin levels are unable to compensate, and hyperglycemia occurs. Three important defects are seen in type 2 diabetes: (1) an increased rate of hepatic glucose release, (2) impaired basal and stimulated insulin secretion, and (3) inefficient use of glucose by peripheral tissues (i.e., insulin resistance). The increase in hepatic glucose release is caused by the reduction of insulin's normal inhibitory effect on the liver, as well as abnormalities in regulation of glucagon secretion. Although relative β-cell insufficiency is significant, type 2 diabetes is characterized by insulin resistance in skeletal muscle, adipose tissue, and the liver. Causes of insulin resistance include (1) an abnormal insulin molecule; (2) circulating insulin antagonists, including counterregulatory hormones, free fatty acids, antiinsulin and insulin receptor antibodies, and cytokines; and (3) target tissue defects at insulin receptors and/or postreceptor sites. It appears that insulin resistance is an inherited component of type 2 diabetes, with obesity and a sedentary lifestyle being acquired and contributing factors. Impaired glucose tolerance is associated with an increase in body weight, a decrease in insulin secretion, and a reduction in peripheral insulin action. The transition to clinical diabetes is characterized by these same factors plus an increase in hepatic glucose production.

The increasing prevalence of type 2 diabetes among children and adolescents appears related to obesity, since 85% of affected children are overweight or obese at the time of diagnosis. Obese patients exhibit a compensatory hyperinsulinemia to maintain normoglycemia. These increased insulin levels may desensitize target tissues, causing a reduced response to insulin. The mechanism for hyperinsulinemia and insulin resistance from weight gain remain elusive.

Diagnosis

The American Diabetes Association has established diagnostic criteria for diabetes mellitus (Table 22.1). Measurement of fasting plasma glucose level is the recommended screening test for diabetes mellitus. The same tests used to screen for and diagnose diabetes can also be used to identify individuals with prediabetes (Table 22.2). Glucose levels, especially in type 2 diabetics, usually increase over years to decades, progressing from the normal range to the impaired glucose tolerance range and finally to clinical diabetes.

The HbA_{1c} test provides a valuable measure of long-term glycemic control. Hemoglobin is nonenzymatically glycosylated by glucose, which freely crosses red blood cell membranes. The percentage of hemoglobin molecules participating in this reaction is proportional to the average plasma glucose concentration during the preceding 60 to 90 days. Evidence suggests that the risk of microvascular and macrovascular disease is increased even in the nondiabetic range, compared with normoglycemia (Table 22.3).

Treatment

The cornerstones of treatment for type 2 diabetes are dietary adjustments along with weight loss, exercise therapy, and oral antidiabetic drugs. Reduction of body weight through diet and exercise is the first therapeutic measure to control type 2 diabetes. The decrease in adiposity improves hepatic and peripheral tissue insulin sensitivity, enhances postreceptor insulin action, and may possibly increase insulin secretion. Nutritional guidelines of the American Diabetes Association emphasize maintenance of optimal plasma glucose and lipid levels.

Oral Antidiabetic Drugs

In the absence of contraindications, metformin, a biguanide, is the preferred initial treatment for patients with newly diagnosed

TABLE 22.1 American Diabetes Association Criteria for the Diagnosis of Diabetes

1. A_{1c} ≥ 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.[a]
2. FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hr.[a]
3. 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.[a]
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

A_{1c}: Glycated hemoglobin; *DCCT:* Diabetes Control and Complications Trial; *FPG:* fasting plasma glucose; *NGSP:* National Glycohemoglobin Standardization Program; *OGTT:* oral glucose tolerance test.
[a]In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.
Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. American Diabetes Association. *Diabetes Care.* 2021;44(suppl 1):S15–S33. doi:10.2337/dc21-S002.

TABLE 22.2 Categories of Increased Risk for Diabetes (Prediabetes)[a]

FPG 100–125 mg/dL (5.6–6.9 mmol/L)—IFG
2-hour postload glucose on the 75 g OGTT 140–199 mg/dL (7.8–11.0 mmol/L)—IGT
A_{1c} 5.7–6.4% (39–46 mmol/mol)

A1C: Glycated hemoglobin; *FPG:* fasting plasma glucose; *IFG:* impaired fasting glucose; *IGT:* impaired glucose tolerance; *OGTT:* oral glucose tolerance test.
[a]For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.
Reprinted with permission from the American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. American Diabetes Association. *Diabetes Care.* 2021;44(suppl 1):S15–S33. doi:10.2337/dc21-S002.

TABLE 22.3 Diagnosing Prediabetes or Diabetes

Normal	<5.7%
Prediabetes	5.7–6.4%
Diabetes	≥6.5%

A normal A_{1c} level is < 5.7%, a level of 5.7–6.4% indicates prediabetes, and a level of ≥ 6.5% indicates diabetes. Within the 5.7–6.4% prediabetes range, the higher your A_{1c}, the greater your risk is for developing type 2 diabetes.

type 2 diabetes who are asymptomatic. This class of drugs decreases hepatic gluconeogenesis and enhances utilization of glucose by skeletal muscle and adipose tissue by increasing glucose transport across cell membranes. In addition, they decrease plasma levels of triglycerides and low-density lipoprotein cholesterol and reduce postprandial hyperlipidemia and plasma-free fatty acids. Lactic acidosis is a rare but serious side effect of the biguanides; the risk is particularly high in patients with renal insufficiency.

The sulfonylureas act by stimulating insulin secretion from pancreatic I cells; they can also enhance insulin-stimulated peripheral tissue utilization of glucose. The second-generation agents (glyburide, glipizide, glimepiride) are more potent and have fewer side effects than their predecessors. Unfortunately, because of the natural history of type 2 diabetes characterized by decreasing _-cell function, these drugs are not effective indefinitely. Hypoglycemia and weight gain are side effects. Sulfonylureas may increase risk of cardiovascular events and may prevent protective ischemic cardiac preconditioning after myocardial infarction.

Other glucose-lowering drugs are available, including gliptins, SGLT-2 inhibitors, and thiazolidinediones (Table 22.4). Primary

TABLE 22.4 Summary of Glucose-Lowering Interventions

Intervention	Expected Decrease in A_{1c} With Monotherapy (%)	Advantages	Disadvantages
Initial Therapy			
Lifestyle change to decrease weight and increase activity	1.0–2.0	Broad benefits	Insufficient for most within first year owing to inadequate weight loss and weight regain
Metformin	1.0–2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency (eGFR _ 30 mL/min)[a]
Additional Therapy			
Insulin (usually with a single daily injection of intermediate- or long-acting insulin initially)	1.5–3.5	No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring weight gain, hypoglycemia, analogs are expensive
Sulfonylurea (shorter-acting agents preferred)	1.0–2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
GLP-1 receptor agonist (daily to weekly injections)	0.5–1.5	Weight loss, reduction in major adverse cardiovascular events (liraglutide, semaglutide, dulaglutide) in patients with established CVD and potentially for those at high risk for CVD	Requires injection, frequent GI side effects, expensive
Thiazolidinedione	0.5–1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, HF, weight gain, bone fractures, potential increase in MI (rosiglitazone) and bladder cancer (pioglitazone)
Glinide	0.5–1.5	Rapidly effective	Weight gain, 3 times/day dosing, hypoglycemia
SGLT-2 inhibitor	0.5–0.7	Weight loss, reduction in systolic blood pressure, reduced cardiovascular mortality in patients with established CVD, improved renal outcomes in patients with nephropathy	Vulvovaginal candidiasis, urinary tract infections, bone fractures, lower limb amputations, acute kidney injury, DKA, long-term safety not established
DPP-4 inhibitor	0.5–0.8	Weight neutral	Possible increased risk of HF with saxagliptin, expensive
I -glucosidase inhibitor	0.5–0.8	Weight neutral	Frequent GI side effects, 3 times/day dosing
Pramlintide	0.5–1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established, expensive

[a]Initiation is contraindicated with eGFR 30 mL/min/1.73 m^2 and not recommended with eGFR 30–45 mL/min/1.73 m^2.

A_{1c}: Glycated hemoglobin; *CVD:* cardiovascular disease; *DPP-4:* dipeptidyl peptidase-4; *DKA:* diabetic ketoacidosis; *eGFR:* estimated glomerular filtration rate; *GI:* gastrointestinal; *GLP-1:* glucagon-like peptide-1; *HF:* heart failure; *MI:* myocardial infarction; *SGLT-2:* sodium-glucose cotransporter 2.

The order of listing of additional therapies does not indicate a preferred order of selection. ΔRepaglinide is more effective in lowering A_{1c} than nateglinide.

Modified with permission from Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009;32:193–203. Copyright © 2009 American Diabetes Association.

management of diabetes is outside the scope of this chapter. Tight control of type 2 diabetes provides significant benefits in preventing and slowing the progression of micro- and macrovascular disease.

Insulin

Insulin is necessary to manage all cases of type 1 diabetes and many cases of type 2 diabetes (Table 22.5). In the United States, 30% of patients with type 2 diabetes are treated with insulin. The various forms of insulin include basal insulins, which are intermediate acting (NPH, Lente, lispro protamine, aspart protamine) administered twice daily or long acting (Ultralente, glargine) administered once daily; and insulins that are short acting (regular) or rapid acting (lispro, aspart), which provide glycemic control at mealtimes. Conventional insulin therapy usually requires twice-daily injections of combinations of intermediate-acting and short- or rapid-acting insulins. Intensive insulin therapy requires three or more daily injections or a continuous infusion (Fig. 22.2).

Hypoglycemia is the most frequent and dangerous complication of insulin therapy. The hypoglycemic effect can be exacerbated by simultaneous administration of alcohol, sulfonylureas, biguanides, thiazolidinediones, angiotensin-converting enzyme (ACE) inhibitors, monoamine oxidase inhibitors, and nonselective ¯blockers. ¬blockers may exacerbate hypoglycemia by inhibiting lipolysis of adipose tissue, which serves as an alternate fuel when patients become hypoglycemic. Defective counterregulatory responses by glucagon and epinephrine to reduce plasma glucose levels contribute to this complication.

Repetitive episodes of hypoglycemia, especially at night, can result in hypoglycemia unawareness, a condition in which the patient does not respond with the appropriate autonomic warning symptoms before neuroglycopenia. The diagnosis in adults requires a plasma glucose level of less than 55 mg/dL. Symptoms are adrenergic (sweating, tachycardia, palpitations, restlessness, pallor) and neuroglycopenic (fatigue, confusion, headache, somnolence, convulsions, coma). Treatment includes the administration of sugar in the form of sugar cubes, glucose tablets, or soft drinks if the patient is conscious, and glucose 0.5 g/kg IV or glucagon 0.5 to 1.0 mg intravenously, intramuscularly, or subcutaneously if the patient is unconscious.

TABLE 22.5 Insulin Preparations

Insulin	Onset	Peak	Duration
Short Acting			
Human regular	30 min	2–4 hr	5–8 hr
Lispro (Humalog)	10–15 min	1–2 hr	3–6 hr
Aspart (NovoLog)	10–15 min	1–2 hr	3–6 hr
Intermediate			
Human NPH	1–2 hr	6–10 hr	10–20 hr
Lente	1–2 hr	6–10 hr	10–20 hr
Long Acting			
Ultralente	4–6 hr	8–20 hr	24–48 hr
Glargine (Lantus)	1–2 hr	–	24 hr

Complications

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is a complication of decompensated diabetes mellitus. Episodes of DKA occur more commonly in patients with type 1 diabetes and are precipitated by infection or acute illness. High glucose levels exceed the threshold for renal tubular absorption, which creates a significant osmotic diuresis with marked hypovolemia. A tight metabolic coupling between hepatic gluconeogenesis and ketogenesis leads to an overproduction of ketoacids by the liver. DKA results in an excess of glucose counterregulatory hormones, with glucagon activating lipolysis and free fatty acids providing the substrate for ketogenesis. An increase in production of ketoacids (⊥hydroxybutyrate, acetoacetate, acetone) creates an anion gap metabolic acidosis (Table 22.6).

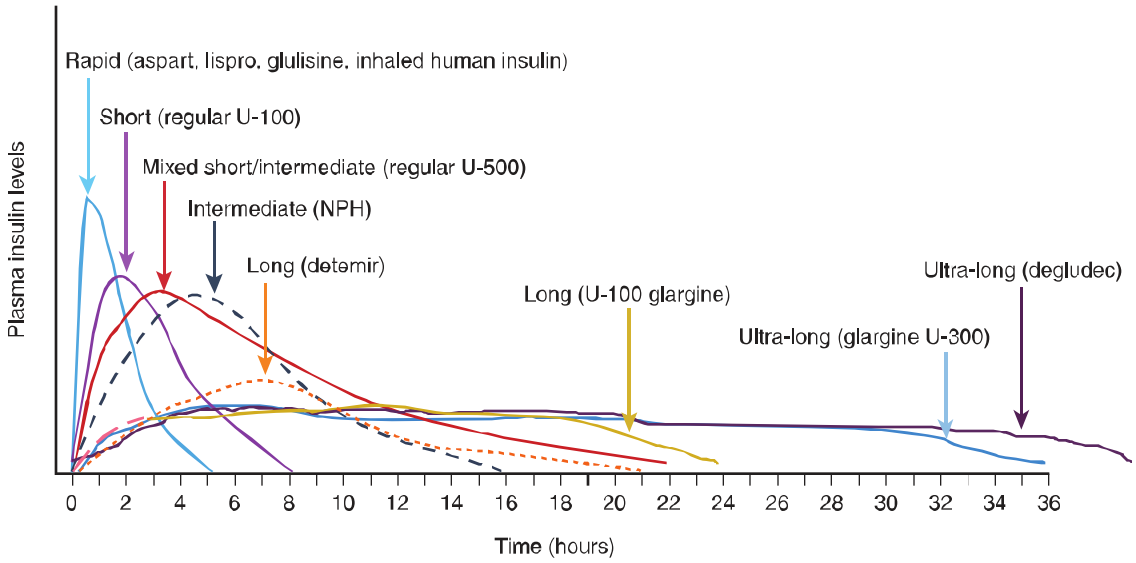

Fig. 22.2 Pharmacokinetic profile of currently available single insulin products. (Reprinted with permission from Neumiller JJ. Insulin update: new and emerging insulins. https://professional.diabetes.org/sites/professional.diabetes.org/files/media/1-neumiller-insulin_update_-_ada_clinical_conference_2018.pdf. Copyright © 2018 American Diabetes Association.)

TABLE 22.6 Diagnostic Features of Diabetic Ketoacidosis

Serum glucose level (mg/dL)	⊔300
pH	⊔7.3
HCO_3^- (mEq/L)	⊔18
Serum osmolarity (mOsm/L)	⊓320
Serum and urine ketone levels	Moderate to high

Substantial deficits of water, potassium, and phosphorus exist, although laboratory values of these electrolytes may be normal or increased. Hyponatremia results from the effect of hyperglycemia and hyperosmolarity on water distribution. The deficit of potassium is usually substantial (3–5 mEq/kg), and the deficit of phosphorus, and can lead to diaphragmatic and skeletal muscle dysfunction and impaired myocardial contractility.

The treatment of DKA consists of large amounts of normal saline and effective doses of insulin, and electrolyte supplementation. An intravenous loading dose of 0.1 unit/kg of regular insulin plus a low-dose insulin infusion of 0.1 unit/kg/hr is initiated. Insulin administration must be continued until a normal acid-base status is achieved. The insulin rate is reduced when hyperglycemia is controlled, the blood pH is higher than 7.3, and bicarbonate level exceeds 18 mEq/L. Potassium, phosphate, and magnesium are replaced as needed. Sodium bicarbonate is administered if the blood pH is less than 7.0. The infrequent but devastating development of cerebral edema can result from correction of hyperglycemia without simultaneous correction of serum sodium level. The overall mortality rate from DKA is 1% to 2% but is significantly higher in patients older than 65 years of age and in those who are comatose at presentation. Mortality rate has fallen significantly over the past 20 years.

Hyperglycemic Hyperosmolar Syndrome

Hyperglycemic hyperosmolar syndrome is characterized by severe hyperglycemia, hyperosmolarity, and dehydration. It usually occurs in patients with type 2 diabetes who are older than 60 years of age in the context of an acute illness. The syndrome evolves over days to weeks with a persistent glycosuric diuresis. When the glucose load exceeds the renal tubular maximum for glucose reabsorption, a massive solute diuresis occurs with total body water depletion. The patient experiences polyuria, polydipsia, hypovolemia, hypotension, tachycardia, and organ hypoperfusion. Hyperosmolarity (340 mOsm/L) is responsible for mental obtundation or coma (Table 22.7). Patients may have some degree of metabolic acidosis but do not demonstrate ketoacidosis. Vascular occlusions secondary to low-flow states and diffuse intravascular coagulation are important complications of hyperglycemic hyperosmolar syndrome.

Treatment includes significant fluid resuscitation, insulin administration, and electrolyte supplementation. If the plasma osmolarity is greater than 320 mOsm/L, large volumes of hypotonic saline (1000–1500 mL/hr) should be administered until the osmolarity is less than 320 mOsm/L, at which time large volumes of isotonic saline (1000–1500 mL/hr) can be given. Insulin therapy is initiated with an intravenous bolus of 0.1 unit/kg of regular insulin followed by a 0.1 unit/kg/hr infusion. The insulin infusion is decreased to 0.02 to 0.05 unit/kg/hr when the glucose level decreases to approximately 250 to 300 mg/dL. Electrolyte deficits are significant but usually less severe than in DKA. The mortality rate of hyperglycemic hyperosmolar syndrome is 10% to 20%.

TABLE 22.7 Diagnostic Features and Symptoms of Hyperglycemic Hyperosmolar Syndrome

Glucose level (mg/dL)	⊔600
pH	⊔7.3
HCO_3^- (mEq/L)	⊔15
Serum osmolarity (mOsm/L)	⊓350
Symptoms	
Thirst and dry mouth	
Increased urination	
Fever	
Drowsiness	
Confusion or hallucination	
Vision loss	
Seizure	
Coma	

Microvascular Complications

Microvascular dysfunction is unique to diabetes and is characterized by nonocclusive, microcirculatory disease and impaired autoregulation of blood flow and vascular tone. Hyperglycemia is essential for the development of these changes, and intensive glycemic control delays the onset and slows the progression of microvascular effects.

Nephropathy

Approximately 30% to 40% of individuals with type 1 diabetes and 5% to 10% of those with type 2 diabetes develop end-stage renal disease. The kidneys demonstrate glomerulosclerosis with glomerular basement membrane thickening, arteriosclerosis, and tubulointerstitial disease. The clinical course is characterized by hypertension, albuminuria, peripheral edema, and a progressive decrease in glomerular filtration rate. When the glomerular filtration rate decreases to less than 15 to 20 mL/min, the ability of the kidneys to excrete potassium and acids is impaired and patients develop hyperkalemia and metabolic acidosis. Hypertension, hyperglycemia, hypercholesterolemia, and microalbuminuria accelerate the decrease in the glomerular filtration rate. Treatment of hypertension can markedly slow the progression of renal dysfunction. ACE inhibitors are particularly beneficial in diabetic patients because they slow the progression of proteinuria and the decrease in glomerular filtration rate. If end-stage renal disease develops, there are four options: hemodialysis, peritoneal dialysis, continuous ambulatory peritoneal dialysis, and transplantation. Patients who receive a kidney transplant, especially if the organ is from a living human leukocyte antigen (HLA)–identical donor, demonstrate a longer survival than those who undergo dialysis. Combined kidney-pancreas transplantation results in lower mortality than dialysis or renal transplantation alone and may prevent recurrence of diabetic nephropathy in the transplanted kidney.

Peripheral Neuropathy

More than 50% of patients who have had diabetes for longer than 25 years develop a peripheral neuropathy. A distal symmetric diffuse sensorimotor polyneuropathy is the most common form. Sensory deficits usually overshadow motor abnormalities and appear in the toes or feet and progress proximally toward the chest in a "stocking and glove" distribution. Loss of large sensory and motor fibers produces loss of light touch and proprioception as well as muscle weakness. Loss of small fibers decreases the perception of pain and temperature and produces dysesthesias, paresthesias, and neuropathic pain. Foot ulcers develop from mechanical and traumatic injury as a result of loss of cutaneous sensitivity to pain and temperature and impaired perfusion. Significant morbidity results from recurrent infection, foot fractures (Charcot joint), and subsequent amputations. The treatment of peripheral neuropathy includes optimal glucose control and use of nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, and anticonvulsants for pain control.

Retinopathy

Diabetic retinopathy results from a variety of microvascular changes, including blood vessel occlusion, dilation, increased permeability, and microaneurysm formation resulting in hemorrhage, exudation, and growth of abnormal blood vessels and fibrous tissue. Visual impairment can range from minor changes in color vision to total blindness. Strict glycemic blood pressure control reduces the risk of development and progression of retinopathy.

Autonomic Neuropathy

Diabetic autonomic neuropathy can affect any part of the autonomic nervous system and is the result of damaged vasoconstrictor fibers, impaired baroreceptor function, and ineffective cardiovascular reactivity. Cardiovascular signs of autonomic neuropathy include abnormalities in heart rate control as well as central and peripheral vascular dynamics. Resting tachycardia and loss of heart rate variability during deep breathing are early signs. A heart rate that fails to respond to exercise is indicative of significant cardiac denervation and is likely to result in substantially reduced exercise tolerance. The heart may demonstrate systolic and diastolic dysfunction with a reduced ejection fraction. Dysrhythmias may be responsible for sudden death. In advanced stages, severe orthostatic hypotension is present.

Diabetic autonomic neuropathy may also impair gastric secretion and gastric motility, eventually causing gastroparesis diabeticorum. Although it is often clinically silent, symptomatic patients will have nausea, vomiting, early satiety, bloating, and epigastric pain. Treatment of gastroparesis includes strict blood glucose control, consumption of multiple small meals, reduction of the fat content of meals, and use of prokinetic agents such as metoclopramide. Diarrhea and constipation are also common. In addition, patients with diabetic autonomic neuropathy may demonstrate altered respiratory reflexes and impaired ventilatory responses to hypoxia and hypercapnia.

Macrovascular Complications

Cardiovascular disease is a major cause of morbidity and the leading cause of mortality in diabetic individuals. Between 20% and 30% of patients coming to the hospital with a myocardial infarction have diabetes. Patients with poorly controlled diabetes demonstrate elevated triglyceride levels, low levels of high-density lipoprotein cholesterol, and an abnormally small, dense, more atherogenic low-density lipoprotein cholesterol. This dyslipidemia is caused by lack of appropriate insulin signaling and is exacerbated by poor glucose control. Measures to prevent coronary artery disease include maintaining lipid levels, glucose level, and blood pressure within normal limits. Aspirin and statin therapy should be considered for all diabetic patients.

Management of Anesthesia

Preoperative Evaluation

The preoperative evaluation should emphasize the cardiovascular, renal, neurologic, and musculoskeletal systems. The index of suspicion should be high for myocardial ischemia and infarction. Silent ischemia is possible if autonomic neuropathy is present, and stress testing should be considered in patients with multiple cardiac risk factors and poor or indeterminate exercise tolerance. Meticulous attention to hydration status, avoidance of nephrotoxins, and preservation of renal blood flow are also essential. The presence of autonomic neuropathy predisposes the patient to perioperative dysrhythmias and intraoperative hypotension. In addition, loss of compensatory sympathetic responses interferes with the detection and treatment of hemodynamic insults. Preoperative evaluation of the musculoskeletal system should look for limited joint mobility caused by nonenzymatic glycosylation of proteins and abnormal cross-linking of collagen. Firm, woody, nonpitting edema of the posterior neck and upper back (scleredema of diabetes) coupled with impaired joint mobility may limit range of motion of the neck and render endotracheal intubation difficult. Gastroparesis may increase the risk of aspiration, regardless of nothing-by-mouth status.

Patients who take oral hypoglycemic drugs or noninsulin injectables can continue their usual antidiabetic medications until the morning of surgery, when oral hypoglycemic and noninsulin injectable drugs should be held. Sulfonylureas increase the risk of hypoglycemia and inhibit the myocardial potassium adenosine triphosphate (ATP) channels that are responsible for myocardial preconditioning, which may theoretically increase the risk of myocardial infarction or increase infarct size. Management of insulin in the preoperative period depends on the type of insulin that the patient takes and the timing of dosing. Several strategies exist, and there is no consensus on the optimal strategy. Between one-third and one-half of the usual morning NPH dose should be given on the day of surgery. The daily morning dose of regular insulin or rapid-acting (e.g., lispro, aspart, glulisine) insulin should be held. For patients who take long-acting insulin (e.g., glargine) once per day or who use a continuous insulin infusion via an insulin pump, the basal rate can continue unchanged as long as the basal insulin dose is appropriately calculated. If there is a concern for preoperative hypoglycemia, for example with a patient who has a history of

low glucose measurements, the basal rate can be reduced by 10% to 25%.

Intraoperative Management

Aggressive glycemic control is important intraoperatively. For long and complex procedures, intravenous insulin is usually required, and dosing may be guided by trial and error or with an algorithm such as EndoTool. Ideally, a continuous infusion of insulin should be initiated at least 2 hours before surgery. Intraoperative serum glucose levels should be maintained between 120 and 180 mg/dL. Levels above 200 mg/dL are likely to cause glycosuria and dehydration and to inhibit phagocyte function and wound healing. Typically, 1 unit of insulin lowers glucose approximately 25 to 30 mg/dL. A typical rate is 0.02 unit/kg/hr, or 1.4 units/hr in a 70-kg patient. Insulin infusion requirements are higher for patients undergoing coronary bypass graft surgery, receiving steroids, with severe infections, and receiving hyperalimentation or vasopressor infusions. An insulin infusion should be accompanied by an infusion of 5% dextrose in half-normal saline with 20 mEq KCl at 100 to 150 mL/hr to provide enough carbohydrate (at least 150 g/day) to inhibit hepatic glucose production and protein catabolism. Serum glucose levels should be monitored at least every hour. Shorter intervals may be needed if blood glucose levels are less than 100 mg/dL, if rate of fall is rapid, or for patients undergoing coronary artery bypass graft surgery or patients with high insulin requirements.

Avoidance of hypoglycemia is especially critical since recognition of hypoglycemia may be delayed in patients receiving anesthetics, sedatives, analgesics, _ blockers, or sympatholytics, and in those with autonomic neuropathy. If hypoglycemia does occur, treatment consists of 50 mL of 50% dextrose in water, which typically increases the glucose level 100 mg/dL or 2 mg/dL/mL.

Postoperative Care

The postoperative management of diabetic patients requires meticulous monitoring of insulin requirements. Hyperglycemia has been associated with poor outcomes in postoperative and critically ill patients. However, the optimal target for blood glucose level in the perioperative period has not yet been defined. In addition, this target may be different for patients with newly diagnosed hyperglycemia than for those with preexisting diabetes. The risks of hypoglycemia must also be considered. Currently, the American Diabetes Association recommends that glucose levels be maintained between 140 and 180 mg/dL in critically ill patients and that insulin treatment be initiated if serum glucose levels exceed 180 mg/dL.

Insulinoma

Insulinomas are rare, benign insulin-secreting pancreatic islet cell tumors. They usually occur as an isolated finding but may present as part of multiple endocrine neoplasia syndrome type I (insulinoma, hyperparathyroidism, and a pituitary tumor). They occur in women twice as often as in men and usually in the fifth or sixth decade of life. The diagnosis is made by demonstrating Whipple triad:

1. Symptoms of hypoglycemia with fasting
2. Glucose level _ 50 mg/dL with symptoms
3. Relief of symptoms by administration of glucose

An inappropriately high insulin level (= 5–10 microunits/mL) during a 48- to 72-hour fast confirms the diagnosis.

Preoperatively, patients are often managed with diazoxide, an agent that directly inhibits insulin release from ¯ cells. Other medical therapies include verapamil, phenytoin, propranolol, glucocorticoids, and the somatostatin analogues octreotide and lanreotide. Surgical treatment is curative. Ninety percent of insulinomas are benign, and tumor enucleation is the procedure of choice. Laparoscopic resection is used in some centers.

Profound hypoglycemia can occur intraoperatively, particularly during manipulation of the tumor; however, marked hyperglycemia can follow removal of the tumor. In a few medical centers, an artificial pancreas that continuously analyzes the blood glucose concentration and automatically infuses insulin or glucose has been used for intraoperative management of these patients. In most cases, serial blood glucose measurements (every 15 minutes) are taken using a standard glucometer. Since evidence of hypoglycemia may be masked under anesthesia, intravenous fluids containing glucose should be considered.

THYROID DISEASE

The thyroid gland weighs approximately 20 g and is composed of two lobes joined by an isthmus. The gland is closely affixed to the anterior and lateral aspects of the trachea, with the upper border of the isthmus located just below the cricoid cartilage. A pair of parathyroid glands is located on the posterior aspect of each lobe. A rich capillary network permeates the entire gland. The gland is innervated by the adrenergic and cholinergic nervous systems. The recurrent laryngeal nerve and external motor branch of the superior laryngeal nerve are in intimate proximity to the gland. Histologically, the thyroid is composed of numerous follicles filled with proteinaceous colloid. The major constituent of colloid is thyroglobulin, an iodinated glycoprotein that serves as the substrate for thyroid hormone synthesis. The thyroid gland also contains parafollicular C cells, which produce calcitonin.

Production of normal quantities of thyroid hormones depends on the availability of exogenous iodine. The diet is the primary source of iodine. Iodine is reduced to iodide in the gastrointestinal tract, rapidly absorbed into the blood, then actively transported from the plasma into thyroid follicular cells. Binding of iodine to thyroglobulin (i.e., organification) is catalyzed by an iodinase enzyme and yields inactive monoiodotyrosine and diiodotyrosine. Approximately 25% of the monoiodotyrosine and diiodotyrosine undergo coupling via thyroid peroxidase to form the active compound triiodothyronine (T_3) and thyroxine (T_4). The remaining 75% never becomes hormones, and eventually the iodine is cleaved and recycled. T_3 and T_4 remain attached to thyroglobulin and are stored as colloid

until they are released into the circulation. Since the thyroid contains a large store of hormones and has a low turnover rate, there is protection against depletion if synthesis is impaired or discontinued.

The T_4/T_3 ratio of secreted hormones is 10:1. Upon entering the blood, T_4 and T_3 reversibly bind to three major proteins: thyroxine-binding globulin (80% of binding), prealbumin (10–15%), and albumin (5–10%). Only the small amount of free fraction of hormone is biologically active. Although only 10% of thyroid hormone secretion is T_3, T_3 is three to four times more active than T_4 per unit of weight and may be the only active thyroid hormone in peripheral tissues. Thyroid hormones stimulate virtually all metabolic processes. They influence growth and maturation of tissues, enhance tissue function, and stimulate protein synthesis and carbohydrate and lipid metabolism.

Thyroid hormone acts directly on cardiac myocytes and vascular smooth muscle cells. In the heart, T_3 is transported via specific proteins across the myocyte cell membrane and enters the nucleus, binding to nuclear receptors that in turn bind to specific target genes. T_3-responsive genes code for structural and regulatory proteins in the heart that are important for systolic contractile function and diastolic relaxation. Thyroid hormone increases myocardial contractility directly, decreases systemic vascular resistance via direct vasodilation, and increases intravascular volume. Most recent studies emphasize the direct effects of T_3 on the heart and vascular smooth muscle as responsible for the exaggerated hemodynamic effects of hyperthyroidism. Even though hyperthyroid patients appear to have increased numbers of _-adrenergic receptors, these receptors demonstrate little or no increased sensitivity to adrenergic stimulation, and surprisingly these patients have normal or low serum concentrations of catecholamines.

Regulation of thyroid function is controlled by the hypothalamus, pituitary, and thyroid glands, which participate in a classic feedback control system. Thyrotropin-releasing hormone (TRH) is secreted from the hypothalamus, traverses the pituitary stalk, and promotes release of thyrotropin-stimulating hormone (TSH) from the anterior pituitary. TSH binds to specific receptors on the thyroid cell membrane and enhances all processes of synthesis and secretion of T_4 and T_3. A decrease in TSH causes a reduction in synthesis and secretion of T_4 and T_3, a decrease in follicular cell size, and a decrease in the gland's vascularity. An increase in TSH yields an increase in hormone production and release and an increase in gland cellularity and vascularity. TSH secretion is also influenced by plasma levels of T_4 and T_3 via a negative feedback loop. In addition to the feedback system, the thyroid gland has an autoregulatory mechanism that maintains a consistent level of hormone stores.

Diagnosis

The third generation of the TSH assay is now the single best test of thyroid hormone action at the cellular level. Small changes in thyroid function cause significant changes in TSH secretion. The normal TSH level is 0.4 to 5.0 milliunits/L.

TABLE 22.8 Laboratory Assessment of Thyroid Function

	TSH	Free T_3/T_4
Subclinical hyperthyroidism	0.1–0.4 milliunits/l	Normal
Overt hyperthyroidism	<0.03 milliunits/L	Increased
Subclinical hypothyroidism	5.0–10 milliunits/L	Normal
Overt hypothyroidism	>20 milliunits/L	Reduced

Table 22.8 provides details on laboratory assessment of thyroid function.

The TRH stimulation test assesses the functional state of the TSH-secreting mechanism in response to TRH and is used to test pituitary function. Other tests that may be helpful in detecting thyroid dysfunction include measurement of serum antimicrosomal antibodies, antithyroglobulin antibodies, and thyroid-stimulating immunoglobulins. Thyroid scans using iodine 123 (^{123}I) or technetium 99m evaluate thyroid nodules as "warm" (normally functioning), "hot" (hyperfunctioning), or "cold" (hypofunctioning). Ultrasonography is 90% to 95% accurate in determining whether a lesion is cystic, solid, or mixed.

HYPERTHYROIDISM

Signs and Symptoms

Hyperthyroidism refers to hyperfunctioning of the thyroid gland with excessive secretion of active thyroid hormones. The majority of cases of hyperthyroidism result from one of three pathologic processes: Graves disease, toxic multinodular goiter, or toxic adenoma. Regardless of the cause, the signs and symptoms of hyperthyroidism are those of a hypermetabolic state (Table 22.9). The patient may demonstrate increased sweating and complain of heat intolerance. The patient usually complains of extreme fatigue but an inability to sleep. Increased

TABLE 22.9 Signs and Symptoms of Hyperthyroidism and Cardiac Effects

Signs and Symptoms	
General:	Anxious
HEENT:	Flushed face
	Fine hair
	Exophthalmos/proptosis
Cardiovascular:	Palpitations
Neurologic:	Wasting, weakness, fatigue of proximal limb muscles
	Fine tremor of hands
	Hyperactive deep tendon reflexes
GI:	Frequent bowel movements/diarrhea
Psych:	Emotionally unstable
Skin:	Warm, moist
Cardiac Effects	
	Tachycardia, arrhythmias (commonly atrial)
	Hyperdynamic
	Increased cardiac output and contractility
	Cardiomegaly

bone turnover and osteoporosis may occur. Weight loss despite an increased appetite occurs secondary to increased calorigenesis. T_3 acts directly on the myocardium and peripheral vasculature to cause the cardiac responses.

Graves disease or toxic diffuse goiter occurs in 0.4% of the US population and is the leading cause of hyperthyroidism. The disease typically occurs in females (female:male ratio is 7:1) between the ages of 20 and 40 years. Although the etiology is unknown, Graves disease appears to be a systemic autoimmune disease caused by thyroid-stimulating antibodies that bind to TSH receptors in the thyroid, stimulating thyroid growth, vascularity, and hypersecretion of T_4 and T_3. The thyroid is usually diffusely enlarged. An ophthalmopathy occurs in 30% of cases and may include upper lid retraction, a wide-eyed stare, muscle weakness, proptosis, and an increase in intraocular pressure. When severe, the condition is termed *malignant opthalmos*. Steroid therapy, bilateral tarsorrhaphy, external radiation therapy, or surgical decompression may be necessary in these cases. The diagnosis of Graves disease is confirmed by the presence of thyroid-stimulating antibodies in the context of low TSH and elevated T_4 and T_3 levels.

Toxic multinodular goiter usually arises from long-standing simple goiter and occurs mostly in patients older than 50 years of age. It may present with extreme thyroid enlargement that can cause dysphagia, globus sensation, and possibly inspiratory stridor from tracheal compression. The latter is especially common when the mass extends into the thoracic inlet behind the sternum. In severe cases, superior vena cava obstruction syndrome may also be present. The diagnosis is confirmed by a thyroid scan demonstrating "hot" patchy foci throughout the gland or one or two "hot" nodules. Radioactive iodine uptake and serum T_4 and T_3 levels may only be slightly elevated. The goiter must be differentiated from a neoplasm, and a computed tomography (CT) scan and biopsy may be necessary.

Treatment

The first line of treatment for hyperthyroidism is an antithyroid drug, either methimazole or propylthiouracil (PTU). These agents interfere with the synthesis of thyroid hormones by inhibiting organification and coupling. PTU has the added advantage of inhibiting the peripheral conversion of T_4 to T_3. A euthyroid state can almost always be achieved in 6 to 8 weeks with either drug if a sufficient dosage is used. Side effects occur in 3% to 12% of patients, with agranulocytosis being the most serious.

Iodide in high concentrations inhibits release of hormones from the hyperfunctioning gland. High concentrations of iodide decrease all phases of thyroid synthesis and release, and result in reduced gland size and possibly a decrease in vascularity. Its effects occur immediately but are short lived. Therefore iodide is usually reserved for preparing hyperthyroid patients for surgery, managing patients with actual or impeding thyroid storm, and treating patients with severe thyrocardiac disease. There is no need to delay surgery in a patient with otherwise well-controlled thyrotoxicosis to initiate iodide therapy.

Iodide is administered orally as a saturated solution of potassium iodide (SSKI). The radiographic contrast dye ipodate or iopanoic acid contains iodide and demonstrates beneficial effects similar to those of inorganic iodide. In addition, ipodate inhibits the peripheral conversion of T_4 to T_3 and may antagonize thyroid hormone binding to receptors. Antithyroid drug therapy should precede the initiation of iodide treatment because administration of iodide alone will increase thyroid hormone stores and exacerbate the thyrotoxic state. Lithium carbonate may be given in place of potassium iodide or ipodate to patients who are allergic to iodide.

β-adrenergic antagonists do not affect the underlying thyroid abnormality but may relieve signs and symptoms of increased adrenergic activity such as anxiety, sweating, heat intolerance, tremors, and tachycardia. Propranolol offers the added features of impairing the peripheral conversion of T_4 to T_3.

Ablative therapy with radioactive ^{131}I or surgery is recommended for patients with Graves disease for whom medical management has failed, as well as for patients with toxic multinodular goiter or a toxic adenoma. Standard doses of ^{131}I deliver approximately 8500 rad to the thyroid and destroy the follicular cells. The remission rate is 80% to 98%. A major disadvantage of therapy is that 40% to 70% of treated patients become hypothyroid within 10 years.

Surgery (subtotal thyroidectomy) results in prompt control of disease and is associated with a lower incidence of hypothyroidism (10–30%) than radioactive iodine therapy. Subtotal thyroidectomy corrects thyrotoxicosis in more than 95% of patients; mortality rate for the procedure is less than 0.1%. Complications from surgery include hypothyroidism, hemorrhage with tracheal compression, unilateral or bilateral damage to the recurrent laryngeal nerve(s), damage to the motor branch of the superior laryngeal nerve, and damage to or inadvertent removal of the parathyroid glands.

Management of Anesthesia

In hyperthyroid patients undergoing surgery, euthyroidism should be established preoperatively. In elective cases, this may mean waiting 6 to 8 weeks for antithyroid drugs to become effective. In emergency cases, the use of an intravenous β blocker, ipodate, glucocorticoids, and PTU is usually necessary. No intravenous preparation of PTU is available, so the drug must be taken orally, via nasogastric tube, or rectally. Glucocorticoids (dexamethasone 2 mg IV every 6 hr) should be administered to decrease hormone release and reduce the peripheral conversion of T_4 to T_3. The anesthesiologist should be prepared to manage thyroid storm, especially in patients with uncontrolled or poorly controlled disease.

Evaluation of the upper airway for evidence of tracheal compression or deviation caused by a goiter is an important part of the preoperative evaluation. Examination of chest radiographs and CT scans is often helpful in this regard. Intraoperatively, the need for invasive monitoring is determined on an individual basis and depends on the type of surgery to be performed and the medical condition of the patient. Controlled studies in hyperthyroid animals demonstrate no clinically significant increase in anesthetic requirements (i.e.,

minimum alveolar concentration). Establishment of adequate anesthetic depth is extremely important to avoid exaggerated sympathetic nervous system responses. Drugs that stimulate the sympathetic nervous system (i.e., ketamine, atropine, ephedrine, epinephrine) should be avoided. Eye protection (eyedrops, lubricant, eye pads) is critical, especially for patients with proptosis.

For maintenance of anesthesia, any of the potent inhalational agents may be used. A concern in hyperthyroid patients is organ toxicity secondary to an increase in drug metabolism. Although animal studies demonstrate an increase in hepatotoxicity in hyperthyroid rats following exposure to isoflurane, these results have not been substantiated in humans. Hyperthyroid patients may have coexisting muscle disease (e.g., myasthenia gravis) with reduced requirements for the nondepolarizing muscle relaxants; therefore careful titration is required.

Removal of the thyrotoxic gland does not mean immediate resolution of thyrotoxicosis. The half-life of T_4 is 7 to 8 days; therefore β-blocker therapy may need to be continued in the postoperative period.

Thyroid Storm

Thyroid storm is a life-threatening exacerbation of hyperthyroidism precipitated by trauma, infection, medical illness, or surgery. Thyroid storm and malignant hyperthermia can present with similar intraoperative and postoperative signs and symptoms (i.e., hyperpyrexia, tachycardia, hypermetabolism); therefore differentiation between the two may be extremely difficult. Surprisingly, thyroid hormone levels in thyroid storm may not be significantly higher than during uncomplicated hyperthyroidism. Thyroid function tests therefore may not be useful in making the diagnosis.

Thyroid storm most often occurs in the postoperative period in untreated or inadequately treated hyperthyroid patients after emergency surgery. Diagnostic criteria for thyroid storm exist and are based on the degree of thermoregulatory dysfunction, central nervous system effects, gastrointestinal-hepatic dysfunction, cardiovascular dysfunction, heart failure, and precipitant history. Treatment includes rapid alleviation of thyrotoxicosis and general supportive care. Table 22.10 provides the initial approach to management of the patient with thyroid storm. If circulatory shock is present, intravenous administration of a direct vasopressor such as phenylephrine is indicated. A β blocker or digitalis is recommended for atrial fibrillation accompanied by a rapid ventricular response. The mortality rate for thyroid storm remains surprisingly high at approximately 20%.

TABLE 22.10 Approach to Treatment of Thyroid Storm

Drug	Effect
Glucose-containing crystalloid solution	Treats dehydration
β blockers	Mitigate signs and symptoms of increased adrenergic tone
Glucocorticoids	Decrease hormone release; decreases conversion of T_4–T_3
Antithyroid drugs	Block new hormone synthesis

HYPOTHYROIDISM

Signs and Symptoms

Hypothyroidism or myxedema is a relatively common disease affecting 0.5% to 0.8% of the adult population. Primary hypothyroidism results in decreased production of thyroid hormones despite adequate or increased levels of TSH and accounts for 95% of all cases of hypothyroidism. The most common cause in the United States is ablation of the gland by radioactive iodine or surgery. The second most common type of hypothyroidism is idiopathic and probably autoimmune in origin, with autoantibodies blocking TSH receptors in the thyroid. Unlike Graves disease, this immune response destroys receptors instead of stimulating them. Hashimoto thyroiditis is an autoimmune disorder characterized by goitrous enlargement and hypothyroidism that usually affects middle-aged women.

In adults, hypothyroidism has a slow, insidious, progressive course. Table 22.11 describes signs and symptoms of hypothyroidism. With time, patients experience cold intolerance. They gain weight despite a decrease in appetite. Accumulation of hydrophilic mucopolysaccharides in the dermis and other tissues is responsible for the immobile, nonpitting edema. Hyponatremia and impairment of free water excretion are also common, related to inappropriate secretion of antidiuretic hormone (ADH). Maximum breathing capacity and diffusion capacity are decreased, and ventilatory responsiveness to hypoxia and hypercarbia is depressed. Pleural effusions may result in

TABLE 22.11 Signs and Symptoms of Hypothyroidism and Cardiac Effects

Signs and Symptoms	
General:	Fatigue, listlessness
HEENT:	Dry brittle hair, large tongue, deep hoarse voice, periorbital edema
Neurologic:	Slow speech, slowing of motor function, prolonged relaxation phase of deep tendon reflexes
GI:	Constipation
Psych:	Apathy
Skin:	Pale, cool, dry thickened skin, nonpitting peripheral edema
Cardiac Effects	
	Decreased cardiac output
	Baroreceptor function impaired
	Flattened or inverted T waves, low-amplitude P waves and QRS complexes, sinus bradycardia, ventricular dysrhythmias on electrocardiogram
	Hypothyroid cardiomyopathy
	Pericardial effusions

dyspnea. Gastrointestinal function is slow, and an adynamic ileus may occur.

Twenty percent of women older than 60 years of age have subclinical hypothyroidism. Subclinical disease is associated with an increased risk of coronary artery disease in patients with a TSH level of more than 10 milliunits/L. Although most patients have few if any signs or symptoms, changes in myocardial structure and contractility can occur secondary to systolic and diastolic dysfunction. Even though these changes are reversible with L-thyroxine therapy, use of thyroid replacement for subclinical disease remains controversial.

Secondary hypothyroidism is diagnosed by reduced levels of free T_4, T_4, and T_3, as well as reduced TSH level. A TRH stimulation test can confirm pituitary abnormality as the cause. This test measures the responsiveness of the pituitary gland to intravenously administered TRH, the hypothalamic stimulator of TSH. In primary hypothyroidism, basal levels of TSH are elevated, and the elevation is exaggerated after TRH administration. With pituitary dysfunction, there is a blunted or absent response to TRH.

Euthyroid sick syndrome is the occurrence of abnormal results on thyroid function tests in critically ill patients with significant nonthyroidal illness. Characteristic findings include low levels of T_3 and T_4 and a normal TSH level. As illness increases in severity, the T_3 and T_4 levels decrease further. The etiology of this response is not understood. Euthyroid sick syndrome may be a physiologic response to stress, and it can be induced by surgery. No treatment for thyroid function is necessary. Differentiating hypothyroidism from euthyroid sick syndrome can be extremely difficult. A serum TSH level is the best aid. Levels higher than 10 milliunits/L indicate hypothyroidism, whereas levels lower than 5.0 milliunits/L indicate euthyroidism.

Treatment

L-thyroxine (levothyroxine sodium) is usually administered for the treatment of hypothyroidism. The first evidence of a therapeutic response to thyroid hormone is sodium and water diuresis and a reduction in the TSH level. In patients with hypothyroid cardiomyopathy, a measurable improvement in myocardial function is often achieved with therapy.

Although angina is uncommon in hypothyroidism, it can appear or worsen during treatment of the hypothyroid state with thyroid hormone. Medical management of such patients is particularly difficult. Therefore patients who have both hypothyroidism and angina should undergo angiographic evaluation of the coronary arteries before hormone replacement is initiated. If surgically remediable disease is demonstrated, coronary artery bypass graft surgery can be successfully accomplished despite hypothyroidism. Coronary revascularization can permit the necessary thyroid hormone replacement and reinstitution of the euthyroid state.

Management of Anesthesia

Hypothyroid patients may be at increased risk when undergoing either general or regional anesthesia for a number of reasons. Airway compromise secondary to a swollen oral cavity, edematous vocal cords, or goitrous enlargement may be present. Decreased gastric emptying increases the risk of regurgitation and aspiration. A hypodynamic cardiovascular system characterized by decreased cardiac output, stroke volume, heart rate, baroreceptor reflexes, and intravascular volume may be compromised by surgical stress and cardiac depressant anesthetic agents. Decreased ventilatory responsiveness to hypoxia and hypercarbia is enhanced by anesthetic agents. Hypothermia occurs quickly and is difficult to treat. Hematologic abnormalities such as anemia (25–50% of patients) and dysfunction of platelets and coagulation factors (especially factor VIII), electrolyte imbalances (hyponatremia), and hypoglycemia are common and require close monitoring intraoperatively. Decreased neuromuscular excitability is exacerbated by anesthetic drugs.

These patients can be extremely sensitive to narcotics and sedatives and may even be lethargic secondary to their disease; therefore preoperative sedation should be undertaken with caution. Hypothyroid patients also appear to have an increased sensitivity to anesthetic drugs, although the effect of thyroid activity on the minimum alveolar concentration of volatile anesthetics is negligible. Increased sensitivity is probably secondary to reduced cardiac output, decreased blood volume, abnormal baroreceptor function, decreased hepatic metabolism, and decreased renal excretion of drugs. In patients with a hypodynamic cardiovascular system, invasive monitoring and/or transesophageal echocardiography may be needed to monitor intravascular volume and cardiac status.

General anesthetics should be administered through an endotracheal tube following either rapid-sequence induction or awake intubation if a difficult airway is present. Hypothyroid patients are very sensitive to the myocardial-depressant effects of the potent inhalational agents. Vasodilation in the presence of possible hypovolemia and impaired baroreceptor activity can produce significant hypotension. Pharmacologic support for intraoperative hypotension is best provided with ephedrine, dopamine, or epinephrine and not a pure α-adrenergic agonist (phenylephrine). Unresponsive hypotension may require supplemental steroid administration.

From a cardiovascular standpoint, pancuronium is a preferred muscle relaxant due to its chronotropic effects; however, reduced skeletal muscle activity in these patients coupled with a reduction in hepatic metabolism necessitates cautious dosing. Controlled ventilation is recommended in all cases since these patients tend to hypoventilate if allowed to breathe spontaneously. Dextrose in normal saline is the recommended intravenous fluid to avoid hypoglycemia and minimize hyponatremia secondary to impaired free water clearance.

If emergency surgery is necessary, the potential for severe intraoperative cardiovascular instability and myxedema coma in the postoperative period is high. Intravenous thyroid replacement therapy should be initiated as soon as possible. Although intravenous L-thyroxine takes 10 to 12 days to yield a peak basal metabolic rate, intravenous triiodothyronine is effective in 6 hours with a peak basal metabolic rate seen in 36 to 72 hours. Steroid coverage with hydrocortisone or dexamethasone is necessary since decreased adrenal cortical function often accompanies hypothyroidism. Phosphodiesterase

inhibitors such as milrinone may be effective in the treatment of reduced myocardial contractility because their mechanism of action does not depend on ⊥ receptors, whose number and sensitivity may be reduced in hypothyroidism.

Myxedema Coma

Myxedema coma is a rare, severe form of hypothyroidism characterized by delirium or unconsciousness, hypoventilation, hypothermia (80% of patients), bradycardia, hypotension, and a severe dilutional hyponatremia. It occurs most commonly in elderly women with a long history of hypothyroidism. Infection, trauma, cold, and central nervous system depressants predispose hypothyroid patients to myxedema coma. Ironically, most patients are not comatose. Hypothermia (as low as 27°C) is a cardinal feature and results from impaired thermoregulation caused by defective function of the hypothalamus (a target tissue of thyroid hormone). Myxedema coma is a medical emergency with a mortality rate higher than 50%. Intravenous L-thyroxine or L-triiodothyronine is the treatment of choice. Intravenous hydration with glucose-containing saline solutions, temperature regulation, correction of electrolyte imbalances, and stabilization of the cardiac and pulmonary systems are necessary. Mechanical ventilation is frequently required. Heart rate, blood pressure, and temperature usually improve within 24 hours, and a relative euthyroid state is achieved in 3 to 5 days. Hydrocortisone is also prescribed to treat possible adrenal insufficiency.

GOITER AND THYROID TUMORS

A goiter is a swelling of the thyroid gland that results from compensatory hypertrophy and hyperplasia of follicular epithelium secondary to a reduction in thyroid hormone output. The cause may be a deficient intake of iodine, ingestion of a dietary (i.e., cassava) or pharmacologic (i.e., phenylbutazone, lithium) goitrogen, or a defect in the hormonal biosynthetic pathway. The size of the goiter is determined by the level and duration of hormone insufficiency. In most cases, a goiter is associated with a euthyroid state, with the increased mass and cellular activity eventually overcoming the impairment in hormone synthesis. However, hypothyroidism or hyperthyroidism occurs in some cases. Patients with simple nontoxic goiter are euthyroid. Nevertheless, simple, nontoxic goiter is a forerunner of toxic multinodular goiter. In the United States, most cases of simple nontoxic goiter are of unknown cause and are treated with L-thyroxine. Surgery is indicated only if medical therapy is ineffective and the goiter is compromising the airway or is cosmetically unacceptable.

If the mass extends into the substernal region (i.e., anterior mediastinal mass), superior vena cava obstruction, major airway obstruction, and/or cardiac compression may occur. The latter two may become apparent only upon induction of general anesthesia. Airway obstruction appears to result from changes in lung and chest wall mechanics that occur with changes in patient position or with the onset of muscle paralysis. During spontaneous respiration, the larger airways are supported by negative intrathoracic pressure, and the effects of extrinsic compression may be apparent in only the most severe cases. With cessation of spontaneous respiration, compensatory mechanisms are removed, and airway obstruction occurs. In addition, positive pressure ventilation may demonstrate total airway occlusion. A preoperative history of dyspnea in the upright or supine position is predictive of possible airway obstruction during general anesthesia. A CT scan must be examined to assess the extent of the tumor. Flow-volume loops in the upright and supine positions will demonstrate the site and degree of obstruction to airflow in the upper airway and trachea. Limitations in the inspiratory limb of the loop indicate extrathoracic airway obstruction, and delayed flow in the expiratory limb indicates intrathoracic obstruction. Echocardiography with the patient in the upright and supine positions can indicate degree of cardiac compression.

The anesthetic management of a patient undergoing surgical removal of a large goiter or thyroid mass that compromises the airway presents a major challenge. If practical, local anesthesia is recommended for patients requiring surgery. If general anesthesia is necessary, preoperative shrinkage of a thyroid tumor by radiation or chemotherapy is recommended. Unfortunately, goiters are not sensitive to radiation therapy. Examination of a CT scan of the neck will demonstrate anatomic abnormalities. Sedatives and narcotics should be avoided or used with great caution before and during endotracheal tube placement. Awake intubation with an armored (anode) tube using fiberoptic bronchoscopy is probably the safest method to assess the degree of obstruction and establish the airway. The patient is placed in semi-Fowler position, and volatile anesthetic with nitrous oxide and oxygen is administered using spontaneous ventilation. Muscle relaxants are avoided. It must be possible to change the patient's position.

Surgical removal of the mass may reveal underlying tracheomalacia and a collapsible airway. Therefore tracheal extubation should be performed with as much caution and concern as intubation. Following tumor resection, the airway should be examined by fiberoptic bronchoscopy to determine whether and when tracheal extubation is appropriate. A rigid bronchoscope should be available to reestablish the airway if collapse occurs. Cardiopulmonary bypass equipment should be on standby during the case.

COMPLICATIONS OF THYROID SURGERY

Morbidity from thyroid surgery approaches 13%. Recurrent laryngeal nerve injury may be unilateral or bilateral and temporary or permanent. The injury may result from excess trauma to the nerve(s) (abductor and/or adductor fibers of the recurrent laryngeal nerve), inadvertent ligation, or transection. When paralysis of the abductor muscles to the vocal cords occurs, the involved cord assumes a median or paramedian position. If trauma is unilateral, the patient experiences hoarseness but no airway obstruction, and function usually returns in 3 to 6 months. Ligation or transection of the nerve results in permanent hoarseness. Bilateral involvement is more serious since the patient usually experiences airway obstruction and problems with coughing and respiratory toilet. Depending on the degree of damage, a temporary or permanent tracheostomy is usually

TABLE 22.12 Signs of Hypocalcemia

Anxiety
Circumoral numbness
Tingling of the fingertips
Muscle cramping
Chvostek sign: facial muscle twitching produced by manual tapping over the area of the facial nerve at angle of mandible
Trousseau sign: carpopedal spasm in response to 3 min limb ischemia produced by a tourniquet

necessary. Injury to the adductor fibers of the recurrent laryngeal nerve(s) results in paralysis of the adductor muscles(s) and increases the risk of pulmonary aspiration. Injury to the motor branch of the superior laryngeal nerve, which innervates the inferior pharyngeal constrictor and cricothyroid muscles, can also occur during thyroid dissection. This injury results in weakening of the voice and the inability to create high tones.

Hypoparathyroidism is also a complication of thyroid surgery. It usually results from damage to the blood supply of the parathyroid glands rather than inadvertent removal. One functioning parathyroid gland with an adequate blood supply is all that is necessary to avoid hypoparathyroidism. The signs and symptoms of hypocalcemia occur in the first 24 to 48 hours postoperatively (Table 22.12). Stridor can occur and can proceed to laryngospasm. Immediate treatment with intravenous calcium gluconate or calcium chloride is necessary.

Tracheal compression from an expanding hematoma may cause rapid respiratory compromise in the period immediately after thyroid surgery. Immediate hematoma evacuation is the first line of treatment. If time permits, the patient should be returned to the operating room. If necessary, the wound should be opened at the bedside, clots evacuated, and bleeding vessels secured to relieve airway obstruction. A thyroid tray, including a tracheostomy set, should always be available at the bedside during the postoperative period so that sutures or clips can be removed and the wound opened emergently, and emergency surgical airway secured if necessary.

ADRENAL GLAND DYSFUNCTION

Each adrenal gland consists of two components, the adrenal cortex and the adrenal medulla. The adrenal cortex is responsible for the synthesis of three groups of hormones classified as glucocorticoids, mineralocorticoids (aldosterone), and androgens. Corticotropin (ACTH) is secreted by the anterior pituitary gland in response to corticotropin-releasing hormone (CRH), which is synthesized in the hypothalamus and carried to the anterior pituitary in the portal blood. ACTH stimulates the adrenal cortex to produce cortisol. Maintenance of systemic blood pressure by cortisol reflects the importance of this hormone in facilitating conversion of norepinephrine to epinephrine in the adrenal medulla. Hyperglycemia in response to cortisol secretion reflects gluconeogenesis and inhibition of the peripheral use of glucose by cells. Retention of sodium and excretion of potassium are facilitated by cortisol. The antiinflammatory effects of cortisol and other glucocorticoids (cortisone, prednisone, methylprednisolone, dexamethasone, triamcinolone) are particularly apparent in the presence of high serum concentrations of these hormones. Aldosterone secretion is regulated by the renin-angiotensin system and the serum concentrations of potassium. Aldosterone regulates the extracellular fluid volume by promoting resorption of sodium by the renal tubules. In addition, aldosterone promotes renal tubular excretion of potassium.

The adrenal medulla is a specialized part of the sympathetic nervous system that is capable of synthesizing norepinephrine and epinephrine. The only important disease process associated with the adrenal medulla is pheochromocytoma. Adrenal medullary insufficiency is not known to occur.

Surgery is one of the most potent and best-studied activators of the hypothalamic-pituitary-adrenal (HPA) axis. The degree of activation of the axis depends on the magnitude and duration of surgery and the type and depth of anesthesia. In patients with an intact, normally functioning HPA axis, CRH, ACTH, and cortisol levels all increase significantly during surgery. Deep general anesthesia or regional anesthesia blunts but does not eliminate this response. Increases in ACTH begin with surgical incision and remain elevated during surgery, with the peak level occurring with pharmacologic reversal of muscle relaxants and extubation of the patient at the end of the procedure. Hormone levels remain elevated for several days postoperatively. During major surgery, cortisol release may increase from a preoperative level of 15 to 25 mg/day to 75 to 150 mg/day, which results in a plasma cortisol level of 30 to 50 _g/dL. Patients in the intensive care unit (ICU) may have plasma cortisol levels of more than 60 _g/dL.

PHEOCHROMOCYTOMA

Pheochromocytomas are catecholamine-secreting tumors that arise from chromaffin cells of the sympathoadrenal system. Although pheochromocytomas account for fewer than 0.1% of all cases of hypertension in adults, their detection is imperative since they have lethal potential and are one of the few truly curable forms of hypertension. Uncontrolled catecholamine release can result in malignant hypertension, cerebrovascular accident, and myocardial infarction.

The precise cause of a pheochromocytoma is unknown. Pheochromocytomas are usually an isolated finding (90% of cases). Ten percent of pheochromocytomas are inherited (familial) as an autosomal dominant trait. Familial pheochromocytomas usually occur as bilateral adrenal tumors or as extraadrenal tumors that appear in the same anatomic site over successive generations. Both sexes are equally affected, and the peak incidence is in the third to fifth decades of life. Ten percent of pheochromocytomas occur in children, and in this population multiple, extraadrenal, and bilateral tumors are relatively more common than in adults. Variability in clinical presentation often leads to difficulties in diagnosis. Recent advances in genetic testing allow early identification of patients with a familial pheochromocytoma before signs and symptoms occur.

Familial pheochromocytomas can also be part of the multiple endocrine neoplastic (MEN) syndromes and can occur

TABLE 22.13 Comparison Between Multiple Endocrine Neoplasia Syndrome (MEN) Type II A vs B

Type IIA	Type IIB
Pheochromocytoma	Pheochromocytoma
Medullary carcinoma of the thyroid	Medullary carcinoma of the thyroid
Hyperparathyroidism	Alimentary tract ganglioneuromatosis
	Thickened corneal nerves
	Marfanoid habitus

in association with several neuroectodermal dysplasias (e.g., von Hippel-Lindau syndrome). Table 22.13 compares MEN type IIA and IIB. Almost 100% of patients with MEN type II have or will develop bilateral benign adrenal medullary pheochromoctyomas.

Eighty percent of pheochromoctyomas are located in the adrenal medulla. The organ of Zuckerkandl near the aortic bifurcation is the most common extraadrenal site. Two percent of extraadrenal pheochromocytomas occur in the neck and thorax. Failure of involution of chromaffin tissue in childhood is the best explanation for the development of extraadrenal pheochromocytomas. Most follow a benign course. Malignant pheochromocytomas usually spread via venous and lymphatic channels with a predilection for liver and bone. The 5-year survival rate for patients with malignancy is 44%. Following resection of benign tumors, 5% to 10% of patients have a benign recurrence.

Most pheochromocytomas secrete norepinephrine, either alone or, more commonly, in combination with a smaller amount of epinephrine in a ratio of 85:15—the inverse of the secretion ratio in the normal adrenal gland. Approximately 15% of tumors secrete predominately epinephrine. Some dopamine-secreting pheochromocytomas have also been described. Most pheochromocytomas are not under neurogenic control and secrete catecholamines autonomously.

Signs and Symptoms

The clinical presentation of pheochromocytoma is variable; attacks range from infrequent (i.e., once a month or fewer) to numerous (i.e., many times per day) and may last from less than a minute to several hours. They may occur spontaneously or be precipitated by physical injury, emotional stress, or medications. Table 22.14 lists common findings with pheochromocytoma. Orthostatic hypotension is also a common finding and is considered to be secondary to hypovolemia and impaired vasoconstrictor reflex responses.

Hemodynamic signs depend on the predominant catecholamine secreted. With norepinephrine, α-adrenergic effects predominate, and patients usually have systolic and diastolic hypertension and a reflex bradycardia. With epinephrine, β-adrenergic effects predominate, and patients usually have systolic hypertension, diastolic hypotension, and tachycardia. Despite the 10-fold higher levels of circulating catecholamines, the hemodynamics are not greatly different in patients with pheochromocytomas and in patients with essential hypertension. Both groups have an increased systemic vascular resistance, usually a normal cardiac output, and a slightly decreased plasma volume. Long-term exposure to high levels of catecholamines does not appear to produce hemodynamic responses characteristic of acute administration. A desensitization of the cardiovascular system or a downregulation of adrenergic receptors may explain this finding.

TABLE 22.14 Findings With Pheochromocytoma

Hypertension: continuous vs. paroxysmal; most frequent finding
Headache
Sweating
Pallor
Palpitations

Cardiomyopathy is a complication of pheochromocytoma. The cause appears multifactorial and includes catecholamine-induced permeability changes in the sarcolemmal membranes leading to excess calcium influx, toxicity from oxidized products of catecholamines, and myocardial damage by free radicals. In addition, high catecholamine levels result in coronary vasoconstriction through α-adrenergic pathways, which reduces coronary blood flow and potentially creates ischemia. Both dilated and hypertrophic cardiomyopathies, as well as left ventricular outflow tract obstruction, have been demonstrated on echocardiogram. Electrocardiogram (ECG) abnormalities may include elevation or depression of the ST segment, flattening or inversion of T waves, prolongation of the QT interval, high or peaked P waves, left axis deviation, and arrhythmias. The cardiomyopathy appears reversible if catecholamine stimulation is removed early before fibrosis has occurred. Distinct from cardiomyopathy, pheochromocytoma patients may develop cardiac hypertrophy with congestive heart failure secondary to sustained hypertension.

Although pheochromocytoma patients rarely have frank diabetes, most have an elevated blood glucose level secondary to catecholamine stimulation of glycogenolysis and inhibition of insulin release.

Diagnosis

When a pheochromocytoma is clinically suspected, excess catecholamine secretion must be demonstrated. For patients with a low probability of having a pheochromocytoma, a 24-hour urine collection for measurement of metanephrines and catecholamines is a useful screening test. However, the most sensitive test for patients at high risk (familial pheochromocytoma or classic symptoms) is measurement of plasma-free metanephrines. Catecholamines are metabolized to free metanephrines within tumor cells, and these metabolites are continuously released into the circulation. A plasma-free normetanephrine level higher than 400 pg/mL and/or a metanephrine level higher than 220 pg/mL confirms the diagnosis of pheochromocytoma. A pheochromocytoma is excluded if the normetanephrine level is less than 112 pg/mL and metanephrine level is less than 61 pg/mL.

Tumor location can be predicted by the pattern of catecholamine production (Table 22.15). CT detects more than 95% of adrenal masses larger than 1.0 cm in diameter. Magnetic

TABLE 22.15 Pattern of Catecholamine Production by Site of Pheochromocytoma

	Adrenal	Extraadrenal	Adrenal + Extraadrenal
Norepinephrine	61%	31%	8%
Epinephrine	100%	–	–
Norepinephrine + epinephrine	95%	–	5%

Adapted from Kaser H. Clinical and diagnostic findings in patients with chromaffin tumors: pheochromocytomas, pheochromoblastomas. *Recent Results Cancer Res.* 1990;118:97–105.

resonance imaging (MRI) offers advantages over CT, including better identification of small adrenal lesions, better differentiation of various types of adrenal lesions, no need for intravenous contrast, and lack of radiation exposure. In contrast to CT and MRI, which provide primarily anatomic information, testing with ^{131}I-metaiodobenzylguanidine (MIBG) and ^{123}I-MIBG provides functional information. MIBG is an analogue of guanethidine, similar in structure to norepinephrine. It is taken up by adrenergic neurons and concentrated in catecholamine-secreting tumors. MIBG is detected by scintigraphy. MIBG scintigraphy is especially useful in detecting extraadrenal pheochromocytomas and metastatic deposits. CT, MRI, and ^{131}I-MIBG scintigraphy are complementary studies in localizing pheochromocytomas. Positron emission scanning and selective venous catheterization with sampling of catecholamines from the adrenal veins and other sites are additional useful tests.

Management of Anesthesia

Preoperative Management

Since most pheochromocytomas secrete predominately norepinephrine, medical therapy has depended on α blockade to lower blood pressure, increase intravascular volume, prevent paroxysmal hypertensive episodes, allow sensitization of adrenergic receptors, and decrease myocardial dysfunction. Although a significantly reduced intravascular volume may accompany a pheochromocytoma, the majority of patients have a normal or only slightly decreased intravascular volume. α blockade appears to protect myocardial performance and tissue oxygenation from the adverse effects of catecholamines.

Phenoxybenzamine is the most frequently prescribed α blocker for preoperative use. It is a noncompetitive α_1 antagonist with some β_2-blocking properties. Because it is a noncompetitive blocker, it is difficult for excess catecholamines to overcome the blockade. Its long duration of action permits oral dosing only twice daily. The goal of therapy is normotension, a resolution of symptoms, elimination of ST-segment and T-wave changes on the ECG, and elimination of arrhythmias. Overtreatment can result in severe orthostatic hypotension. The optimal duration of α-blockade therapy is undetermined and may range from 3 days to 2 weeks or longer. Because of the prolonged effect of phenoxybenzamine on α receptors, the recommendation has been to discontinue its use 24 to 48 hours before surgery to avoid vascular unresponsiveness immediately following removal of the tumor. Prazosin and doxazosin, pure α_1-competitive blockers, are alternatives to phenoxybenzamine. They are shorter acting, cause less tachycardia, and are easier to titrate to a desired end point than phenoxybenzamine.

If tachycardia (i.e., heart rates $\geq$120 beats per minute) or other arrhythmias result after α blockade with phenoxybenzamine, a β-adrenergic blocker is prescribed. A nonselective β blocker should never be administered before α blockade because blockade of vasodilatory β_2 receptors results in unopposed α agonism, leading to vasoconstriction and hypertensive crises. Propranolol, a nonselective β blocker with a half-life longer than 4 hours is most frequently used. Atenolol, metoprolol, and labetalol have also been used successfully. A patient with a pheochromocytoma secreting solely epinephrine and with coronary artery disease may benefit greatly from the β_1-selective antagonist esmolol. Esmolol has a fast onset and short elimination half-life and can be administered intravenously in the period immediately before surgery.

α-methylparatyrosine (metyrosine) inhibits the rate-limiting enzyme tyrosine hydroxylase of the catecholamine synthetic pathway and may decrease catecholamine production by 50% to 80%. In combination with phenoxybenzamine, it has been shown to facilitate intraoperative hemodynamic management. Side effects, including sedation, extrapyramidal reactions, and crystalluria, have limited its application.

Calcium channel blockers may also be used to control hypertension. Calcium is a trigger for catecholamine release from the tumor, and excess calcium entry into myocardial cells contributes to a catecholamine-mediated cardiomyopathy. Nifedipine, diltiazem, and verapamil have all been used to control preoperative hypertension. An α_1 blocker plus a calcium channel blocker is an effective combination in treatment-resistant cases.

Intraoperative Management

Optimal preparation for pheochromocytoma resection involves preoperative administration of an α-adrenergic blocker with or without a β blocker, as well as correction of possible hypovolemia. Intraoperative goals include avoidance of drugs or maneuvers that may provoke catecholamine release or potential catecholamine actions, and maintenance of cardiovascular stability, preferably with short-acting drugs. Hypertension frequently occurs during pneumoperitoneum as well as during tumor manipulation. On the other hand, significant hypotension may develop following ligation of the tumor's venous drainage. Intraoperative monitoring should include standard plus invasive monitoring methods. An arterial catheter enables monitoring of blood pressure on a beat-to-beat basis and should be placed preinduction. A central venous pressure catheter is usually sufficient for patients without cardiac symptoms or other clinical evidence of cardiac involvement. A pulmonary artery catheter or transesophageal echocardiography may be necessary to manage the large fluid requirements, major volume shifts, and possible underlying myocardial dysfunction in patients with very active tumors. A large positive fluid balance is usually required to manage hypotension and keep intravascular volumes within a normal range.

Intraoperative ultrasonography can be used to localize small, functional tumors and to perform adrenal-sparing procedures

or partial adrenalectomies. Adrenal-sparing procedures are particularly valuable when bilateral adrenal pheochromocytomas must be removed. Laparoscopy is the preferred procedure for tumors smaller than 8 cm in diameter without malignant radiologic features.

Factors that stimulate catecholamine release such as fear, stress, pain, shivering, hypoxia, and hypercarbia must be minimized in the perioperative period. Although all anesthetic drugs have been used with some degree of success, certain drugs should theoretically be avoided to prevent possible adverse hemodynamic responses. Morphine and atracurium can cause histamine release, which may provoke release of catecholamines from the tumor. Atropine, ketamine, pancuronium, and succinylcholine are examples of vagolytic or sympathomimetic drugs that may stimulate the sympathetic nervous system.

Virtually all patients exhibit increases in systolic arterial pressure in excess of 200 mm Hg for periods of time intraoperatively irrespective of preoperative initiation of _ blockade. A number of antihypertensive drugs must be prepared and ready for immediate administration. Sodium nitroprusside, a direct vasodilator, is the agent of choice because of its potency, immediate onset of action, and short duration of action. Phentolamine, a competitive Γ-adrenergic blocker and a direct vasodilator, is effective, although tachyphylaxis and tachycardia are associated with its use. Nitroglycerin is effective, but large doses are often required and may cause tachycardia. Labetalol, with more Π-blocking than ¯l-blocking properties, is preferred for predominantly epinephrine-secreting tumors. Magnesium sulfate inhibits release of catecholamines from the adrenal medulla and peripheral nerve terminals, reduces sensitivity of ⊥ receptors to catecholamines, is a direct vasodilator, and is an antiarrhythmic. However, like all antihypertensive medications it is suboptimal in controlling hypertension during tumor manipulation. Mixtures of antihypertensive drugs such as nitroprusside, esmolol, diltiazem, and phentolamine have been recommended to control refractory hypertension. Increasing the depth of anesthesia is also an option, although this approach may accentuate the hypotension accompanying tumor vein ligation.

Arrythmias are usually ventricular in origin and are managed with either lidocaine or ¯ blockers. Lidocaine is short acting and has minimal negative inotropic action. Although propranolol has been widely used, esmolol, a selective ¯$_1$ blocker, offers several advantages. Esmolol has a rapid onset and is short acting (i.e., elimination half-life of 9 min), which allows adequate control of heart rate; it may also provide protection against catecholamine-induced ischemia and the development of postoperative hypoglycemia. Amiodarone, an antiarrhythmic agent that prolongs the duration of the action potential of atrial and ventricular muscle, has been used as an alternative to ⊐ blockers to treat supraventricular tachycardia associated with hypercatecholaminemia.

Hypotension following tumor vein ligation is usually significant and occurs secondary to a combination of factors, including an immediate decrease in plasma catecholamine levels (half-lives of norepinephrine and epinephrine are approximately 1–2 min), vasodilation from residual ¯ blockade with phenoxybenzamine, intraoperative fluid and blood loss, and increased anesthetic depth. Hypotension with systolic pressures in the range of 70 to 79 mm Hg is not infrequent. To prevent precipitous hypotension, volume expansion with intravenous fluids should be attained before tumor vein ligation. Rapidly acting vasopressors may also be needed. Residual ⊏-adrenergic blockade and downregulation of receptors make patients relatively less responsive to vasopressors. Intraoperative administration of blood salvage products has resulted in postresection hypertension secondary to the catecholamine content of the blood. A decrease in anesthetic depth will also aid in controlling hypotension. With a decrease in plasma catecholamine levels immediately following resection, insulin levels increase, and hypoglycemia may occur. Glucocorticoid therapy should be administered if a bilateral adrenalectomy is performed or if hypoadrenalism is a possibility.

Postoperative Management

The majority of patients become normotensive following complete tumor resection. However, plasma catecholamine levels do not return to normal until 7 to 10 days after surgery because of a slow release of stored catecholamines from peripheral nerves. Fifty percent of patients are hypertensive for several days after surgery, and 25% to 30% of patients remain hypertensive indefinitely. In these patients, hypertension is sustained rather than paroxysmal, lower than before surgery, and not accompanied by the classic features of hypercatecholaminemia. The differential diagnosis of persistent hypertension includes a missed pheochromocytoma, surgical complications with subsequent renal ischemia, and underlying essential hypertension.

Hypotension is the most frequent cause of death in the period immediately after surgery. Large volumes of fluid are necessary since the peripheral vasculature is poorly responsive to reduced levels of catecholamines. Vasopressors may be necessary. Steroid supplementation may be necessary if hypoadrenalism is present. Dextrose-containing solutions may be needed, and plasma glucose levels should be monitored for 24 hours.

HYPERCORTISOLISM (CUSHING SYNDROME)

Cushing syndrome is divided into two forms: ACTH dependent and ACTH independent. In ACTH-dependent Cushing syndrome, inappropriately high plasma ACTH concentrations stimulate the adrenal cortex to produce excessive amounts of cortisol. The ACTH-independent variant is caused by excessive production of cortisol by abnormal adrenocortical tissue that is not regulated by secretion of CRH and ACTH. In this latter form of Cushing syndrome, CRH and ACTH levels are actually suppressed. The term *Cushing disease* is reserved for Cushing syndrome caused by excessive secretion of ACTH by pituitary ACTH tumors (microadenomas). These microadenomas account for nearly 70% of cases of ACTH-dependent Cushing syndrome. Acute ectopic ACTH syndrome is another form of ACTH-dependent Cushing syndrome and is most often associated with small cell lung carcinoma. Benign or malignant adrenocortical tumors are the most common cause of ACTH-independent Cushing syndrome.

Diagnosis

There are no pathognomonic signs or symptoms that confirm the diagnosis of Cushing syndrome. The most common symptom is the relatively sudden onset of weight gain, which is usually central and often accompanied by thickening of the facial fat, which rounds the facial contour (moon facies), and a florid complexion resulting from telangiectasias. Systemic hypertension, glucose intolerance, oligomenorrhea or amenorrhea in premenopausal women, decreased libido in men, and spontaneous ecchymoses are frequent concomitant findings. Skeletal muscle wasting and weakness manifest as difficulty climbing stairs. Depression and insomnia are often present. The diagnosis of Cushing syndrome is confirmed by demonstrating cortisol hypersecretion based on 24-hour urinary secretion of cortisol. Determining whether a patient's hypercortisolism is ACTH dependent or ACTH independent requires reliable measurements of plasma ACTH using immunoradiometric assays. The high-dose dexamethasone suppression test distinguishes Cushing disease from ectopic ACTH syndrome (presence of complete resistance). Imaging procedures provide no information about adrenal cortex function and are useful only for determining the location of a tumor.

Treatment

The treatment of choice for patients with Cushing disease is transsphenoidal microadenomectomy if a clearly circumscribed microadenoma can be identified and is amenable to resection. Alternatively, patients may undergo 85% to 90% resection of the anterior pituitary. Pituitary irradiation and bilateral total adrenalectomy are necessary in some patients. Surgical removal of the adrenal gland is the treatment for adrenal adenoma or carcinoma.

Management of Anesthesia

Management of anesthesia in patients with hypercortisolism must consider the physiologic effects of excessive cortisol secretion (Table 22.16). Preoperative evaluation of systemic blood pressure, electrolyte balance, and blood glucose concentration are especially important. Osteoporosis is a consideration when positioning patients for the operative procedure. The choice of drugs for preoperative medication, induction of anesthesia, and maintenance of anesthesia is not influenced by the presence of hypercortisolism. Etomidate may transiently decrease the synthesis and release of cortisol by the adrenal cortex. Doses of muscle relaxants should probably be decreased initially in view of the skeletal muscle weakness that frequently accompanies hypercortisolism. In addition, the presence of hypokalemia may influence responses to nondepolarizing muscle relaxants. Mechanical ventilation of the patient's lungs during surgery is recommended because skeletal muscle weakness, with or without coexisting hypokalemia, may decrease the strength of the muscles of breathing. Regional anesthesia should be considered where applicable.

Plasma cortisol concentrations decrease promptly after microadenomectomy or bilateral adrenalectomy, and replacement therapy is recommended. Patients may develop acute adrenal insufficiency, which requires the initiation of supplemental therapy. Transient diabetes insipidus and meningitis may also occur after microadenomectomy.

TABLE 22.16 Physiologic Effects of Excess Cortisol Secretion

Systemic hypertension
Hyperglycemia
Skeletal muscle weakness
Osteoporosis
Obesity
Menstrual disturbances
Poor wound healing
Susceptibility to infection

PRIMARY HYPERALDOSTERONISM (CONN SYNDROME)

Primary hyperaldosteronism (Conn syndrome) is present when there is excess secretion of aldosterone from a functional tumor (aldosteronoma) that acts independently of a physiologic stimulus. Aldosteronomas occur more often in women than in men and only rarely in children. Occasionally, primary aldosteronism is associated with pheochromocytoma, primary hyperparathyroidism, or acromegaly. Secondary hyperaldosteronism is present when increased circulating serum concentrations of renin, as are associated with renovascular hypertension, stimulate the release of aldosterone. Aldosteronism associated with Bartter syndrome (hyperplasia of the juxtaglomerular apparatus) is not accompanied by systemic hypertension. The prevalence of primary aldosteronism in patients with essential hypertension appears to be less than 1%.

Signs and Symptoms

Clinical signs and symptoms of primary aldosteronism are nonspecific, and some patients are completely asymptomatic (Table 22.17). Systemic hypertension (diastolic blood pressure is often 100–120 mm Hg) is a function of aldosterone-induced sodium retention and increase in extracellular fluid volume. Aldosterone promotes renal excretion of potassium, which results in hypokalemic metabolic alkalosis. Increased urinary excretion of potassium ($^{-}$30 mEq/day) in the presence of hypokalemia suggests primary aldosteronism. Hypokalemic nephropathy can result in polyuria and loss of urine concentrating ability. Hypomagnesemia and abnormal glucose tolerance may also be present.

TABLE 22.17 Signs and Symptoms of Primary Aldosteronism

Headache
Polyuria
Nocturia
Skeletal muscle cramps
Skeletal muscle weakness

Diagnosis

Spontaneous hypokalemia in patients with systemic hypertension is highly suggestive of aldosteronism. Plasma renin activity is suppressed in almost all patients with untreated primary aldosteronism and in many with essential hypertension; with secondary aldosteronism, however, the plasma renin activity is high. A plasma aldosterone concentration of less than 9.5 ng/dL at the end of a saline infusion rules out primary aldosteronism. A syndrome exhibiting all the features of hyperaldosteronism (systemic hypertension, hypokalemia, suppression of the renin-angiotensin system) may result from long-term ingestion of licorice (glycyrrhizic acid).

Treatment

Initial treatment of hyperaldosteronism consists of potassium supplementation and administration of a competitive aldosterone antagonist such as spironolactone. Skeletal muscle weakness resulting from hypokalemia may require treatment with intravenous potassium. Systemic hypertension is treated with antihypertensive drugs. Accentuation of hypokalemia caused by drug-induced diuresis is decreased by use of a potassium-sparing diuretic such as triamterene. Definitive treatment for an aldosterone-secreting tumor is surgical excision. Bilateral adrenalectomy may be necessary if multiple aldosterone-secreting tumors are found.

Management of Anesthesia

Management of anesthesia for the surgical treatment of hyperaldosteronism is facilitated by preoperative correction of hypokalemia and treatment of systemic hypertension. Persistence of hypokalemia may modify responses to nondepolarizing muscle relaxants. Intraoperative hyperventilation can decrease the plasma potassium concentration and should be avoided. Inhaled or intravenous drugs are acceptable for maintenance of anesthesia. The use of sevoflurane is questionable, however, if hypokalemic nephropathy and polyuria are present preoperatively.

Measurement of cardiac filling pressures via a right pulmonary artery catheter or monitoring with transesophageal echocardiography may be useful during surgery for adequate evaluation of the intravascular fluid volume and the response to intravenous infusion of fluids. Indeed, aggressive preoperative preparation can convert the excessive intravascular fluid volume status of these patients to unexpected hypovolemia, manifesting as hypotension in response to administration of vasodilating anesthetic drugs, positive pressure ventilation, changes in body position, or surgical blood loss. The detection of orthostatic hypotension during the preoperative evaluation is a clue to underlying hypovolemia. Acid-base status and plasma electrolyte concentrations should be measured frequently.

Supplementation with exogenous cortisol is probably unnecessary for surgical excision of a solitary adenoma in the adrenal cortex. Bilateral mobilization of the adrenal glands to excise multiple functional tumors, however, may introduce the need for exogenous cortisol administration.

HYPOALDOSTERONISM

Hyperkalemia in the absence of renal insufficiency suggests the presence of hypoaldosteronism. Hyperkalemia is sometimes abruptly enhanced by hyperglycemia. Hyperchloremic metabolic acidosis is a predictable finding in the presence of hypoaldosteronism. Heart block secondary to hyperkalemia, orthostatic hypotension, and hyponatremia may also be present.

Isolated deficiency of aldosterone secretion may reflect congenital deficiency of aldosterone synthetase or hyporeninemia resulting from defects in the juxtaglomerular apparatus or treatment with ACE inhibitors leading to loss of angiotensin stimulation. Hyporeninemic hypoaldosteronism typically occurs in patients older than 45 years of age with chronic renal disease and/or diabetes mellitus. Indomethacin-induced prostaglandin deficiency is a reversible cause of this syndrome. Treatment of hypoaldosteronism includes liberal sodium intake and daily administration of fludrocortisone.

ADRENAL INSUFFICIENCY

Signs and Symptoms

There are two types of adrenal insufficiency (AI): primary and secondary. In primary disease (Addison disease), the adrenal glands are unable to produce sufficient quantities of glucocorticoid, mineralocorticoid, and androgen hormones. The most common cause of this rare endocrinopathy is bilateral adrenal destruction from autoimmune disease. More than 90% of the glands must be involved before signs of AI appear. The onset of Addison disease is insidious (Table 22.18). Secondary AI results from a failure in the production of CRH or ACTH caused by hypothalamic-pituitary disease or suppression of the hypothalamic-pituitary axis. Unlike in Addison disease, there is only a glucocorticoid deficiency in secondary disease. In the majority of cases the cause is iatrogenic, such as pituitary surgery, pituitary irradiation, or most commonly the use of synthetic glucocorticoids. These patients lack cutaneous hyperpigmentation and may demonstrate only mild electrolyte abnormalities.

Cortisol is one of the few hormones essential for life. It participates in carbohydrate and protein metabolism, fatty acid mobilization, electrolyte and water balance, and the antiinflammatory response. It facilitates catecholamine synthesis and action; modulates β-receptor synthesis, regulation, coupling, and responsiveness; and contributes to normal vascular permeability,

TABLE 22.18 Signs and Symptoms of Adrenal Insufficiency

Fatigue
Weakness
Anorexia
Nausea and vomiting
Cutaneous/mucosal hyperpigmentation
Hypovolemia
Hyponatremia
Hyperkalemia

tone, and cardiac contractility. Cortisol accounts for 95% of adrenal gland glucocorticoid activity, with corticosterone and cortisone contributing some activity. Estimated daily cortisol secretion is the equivalent of 15 to 25 mg/day or 5 to 7 mg/day of prednisone.

Diagnosis

The classic definition of AI includes a baseline plasma cortisol concentration of less than 20 ¯g/dL and a cortisol level of less than 20 ¯g/dL after ACTH stimulation. The short 250-Γg ACTH stimulation test is a reliable test of the integrity of the entire HPA axis. All steroids except dexamethasone must be discontinued for 24 hours before testing. Cortisol levels are measured at 30 and 60 minutes following the administration of ACTH. A normal ACTH stimulation test result is a plasma cortisol level greater than 25 _g/dL. A positive test finding demonstrates a poor response to ACTH and indicates an impairment of the adrenal cortex. Absolute AI is characterized by a low baseline cortisol level and a positive result on the ACTH stimulation test. Relative AI is indicated when the baseline cortisol level is higher but the result on the ACTH stimulation test is positive.

Treatment

The most common cause of AI is exogenous steroids (Table 22.19). Patients are prescribed steroids to treat a number of illnesses, including arthritis, bronchial asthma, malignancies, allergies, collagen vascular diseases, and inflammatory conditions. Those who take steroids long term may exhibit signs and symptoms of AI during periods of stress, such as surgery or acute illness. For patients with a history of long-term steroid use, it may take 6 to 12 months from the time of discontinuation of the steroids for the adrenal glands to recover full function. Recovery from short courses of steroids may take several days. For example, prednisone 25 mg PO twice daily for 5 days results in a reduced response to exogenous ACTH for 5 days.

Preoperative glucocorticoid coverage should be provided for patients with a positive result on the ACTH stimulation test, Cushing syndrome, or AI as well as for those at risk of HPA axis suppression or AI based on prior glucocorticoid therapy. Adrenal suppression is much more common than AI and is of concern because overt AI, although uncommon, may occur under the stressful conditions of surgery and anesthesia. Patients taking prednisone in dosages of less than 5 mg/day for any length of time, even years, do not demonstrate clinically significant HPA axis suppression and do not require perioperative supplementation, although they should receive their normal daily steroid dose. Any patient who received a glucocorticoid in dosages equivalent to more than 20 mg/day of prednisone for more than 3 weeks within the previous year is at risk for AI and should receive perioperative supplementation. Patients receiving dosages of steroids between these two extremes may have HPA axis suppression and should probably receive supplementation. Similarly, patients receiving more than 2 g/day of topical steroids or more than 0.8 mg/day of inhaled steroids on a long-term basis should probably receive supplementation.

Patients with known or suspected adrenal suppression or AI should receive their baseline steroid therapy plus supplementation in the perioperative period. Supplementation is individualized based on the surgery (Table 22.20). When more than 100 mg/day of hydrocortisone is administered, it may be wise to consider substituting methylprednisolone for hydrocortisone; given its lower mineralocorticoid activity, it is less likely to cause fluid retention, edema, and hypokalemia.

Management of Anesthesia

Acute AI should be considered in the differential diagnosis of hemodynamic instability, especially in patients unresponsive to the usual therapeutic interventions. Therapy includes treatment of the cause, repletion of circulating glucocorticoids, and replacement of water and sodium deficits. Glucocorticoid replacement may include intravenous hydrocortisone, methylprednisolone, or dexamethasone. If ACTH stimulation testing

TABLE 22.19 Glucocorticoid Preparations

Steroid	POTENCY: Antiinflammatory (Glucocorticoid)	POTENCY: Na Retention (Mineralocorticoid)	Equivalent Dose (Oral or IV, mg)
Short Acting			
Cortisol (hydrocortisone)	1	1	20
Cortisone	0.8	0.8	25
Intermediate Acting			
Prednisone	4	0.8	5
Prednisolone	4	0.8	5
Methylprednisolone	5	0.5	4
Triamcinolone	5	0	4
Long Acting			
Dexamethasone	30–40	0	0.75

Adapted from Stoelting RK, Dierdorf SF. Endocrine disease. In: Stoelting RK, ed. *Anesthesia and Co-Existing Disease*. New York, NY: Churchill Livingstone; 1993:358.

TABLE 22.20 Perioperative Steroid (Hydrocortisone) Supplementation

Superficial surgery (e.g., dental surgery, biopsy)	None
Minor surgery (e.g., inguinal hernia repair)	25 mg IV
Moderate surgery (e.g., cholecystectomy, colon resection)	50–75 mg IV, taper 1–2 days
Major surgery (e.g., cardiovascular surgery, Whipple procedure)	100–150 mg IV, taper 1–2 days
Intensive care unit (e.g., sepsis, shock)	50–100 mg q6-8h for 2 days to 1 wk, followed by slow taper

will be required to assist in establishing a diagnosis of primary or secondary disease, dexamethasone is preferred because it does not alter cortisol levels.

A bolus of 100 mg of hydrocortisone every 6 hours is an acceptable treatment option. When the patient's condition stabilizes, the steroid dosage is reduced with eventual conversion to an oral preparation. Volume deficits may be substantial (2–3 L). Hemodynamic support with vasopressors may be necessary. Metabolic acidosis and hyperkalemia usually resolve with fluid and steroid administration.

No specific anesthetic agent(s) and/or technique(s) are recommended in managing patients with or at risk of AI. However, etomidate inhibits the synthesis of cortisol transiently and should be avoided in this patient population. Patients with untreated AI undergoing emergency surgery should be managed aggressively with invasive monitoring, intravenous corticosteroids, and fluid and electrolyte resuscitation. Minimizing doses of anesthetic agents and drugs is recommended, since myocardial depression and skeletal muscle weakness are frequently part of the clinical presentation.

ICU Management

AI is a common and underdiagnosed entity among critically ill patients. Patients at risk include those with infection and systemic inflammation from tuberculosis, meningococcemia, human immunodeficiency virus (HIV) infection, sepsis, and/or diffuse intravascular coagulation. The incidence of AI in high-risk, critically ill patients with hypotension, shock, and sepsis is approximately 30% to 40%. Approximately 33% of HIV-infected patients admitted to the ICU have AI, most likely caused by high levels of cytokines (interleukin-1 [IL1], IL6, interferon-I) and inflammatory peptides that impair the response of pituitary cells and inhibit the HPA axis. Cytokines also cause glucocorticoid resistance by impairing glucocorticoid receptor binding affinity. Hypotension is a common presentation, and hydrocortisone is required to maintain vascular tone, endothelial cell integrity, normal vascular permeability, -receptor function, and catecholamine synthesis and action.

In critically ill patients, ACTH stimulation testing and plasma cortisol levels can be unreliable, and testing has not consistently shown the ability to predict those who would benefit from glucocorticoid use. Refer to the international guidelines from the Society of Critical Care Medicine and European Society of Intensive Care Medicine for the diagnosis and management of critical illness–related corticosteroid insufficiency.

PARATHYROID GLAND DYSFUNCTION

The four parathyroid glands are located behind the upper and lower poles of the thyroid gland and produce parathyroid hormone (PTH), which is released into the systemic circulation by a negative feedback mechanism that depends on the plasma calcium concentration. Hypocalcemia stimulates the release of PTH, whereas hypercalcemia suppresses both hormonal synthesis and release. PTH maintains normal plasma calcium concentrations (4.5–5.5 mEq/L) by promoting the movement of calcium across three interfaces represented by the gastrointestinal tract, renal tubules, and bone.

HYPERPARATHYROIDISM

Hyperparathyroidism is present when the secretion of PTH is increased. Serum calcium concentrations may be increased, decreased, or unchanged. Hyperparathyroidism is classified as primary, secondary, or ectopic.

Primary Hyperparathyroidism

Primary hyperparathyroidism results from excessive secretion of PTH due to a benign parathyroid adenoma, carcinoma of a parathyroid gland, or hyperplasia of one or more parathyroid glands. A benign parathyroid adenoma is responsible for primary hyperparathyroidism in approximately 90% of patients; carcinoma is responsible for fewer than 5% of cases. Hyperplasia usually involves all four parathyroid glands, although not all glands may be enlarged to the same degree. Hyperparathyroidism resulting from an adenoma or hyperplasia is the most common presenting symptom of multiple endocrine neoplasia syndrome type I.

Diagnosis

Hypercalcemia (serum calcium concentration 5.5 mEq/L and ionized calcium concentration 2.5 mEq/L) is the hallmark of primary hyperparathyroidism. Primary hyperparathyroidism is the most common cause of hypercalcemia in the general population, whereas cancer is the most common cause in hospitalized patients. Modest increases in plasma calcium concentrations discovered incidentally in otherwise asymptomatic patients are most likely due to parathyroid adenomas, whereas marked hypercalcemia (17.5 mEq/L) is more likely due to cancer. Patients in surgical ICUs for prolonged periods of time may develop hypercalcemia, which may reflect increased secretion of PTH in response to repeated episodes of hypocalcemia resulting from sepsis, shock, and/or blood transfusions. Measurement of serum PTH concentrations is not always sufficiently reliable to confirm the diagnosis. Twenty-four-hour urinary calcium and serum 25-hydroxyvitamin D measurements may also aid in diagnosis and management.

Signs and Symptoms

Hypercalcemia is responsible for the broad spectrum of signs and symptoms that accompany primary hyperparathyroidism

TABLE 22.21 Signs and Symptoms of Hypercalcemia Due to Hyperparathyroidism

Organ System	Signs and Symptoms
Neuromuscular	Skeletal muscle weakness
Renal	Polyuria and polydipsia
	Decreased glomerular filtration rate kidney stones
Hematopoietic	Anemia
Cardiac	Prolonged PR interval
	Shortened QT interval
	Systemic hypertension
Gastrointestinal	Vomiting
	Abdominal pain
	Peptic ulcer
	Pancreatitis
Skeletal	Skeletal demineralization
	Collapse of vertebral bodies
	Pathologic fractures
Nervous	Somnolence
	Decreased pain sensation
	Psychosis
Ocular	Calcifications (band keratopathy)
	Conjunctivitis

(Table 22.21). Symptoms due to hypercalcemia reflect changes in the ionized calcium concentration, which is the physiologically active form of calcium and represents approximately 45% of the total serum calcium concentration.

Early signs and symptoms of primary hyperparathyroidism and associated hypercalcemia include sedation and vomiting. Loss of skeletal muscle strength and mass is most notable in the proximal musculature of the lower extremities. This skeletal muscle weakness is a neuropathy (muscle biopsy specimens resemble those in amyotrophic lateral sclerosis) and not a myopathy. Loss of sensation for pain and vibration may also be present. The cause of the neuropathy is unclear, but it is not related to hypercalcemia: it is reversible because skeletal muscle strength often improves following surgical removal of excess PTH-producing tissues.

Persistent increases in plasma calcium concentrations can interfere with urine-concentrating ability, and polyuria results. Oliguric renal failure can occur in advanced cases of hypercalcemia. Renal stones, especially in the presence of polyuria and polydipsia, must arouse suspicion of primary hyperparathyroidism. Increased serum chloride concentration (> 102 mEq/L) is most likely due to the influence of PTH on renal excretion of bicarbonate, which produces a mild metabolic acidosis. Anemia, even in the absence of renal dysfunction, is a consequence of primary hyperparathyroidism. Peptic ulcer disease (PUD) is frequent and may reflect potentiation of gastric acid secretion by calcium. Even in the absence of PUD or pancreatitis, the abdominal pain that often accompanies hypercalcemia can mimic an acute surgical abdomen. When the serum calcium concentration exceeds 8 mEq/L, cardiac conduction disturbances are likely. The classic skeletal consequence of primary hyperparathyroidism is osteitis fibrosa cystica. Radiographic evidence of skeletal involvement includes generalized osteopenia, subcortical bone resorption in the phalanges and distal ends of the clavicles, and the appearance of bone cysts.

In addition, patients may exhibit deficits of memory and cerebration, with or without personality changes or mood disturbances, including hallucinations.

Treatment

Definitive treatment of primary hyperparathyroidism is surgical removal of the diseased or abnormal portions of the parathyroid glands. Successful surgical treatment is reflected by normalization of serum calcium concentrations within 3 to 4 days. Postoperatively, the first potential complication is hypocalcemic tetany. The hypomagnesemia that occurs postoperatively aggravates the hypocalcemia and renders it refractory to treatment. Hyperchloremic metabolic acidosis, in association with deterioration of renal function, may occur transiently after parathyroidectomy. For poor surgical candidates, the Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism guidelines delineate recommendations for medical management.

Management of Anesthesia

There is no evidence that any specific anesthetic drugs or techniques are necessary in patients with primary hyperparathyroidism undergoing elective surgical treatment. Maintenance of hydration and urine output is important in the perioperative management of hypercalcemia. Careful positioning of hyperparathyroid patients is necessary because of the likely presence of osteoporosis and the associated vulnerability to pathologic fractures. The existence of somnolence before induction of anesthesia introduces the possibility that intraoperative anesthetic requirements could be decreased. Owing to its psychotropic effects, ketamine is an unlikely selection in patients with coexisting personality changes attributed to chronic hypercalcemia. The possibility of coexisting renal dysfunction is a consideration in the use of sevoflurane. Coexisting skeletal muscle weakness suggests the possibility of decreased requirements for muscle relaxants, whereas hypercalcemia might be expected to antagonize the effects of nondepolarizing muscle relaxants. In view of the unpredictable response to muscle relaxants, careful titration is recommended. The ECG should be monitored for manifestations of adverse cardiac effects of hypercalcemia.

Secondary Hyperparathyroidism

Secondary hyperparathyroidism reflects an appropriate compensatory response of the parathyroid glands to counteract a disease process that produces hypocalcemia. For example, chronic renal disease impairs elimination of phosphorus and decreases hydroxylation of vitamin D, which results in hypocalcemia and compensatory hyperplasia of the parathyroid glands with increased release of PTH. Because secondary hyperparathyroidism is adaptive rather than autonomous, it seldom produces hypercalcemia. Treatment of secondary hyperparathyroidism is directed at controlling the underlying disease, as is achieved by normalizing serum phosphate concentrations in patients with renal disease by administering an oral phosphate binder.

HYPOPARATHYROIDISM

Hypoparathyroidism is present when secretion of PTH is absent or deficient or peripheral tissues are resistant to the effects of the hormone (Table 22.22). Absence or deficiency of PTH is almost always iatrogenic, reflecting inadvertent removal of the parathyroid glands, as during thyroidectomy. Pseudohypoparathyroidism is a congenital disorder in which the release of PTH is intact, but the kidneys are unable to respond to the hormone. Affected patients manifest mental retardation, calcification of the basal ganglia, obesity, short stature, and short metacarpals and metatarsals.

Diagnosis

The diagnosis should be suspected in a patient with persistent hypocalcemia with a low or inappropriately normal PTH level and hyperphosphatemia. A serum calcium concentration of less than 4.5 mEq/L and an ionized calcium concentration of less than 2.0 mEq/L are indicative of hypoparathyroidism.

Signs and Symptoms

Signs and symptoms of hypoparathyroidism depend on the rapidity of the onset of hypocalcemia. Acute hypocalcemia can occur after accidental removal of the parathyroid glands during thyroidectomy (see Table 22.12). Inspiratory stridor reflects neuromuscular irritability of the intrinsic laryngeal musculature.

Chronic hypocalcemia is associated with complaints of fatigue and skeletal muscle cramps that may be associated with a prolonged QT interval on the ECG. The QRS complex, PR interval, and cardiac rhythm usually remain normal. Neurologic changes include lethargy, cerebration deficits, and personality changes reminiscent of those occurring in hyperparathyroidism. Chronic hypocalcemia is associated with the formation of cataracts, calcification involving the subcutaneous tissues and basal ganglia, and thickening of the skull. Chronic renal failure is the most common cause of chronic hypocalcemia.

Treatment

Treatment of acute hypocalcemia consists of replacement with calcium gluconate or calcium chloride until signs of neuromuscular irritability disappear. Correction of any coexisting respiratory or metabolic alkalosis is indicated. For treatment of hypoparathyroidism not complicated by symptomatic hypocalcemia, the approach is oral administration of calcium and vitamin D. Thiazide diuretics may be useful because these drugs cause sodium depletion without proportional potassium excretion and thereby tend to increase serum calcium concentrations. Hormone replacement therapy with recombinant human PTH 1-84 is available but is not yet initial therapy because of the high cost, requirement for subcutaneous administration, and unknown long-term safety profile.

TABLE 22.22 Causes of Hypoparathyroidism

Decreased or Absent Parathyroid Hormone
Accidental removal of parathyroid glands during thyroidectomy
Parathyroidectomy to treat hyperplasia
Idiopathic (DiGeorge syndrome)
Resistance of Peripheral Tissues to Effects of Parathyroid Hormone
Congenital
Pseudohypoparathyroidism
Acquired
Hypomagnesemia
Chronic renal failure
Malabsorption
Anticonvulsive therapy (phenytoin)
Osteoblastic metastases
Acute pancreatitis

Management of Anesthesia

Management of anesthesia in the presence of hypocalcemia is designed to prevent any further decrease in the serum calcium concentration and to treat the adverse effects of hypocalcemia, particularly those involving the heart. Iatrogenic hyperventilation and administration of bicarbonate can decrease serum calcium intraoperatively. Routine administration of whole blood containing citrate usually does not decrease serum calcium concentrations because calcium is rapidly mobilized from body stores. Ionized calcium concentrations can be decreased, however, when infusions of blood are rapid (500 mL every 5–10 min, as during cardiopulmonary bypass or liver transplantation), during massive transfusion, or when metabolism or elimination of citrate is impaired by hypothermia, cirrhosis of the liver, or renal dysfunction.

PITUITARY GLAND DYSFUNCTION

The pituitary gland, located in the sella turcica at the base of the brain, consists of the anterior pituitary and posterior pituitary. The anterior pituitary secretes six hormones under the control of the hypothalamus (Table 22.23). The hypothalamus controls the function of the anterior pituitary by means of vascular connections (hormones travel via the hypophyseal portal veins to reach the anterior pituitary). The hypothalamic–anterior pituitary–target organ axis is composed of tightly coordinated systems in which hormonal signals from the hypothalamus stimulate or inhibit secretion of anterior pituitary hormones, which in turn act on target organs and modulate hypothalamic and anterior pituitary activity (closed-loop, negative feedback system). The posterior pituitary is composed of terminal neuron endings that originate in the hypothalamus. Vasopressin (ADH) and oxytocin are synthesized in the hypothalamus and are subsequently transported along the hypothalamic neuronal axons for storage in the posterior pituitary. The stimulus for the release of these hormones from the posterior pituitary arises from osmoreceptors in the hypothalamus that sense plasma osmolarity.

Overproduction of anterior pituitary hormones is most often associated with hypersecretion of ACTH (Cushing syndrome) by anterior pituitary adenomas. Hypersecretion of other tropic hormones rarely occurs. Underproduction of a single anterior pituitary hormone is less common than generalized pituitary hypofunction (panhypopituitarism). The anterior pituitary gland is the only endocrine gland in which a tumor,

TABLE 22.23 Hypothalamic and Related Pituitary Hormones

Hypothalamic Hormone	Action	Pituitary Hormone or Organ Affected	Action
Corticotropin-releasing hormone	Stimulatory	Corticotropin	Stimulates secretion of cortisol and androgens
Thyrotropin-releasing hormone	Stimulatory	Thyrotropin	Stimulates secretion of thyroxine and triiodothyronine
Gonadotropin-releasing hormone	Stimulatory	Follicle-stimulation hormone, lutenizing hormone	Stimulate secretion of estradiol and progesterone, stimulate ovulation, stimulate secretion of testosterone, stimulate spermatogenesis
Growth hormone–releasing hormone	Stimulatory	Growth hormone	Stimulates production of insulin-like growth factor
Dopamine	Inhibitory	Prolactin	Stimulates lactation
Somatostatin	Inhibitory	Pituitary, gastrointestinal tract, pancreas	Inhibits secretion of growth hormone and thyroid-stimulating hormone, suppresses release of gastrointestinal and pancreatic hormones
Vasopressin (antidiuretic hormone)	Stimulatory	Kidneys	Stimulates free water reabsorption
Oxytocin	Stimulatory	Uterus	Stimulates uterine contractions
		Breasts	Stimulates milk ejection

most often a chromophobe adenoma, causes destruction by compressing the gland against the bony confines of the sella turcica. Metastatic tumor, most often from the breast or lung, also occasionally produces pituitary hypofunction. Endocrine features of panhypopituitarism are highly variable and depend on the rate at which the deficiency develops and the patient's age. Gonadotropin deficiency (amenorrhea, impotence) is typically the first manifestation of global pituitary dysfunction. Hypocortisolism occurs 4 to 14 days after hypophysectomy, whereas hypothyroidism is not likely to manifest before 4 weeks. CT and MRI are useful for radiographic assessment of the pituitary gland.

ACROMEGALY

Acromegaly is due to excessive secretion of growth hormone in adults, most often by an adenoma in the anterior pituitary gland. Serum insulin-like growth factor 1 (IGF-1) is elevated in patients with acromegaly. If results are equivocal, an oral glucose tolerance test can be performed by measuring plasma growth hormone, which remains above 1 ng/mL 2 hours after ingestion of 75 g glucose. An algorithm for diagnosis is available from the Endocrine Society Clinical Guidelines Subcommittee.

Signs and Symptoms

Manifestations of acromegaly reflect parasellar extension of the anterior pituitary adenoma and peripheral effects produced by the presence of excess growth hormone (Table 22.24). Headache and papilledema reflect increased intracranial pressure resulting from expansion of the anterior pituitary adenoma. Visual disturbances are due to compression of the optic chiasm by the expanding overgrowth of surrounding tissues.

Overgrowth of soft tissues of the upper airway (enlargement of the tongue and epiglottis) makes patients susceptible to upper airway obstruction. Hoarseness and abnormal movement of the vocal cords or paralysis of a recurrent laryngeal nerve may result from stretching caused by overgrowth of the surrounding cartilaginous structures. In addition, involvement of the cricoarytenoid joints can result in alterations in the patient's voice resulting from impaired movement of the vocal cords.

TABLE 22.24 Manifestations of Acromegaly

Parasellar Tumor
Enlarged sella turcica
Headache
Visual field defects
Rhinorrhea

Excess Growth Hormone
Skeletal overgrowth (prognathism)
Soft tissue overgrowth (lips, tongue, epiglottis, vocal cords)
Connective tissue overgrowth (recurrent laryngeal nerve paralysis)
Peripheral neuropathy (carpal tunnel syndrome)
Visceromegaly
Glucose intolerance
Osteoarthritis
Osteoporosis
Hyperhidrosis
Skeletal muscle weakness

Peripheral neuropathy is common and likely reflects trapping of nerves by skeletal, connective, and soft tissue overgrowth. Flow through the ulnar artery may be compromised in patients, exhibiting symptoms of carpal tunnel syndrome. Even in the absence of such symptoms, approximately one-half of patients with acromegaly have inadequate collateral blood flow through the ulnar artery in one or both hands.

Glucose intolerance and, on occasion, diabetes mellitus requiring treatment with insulin reflect the effects of growth hormone on carbohydrate metabolism. The incidence of systemic hypertension, ischemic heart disease, osteoarthritis, and osteoporosis seems to be increased in these patients. Lung volumes are increased, and ventilation/perfusion mismatching may be present. The patient's skin becomes thick and oily, skeletal muscle weakness may be prominent, and complaints of fatigue are common.

Treatment

Transsphenoidal surgical excision of pituitary adenomas is the preferred initial therapy. When adenomas have extended

beyond the sella turcica, surgery or radiation therapy is no longer feasible; medical treatment with a long-acting somatostatin analogue is recommended. Further recommendations can be found in the Endocrine Society Clinical Guidelines Subcommittee clinical practice guidelines on acromegaly.

Management of Anesthesia

Management of anesthesia in patients with acromegaly is complicated by changes induced by excessive secretion of growth hormone. Particularly important are changes in the upper airway. Distorted facial anatomy may interfere with placement of an anesthesia face mask. Enlargement of the tongue and epiglottis predisposes to upper airway obstruction and interferes with visualization of the vocal cords by direct laryngoscopy. The distance between the lips and vocal cords is increased due to overgrowth of the mandible. The glottic opening may be narrowed because of enlargement of the vocal cords. This, in addition to subglottic narrowing, may necessitate use of a tracheal tube with a smaller internal diameter than would be predicted based on the patient's age and size. Nasal turbinate enlargement may preclude the passage of nasopharyngeal or nasotracheal airways. A preoperative history of dyspnea on exertion or the presence of hoarseness or stridor suggests involvement of the larynx by acromegaly. In this instance, indirect laryngoscopy may be indicated to view the extent of vocal cord dysfunction. When difficulty placing a tracheal tube is anticipated, it may be prudent to consider an awake fiberoptic tracheal intubation.

When a catheter is placed in the radial artery, it is important to consider the possibility of inadequate collateral circulation at the wrist. Monitoring blood glucose concentrations is useful if diabetes mellitus or glucose intolerance accompanies acromegaly. Peripheral nerve stimulation is used to guide dosing of nondepolarizing muscle relaxants, particularly if skeletal muscle weakness is present. There is no evidence that hemodynamic instability or alterations in pulmonary gas exchange accompany anesthesia in acromegalic patients.

DIABETES INSIPIDUS

Diabetes insipidus (DI) reflects the absence of vasopressin (ADH) owing to destruction of the posterior pituitary (neurogenic DI) or failure of renal tubules to respond to ADH (nephrogenic DI). Neurogenic and nephrogenic DI are differentiated based on the response to desmopressin (DDAVP), a vasopressin analogue that leads to concentration of the urine in the presence of neurogenic, but not nephrogenic, DI. Classic manifestations of DI are polydipsia and a high output of poorly concentrated urine despite increased serum osmolarity. DI that develops during or immediately after pituitary gland surgery is generally due to reversible trauma to the posterior pituitary and is usually transient.

Initial treatment of DI consists of intravenous infusion of electrolyte solutions if oral intake cannot offset polyuria. Treatment of neurogenic DI is with desmopressin, which can be administered intranasally, in tablet form, or intravenously. In nephrogenic DI, a low-salt, low-protein diet, diuretics, and NSAIDs are typically administered.

Management of anesthesia for patients with DI includes monitoring the urine output and serum electrolyte concentrations during the perioperative period.

INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE

Inappropriate secretion of ADH can occur in the presence of diverse pathologic processes, including intracranial tumors, hypothyroidism, porphyria, and carcinoma of the lung. Inappropriate secretion of ADH is alleged to occur in most patients following major surgery. Inappropriately increased urinary sodium concentrations and osmolarity in the presence of hyponatremia and decreased serum osmolarity are highly suggestive of inappropriate ADH secretion. Hyponatremia is due to dilution, reflecting expansion of the intravascular fluid volume secondary to hormone-induced resorption of water by the renal tubules. Abrupt decreases in serum sodium concentration, especially to less than 110 mEq/L, can result in cerebral edema and seizures.

Treatment of inappropriate secretion of ADH consists of restriction of oral fluid intake (to < 800 mL/day), high solute intake, and oral salt tablets. Loop diuretics, vasopressin receptor antagonists, and demeclocycline may also be used. Often fluid restriction is sufficient treatment for inappropriate secretion of ADH not associated with symptoms secondary to hyponatremia. However, restriction of oral fluid intake and administration of demeclocycline are not immediately effective in the management of patients manifesting acute neurologic symptoms resulting from hyponatremia. In these patients, intravenous infusions of hypertonic saline sufficient to increase serum sodium concentrations are recommended. The optimal rate of correction for chronic hyponatremia should be less than 8 mEq/L within a 24-hour period. Overly rapid correction of chronic hyponatremia has been associated with central pontine myelinolysis, a type of brain cell dysfunction caused by destruction of the myelin sheath of nerve cells in the brainstem.

KEY POINTS

- Diabetes mellitus results from an inadequate supply of and/or inadequate tissue response to insulin, which leads to increased circulating glucose levels.
- The effects of chronic hyperglycemia are many and include hypertension, coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular accident, chronic renal failure, and autonomic neuropathy.
- Aggressive perioperative glucose control has been shown to limit infection risk, improve wound healing, and result in overall reductions in morbidity and mortality.

- The direct effects of T_3 on the heart and vascular smooth muscle are responsible for the exaggerated hemodynamic effects of hyperthyroidism.
- The third-generation TSH assay is the single best test of thyroid hormone action at the cellular level.
- Every effort should be made to render patients euthyroid before surgery. When caring for surgical patients with hyperthyroidism or hypothyroidism, the clinician must be prepared to manage thyroid storm or myxedema coma during the perioperative period.
- Since most pheochromocytomas secrete predominantly norepinephrine, preoperative blockade is necessary to lower blood pressure, increase intravascular volume, prevent paroxysmal hypertensive episodes, allow resensitization of adrenergic receptors, and decrease myocardial dysfunction.
- During surgical excision of a pheochromocytoma, the patient often exhibits an exaggerated hypertensive response to anesthetic induction, intubation, surgical excision, and particularly tumor manipulation. Conversely, hypotension may occur following ligation of the tumor's venous drainage.
- The physiologic response to surgical stress is an increase in CRH, ACTH, and cortisol secretion that begins at surgical incision and continues into the postoperative period.
- The most common cause of AI is administration of exogenous steroids.
- Patients who receive glucocorticoids in dosages equivalent to more than 20 mg/day of prednisone for longer than 3 weeks within the previous year are considered to have adrenal suppression and are at increased risk of AI. Susceptible patients require perioperative corticosteroid supplementation.
- Hydrocortisone 200 to 300 mg/day for a minimum of 5 to 7 days followed by a tapering regimen over 5 to 7 days results in overall improvement in patients with vasopressor-dependent septic shock.
- Primary hyperparathyroidism is the most common cause of hypercalcemia in the general population and usually results from a benign parathyroid adenoma. Hypercalcemia can be treated medically by saline infusion, furosemide, and/or bisphosphonates before surgery.
- Overproduction of anterior pituitary hormones is most commonly manifested as Cushing syndrome caused by ACTH hypersecretion by an adenoma in the anterior pituitary.
- Inappropriate secretion of ADH is common in the postoperative period and usually responds to fluid restriction.

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23

Hematologic Disorders

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OUTLINE

Disease states related to erythrocytes include anemia and polycythemia. Anemia is characterized by a decrease in the red cell mass, with the main adverse effect being a decrease in the oxygen-carrying capacity of blood. Polycythemia (erythrocytosis) represents an increase in hematocrit (Hct). Its consequences are primarily related to an expanded red cell mass and a resulting increase in blood viscosity.

PHYSIOLOGY OF ANEMIA

Anemia is a disease sign manifesting clinically as a reduced absolute number of circulating red blood cells (RBCs). Although a decrease in Hct is used most often as an indicator, anemia has been defined as a reduction in one or more of the major RBC indices: hemoglobin (Hb) concentration, Hct, and RBC count. In adults, the World Health Organization (WHO) defines anemia as Hb concentration less than 12 g/dL for women and less than 13 g/dL for men. In pregnancy, a decreased Hct reflects the increase in plasma volume in relationship to the RBC mass (physiologic anemia). However, Hb less than 11 g/dL in a pregnant patient is considered truly anemic. In acute blood loss the Hct may initially be unchanged. Decreases in Hct that exceed 1% every 24 hours can only be explained by acute blood loss or intravascular hemolysis.

The most important adverse effect of anemia is the reduction in arterial oxygen concentration and the potential for decreased tissue oxygen delivery. For example, a decrease in Hb concentration from 15 g/dL to 10 g/dL results in a 33% decrease in arterial oxygen content. The initial compensation for this decrease in oxygen content is an increase in cardiac

output. This occurs via enhanced sympathetic nervous system activity and the decrease in blood viscosity that accompanies anemia. There is also a rightward shift of the oxyhemoglobin dissociation curve, which facilitates release of oxygen from Hb to tissues. This is followed by redistribution of blood flow to the myocardium, lungs, and brain. Muscle and skin blood flow decrease (which results in pallor), as does blood flow to the kidneys (which stimulates erythroid precursors in bone marrow to produce additional RBCs). Fatigue and low exercise tolerance indicate the inability of cardiac output to increase further to maintain tissue oxygenation. This is most notable in anemic patients who are physically active or in patients with coronary artery disease. Orthopnea and dyspnea on exertion, cardiomegaly, pulmonary congestion, ascites, and edema can occur as a consequence of high-output heart failure in chronic severe anemia.

There are many causes and forms of anemia. The most common causes of chronic anemia are iron deficiency, anemia of chronic disease (ACD), thalassemia, and ongoing blood loss.

The Transfusion Trigger

Preoperative transfusion for the sole purpose of facilitating elective surgery is rarely justified in an asymptomatic anemic patient. During the perioperative period, transfusion should be considered based on the lost circulating blood volume, Hb level, ongoing bleeding, and the risk of end-organ dysfunction due to inadequate oxygenation.

The most appropriate Hb level to serve as the trigger for perioperative blood transfusion is uncertain. The 10/30 rule (transfuse if the Hb level is <10 g/dL or the Hct is <30%) was once a commonly cited reference point. However, there is no evidence that Hb values below this level mandate the need for perioperative RBC transfusion, but there is clear evidence that patients with Hb levels of 6 g/dL benefit from red cell transfusion. Patients with compensated chronic anemia with Hb values between 6 and 10 g/dL can tolerate these levels without evidence of end-organ ischemia.

The strongest evidence regarding perioperative transfusion comes from the Transfusion Requirements in Critical Care (TRICC) trial, which found no significant difference in 30-day mortality rates between a group managed using a "restrictive" transfusion strategy (transfusions were administered as necessary to keep Hb values between 7 and 8 g/dL) and a group treated using a "liberal" strategy (Hb was kept between 10 and 12 g/dL). The restrictive regime did not cause a significant increase in mortality, cardiac morbidity, or duration of hospitalization. Other studies also show no short- or long-term mortality benefit when a liberal transfusion strategy (transfusion when Hb was <10 g/dL) is used in patients with underlying coronary artery disease undergoing hip surgery (vs a more restrictive strategy [i.e., transfusion when Hb <8 g/dL]). Recent data confirm noninferiority of a restrictive transfusion strategy (when Hb <7.5 g/dL) versus a liberal one (transfusion when Hb <9.5 g/dL) in regard to outcomes.

RBC transfusions have been associated with direct transmission of infectious diseases such as hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) infection. In critically ill and trauma patients, transfusions are independently associated with longer intensive care unit and hospital lengths of stay, higher mortality rates, an increased incidence of ventilator-associated pneumonia, and increased mortality. The immunomodulatory effects of RBC transfusion can lead to cancer recurrence, postoperative bacterial infection, transfusion-related acute lung injury, and hemolytic transfusion reactions.

An expected blood loss of 15% or less of total blood volume usually requires no blood replacement during surgery. A loss of up to 30% can be replaced exclusively with crystalloid solutions. A loss of more than 30% to 40% generally requires RBC transfusion to restore oxygen-carrying capacity. The transfusion is given with crystalloid or colloid solutions to restore intravascular volume and maintain tissue perfusion. In cases of massive transfusion (>50% of blood volume replaced within 24 hours), RBC transfusion may need to be accompanied by administration of fresh frozen plasma and platelets at a ratio of 1:1:1.

Patients with active coronary artery disease (unstable angina or acute myocardial infarction) merit special consideration. The literature suggests that Hct of 28% to 30% may be an appropriate transfusion trigger in patients with unstable coronary syndromes.

Management of Anesthesia: General Concepts for Anemia

If elective surgery is performed in the presence of chronic anemia, it is prudent to minimize the likelihood of significant changes that could further interfere with oxygen delivery to tissues. For example, drug-induced decreases in cardiac output or a leftward shift of the oxyhemoglobin dissociation curve due to respiratory alkalosis from iatrogenic hyperventilation could interfere with tissue oxygen delivery. Decreased body temperature also shifts the oxyhemoglobin dissociation curve to the left (i.e., there is less oxygen release to tissues). Decreased tissue oxygen requirements may accompany the myocardial depressant effects of anesthetic drugs and hypothermia. These offset the decrease in tissue oxygen delivery associated with anemia but to an unpredictable degree. Signs and symptoms of inadequate tissue oxygen delivery due to anemia may be difficult to appreciate during general anesthesia. Effects of anesthesia on the sympathetic nervous system and cardiovascular responses may blunt the usual increase in cardiac output associated with acute normovolemic anemia. Efforts to offset the impact of surgical blood loss by measures such as normovolemic hemodilution and intraoperative blood salvage can be considered in selected patients.

Volatile anesthetics may be less soluble in the plasma of anemic patients because of the decrease in concentration of lipid-rich RBCs. As a result, uptake of volatile anesthetics might be accelerated. However, the effect of this decreased solubility is likely offset by an increased cardiac output. Therefore it seems unlikely that clinically detectable differences in the rate of induction of inhalation anesthetics or vulnerability to an anesthetic overdose would be present in anemic patients compared to patients without anemia.

EVALUATION AND CLASSIFICATION OF ANEMIA

Anemia can be classified based on erythrokinetic mechanisms—that is, anemia due to ineffective erythropoiesis, anemia due to increased destruction of RBCs, and anemia due to blood loss. Anemia can also be classified based on morphologic characteristics—that is, microcytic, normocytic, or macrocytic based on mean corpuscular volume.

Initial evaluation of an anemic patient should include a complete blood cell count (CBC) with RBC count and standard indices, white blood cell (WBC) count, and platelet count. In addition, special indices such as RBC distribution width (RDW), which represents a measure of variation in red cell size (>14 is abnormal) and a reticulocyte count (>2% is abnormal) can indicate increased RBC destruction. Analysis of the peripheral blood smear is essential to evaluate RBC morphology.

Microcytic Anemias

Microcytic anemias are those with a mean corpuscular volume less than 80 fL. The most common causes of microcytic anemia are iron deficiency and the thalassemias. Sideroblastic anemia and (rarely) anemia of chronic disease can also present as microcytic anemias.

Iron-Deficiency Anemia

Nutritional deficiency of iron as a cause of anemia is found only in infants and small children. In adults, iron-deficiency anemia (IDA) reflects depletion of iron stores caused by chronic blood loss. Typically these losses are from the gastrointestinal (GI) tract or from the female genital tract (menstruation). Pregnant women are susceptible to development of IDA because of the increased RBC mass required during gestation and the needs of the fetus for iron.

Diagnosis. Patients experiencing chronic blood loss may not be able to absorb sufficient iron from the diet to form Hb as rapidly as RBCs are lost. As a result, RBCs are produced with too little Hb. Most cases of IDA in the United States are mild, with Hb concentrations of 9 to 12 g/dL. There is a concomitant decrease in serum ferritin concentration (<41 ng/mL), a low reticulocyte count, a decreased serum iron level, and a reduced transferrin saturation (<20%). The absence of stainable iron in a bone marrow aspirate is confirmatory evidence for IDA.

Treatment. Ideally IDA should be treated with ferrous iron salts administered orally and the iron stores replenished slowly. Oral iron should be considered if elective surgery can be postponed for 2 to 4 months to allow correction of the iron deficiency. Evidence of a favorable response to iron therapy is an increase in Hb concentration of approximately 2 g/dL in about 3 weeks and a return of Hb concentration to normal in about 6 weeks. Continued bleeding is indicated by reticulocytosis and failure of the Hb concentration to increase in response to iron therapy. Oral iron therapy should be continued for at least 1 year after the source of blood loss that caused the iron deficiency has been corrected.

If surgery is scheduled within just a few weeks, intravenous (IV) iron preparations can be used for correction of anemia. The efficacy of IV iron is superior to that of oral preparations, and newer preparations have less risk of anaphylactic reactions. A total dose of 1000 to 1500 mg iron is usually adequate to replenish stores preoperatively and decrease the need for perioperative transfusion.

In addition, while erythropoietin is not generally recommended for treatment of IDA, it is recommended and US Food and Drug Administration (FDA) approved for use for treatment of preoperative IDA, in conjunction with IV iron preparations. Anemic patients (Hb >10 g/dL and <13 g/dL) benefit from erythropoietin preparations prior to elective procedures, including cardiac surgery.

Thalassemia

Globin chains are assembled in the final globin molecule, which is a tetramer of two α-globin and two non–α-globin chains. In the adult, almost all Hb is made up of two α-globin and two β-globin chains (HbA), with minor components of HbF and HbA_2.

An inherited defect in globin chain synthesis known as thalassemia is one of the leading causes of microcytic anemia in children and adults. This disorder shows a strong geographic influence, with β thalassemia predominating in Africa and the Mediterranean area, and α thalassemia and HbE in Southeast Asia.

Thalassemia differs from IDA in several ways: presence of a family history of thalassemia, iron stores and ferritin are normal or increased, and RBC production is maintained or even disproportionately high. The diagnosis is confirmed by Hb electrophoresis, which determines the types of globin chains present.

Thalassemia minor. Most individuals with thalassemia have thalassemia minor and are heterozygous for either an α-globin (α-thalassemia trait) or β-globin (β-thalassemia trait) gene mutation. Although the mutations may decrease synthesis of the affected globin chain by up to 50%, producing hypochromic and microcytic RBCs, the anemia is usually modest with relatively little accumulation of the unaffected globin. Therefore morbidity associated with chronic hemolysis and ineffective erythropoiesis is rarely encountered.

Thalassemia intermedia. Patients with thalassemia intermedia show more severe anemia and prominent microcytosis and hypochromia. These individuals may have a mild form of homozygous β thalassemia, a combined α- and β-thalassemia defect, or β thalassemia with high levels of HbF. They can present with symptoms attributable to both anemia and iron overload from repeated transfusions, such as hepatosplenomegaly, cardiomegaly, pulmonary hypertension, and skeletal changes.

Additionally, patients with thalassemia intermedia can present with a hypercoagulable state. The etiology is multifactorial and is thought to include exposure of phosphatidylserine on the surface of the RBC, the increased fragility of phosphatidylserine-positive red cells, and the absence of the spleen.

For thalassemia intermedia, conventional therapy includes splenectomy, transfusion, iron chelation, and HbF modulation (hydroxyurea). New therapies are being evaluated such as JAK2 inhibition, hepcidin modulation, and gene therapy; however,

stem cell transplantation remains the only curative treatment so far.

Thalassemia major. Patients with thalassemia major develop severe life-threatening anemia during the first few years of life. To survive childhood, they require repeated transfusion therapy to correct anemia and suppress the high level of ineffective erythropoiesis. The severity of this form of thalassemia is remarkably variable, even among patients with seemingly identical genetic mutations. In the most severe forms, patients exhibit three defects that markedly depress their oxygen-carrying capacity: (1) ineffective erythropoiesis, (2) hemolytic anemia, and (3) hypochromia with microcytosis. The deficit in oxygen-carrying capacity produces maximum erythropoietin release, and marrow erythroblasts respond by increasing their unbalanced globin synthesis. The accumulating unpaired globin chains aggregate and precipitate, forming inclusion bodies that cause membrane damage to the RBCs. Some of these defective red cells are destroyed within the marrow, which results in ineffective erythropoiesis. Some abnormal erythrocytes escape into the circulation, where their altered morphology causes accelerated clearance (hemolytic anemia) or, at best, reduced oxygen-carrying capacity resulting from the lower Hb content (hypochromia with microcytosis). Other features of severe thalassemia include those attributable to bone marrow hyperplasia, such as frontal bossing, maxillary overgrowth, overall stunted growth, osteoporosis, and extramedullary hematopoiesis (hepatomegaly). Chronic hemolytic anemia leads to splenomegaly with dyspnea and orthopnea. Patients with thalassemia major also present with heart failure due to biventricular dilation and/or pulmonary hypertension and restrictive lung disease. Transfusion therapy will ameliorate many of these changes, but complications resulting from iron overload (e.g., cirrhosis, right-sided heart failure, endocrinopathy) frequently require zinc or chelation therapy (desferrioxamine). Splenectomy should be reserved for patients with hypersplenism or increasing transfusion demand, since it results in an increased infectious and thromboembolic risk. The risk of postsplenectomy sepsis in very young patients argues for deferring this surgery until after age 5 if possible. Bone marrow transplantation is a therapeutic option for young patients with a human leukocyte antigen (HLA)–identical sibling.

Management of anesthesia. The severity of thalassemia is the critical determinant of the amount of end-organ damage and anesthetic risk. In its mildest forms a chronic compensated anemia is a concern. With more severe forms the anemia is much more significant, as are the associated features of splenomegaly and hepatomegaly, skeletal malformations, congestive heart failure, pulmonary hypertension, intellectual disability, and complications of iron overload such as cirrhosis, right-sided heart failure, and endocrinopathies. Skeletal malformations can make tracheal intubation and regional anesthesia difficult; however, all anesthesia techniques (general and regional) can be safely used in these patients.

In thalassemic patients undergoing splenectomy, a hypertensive response can be seen due to autotransfusion, requiring aggressive treatment to prevent neurologic complications.

A hemoglobin level of 10 g/dL is desirable and accepted as a safe threshold for proceeding with a surgical procedure. As mentioned, patients with thalassemia intermedia and those postsplenectomy have an increased thromboembolic risk, requiring appropriated perioperative surgical prophylactic measures.

Normocytic Anemias

Normocytic anemias have a mean corpuscular volume of 80 to 100 fL. Evaluation of normocytic anemia includes examination of the peripheral blood smear (for the presence of abnormally shaped RBCs), measuring the reticulocyte count (which will be low in cases of bone marrow suppression but high with a hemolytic anemia), and measuring other indices of hemolysis such as increased lactate dehydrogenase (LDH), haptoglobin, and indirect bilirubin levels. Creatinine levels will be elevated with the anemia of kidney disease. A search for a source of acute blood loss should also be undertaken.

The most common normocytic anemias are hemolytic anemias, anemia of chronic disease, anemia of kidney disease, aplastic anemia, and acute blood loss.

Hemolytic Anemias

Hemolytic anemia represents accelerated destruction (hemolysis) of erythrocytes, caused most often by hemoglobinopathies and immune disorders. In hemolytic anemias, either RBCs are removed from the circulation by the reticuloendothelial system (extravascular hemolysis) or the cells are lysed within the circulation (intravascular hemolysis). Therefore RBC life span is shorter than the normal 120 days.

Hemolytic anemia is characterized by reticulocytosis, an increased mean corpuscular volume (reflecting the presence of immature erythrocytes), unconjugated hyperbilirubinemia, increased LDH levels, and decreased serum levels of haptoglobin. Confirmation of a hemolytic anemia should be followed by examination of a peripheral blood smear and a direct antiglobulin test (DAT; also known as the Coombs test) to rule out an immunologic cause.

Disorders of red cell structure. The mature RBC has the shape of a biconcave disk. It lacks a nucleus and mitochondria, and one-third of its mass is made up of a single protein, Hb. Intracellular energy requirements are supplied by glucose metabolism, which is targeted at maintaining Hb in a soluble reduced state, providing appropriate amounts of 2,3-diphosphoglycerate (2,3-DPG) and generating adenosine triphosphate (ATP) to support membrane function. Without a nucleus or protein metabolic pathway, the cell has a limited life span of about 120 days. However, the unique structure of the adult RBC provides maximum flexibility as the cell travels throughout the microvasculature.

Hereditary spherocytosis. Abnormalities in membrane protein composition can result in lifelong hemolytic anemia. Hereditary spherocytosis is inherited in an autosomal dominant pattern. It is the most common inherited hemolytic anemia in patients of Northern European ancestry, with a frequency of 1 in 2000 individuals. The principal defect is a deficiency in membrane skeletal proteins spectrin, ankyrin, band 3, and band 4.2. Affected cells show abnormal osmotic

fragility and a shortened circulation half-life. Hereditary spherocytosis can be clinically silent, and about one-third of patients have only a very mild hemolytic anemia and spherocytes rarely visible on peripheral blood smear. Some patients, however, have a more severe degree of hemolysis and anemia, but fewer than 5% of patients with spherocytosis develop life-threatening anemia. Patients with hereditary spherocytosis often have splenomegaly and experience easy fatigability that is out of proportion to the degree of anemia. These patients are at risk for episodes of hemolytic crisis, often precipitated by viral or bacterial infection. These crises worsen the chronic anemia and may be associated with jaundice. Infection with parvovirus B19 can produce a transient (10–14 days) but profound aplastic crisis. The risk of pigment gallstones is high in patients with hereditary spherocytosis and should be considered in patients complaining of biliary colic.

Management of anesthesia. Anesthetic risk in these patients is dictated by the severity of the anemia and whether the hemolysis is stable or in a period of exacerbation due to concurrent infection.

Episodic anemia, often triggered by viral or bacterial infection and cholelithiasis, must be considered in the preoperative evaluation. Patients undergoing cardiac surgery merit special consideration. Mechanical heart valves should be avoided as they may lead to excessive hemolysis because spherocytes are more susceptible to mechanical and shear stress than normal erythrocytes. Similarly, the use of cardiopulmonary bypass accelerates hemolysis; this process should be closely monitored, as both anemia and occlusion of small vasculature by plasma-free hemoglobin may cause end-organ damage. Moreover, free hemoglobin within the plasma is a potent nitric oxide scavenger, leading to increased systemic and pulmonary vascular resistances. In addition, patients with spherocytosis who have undergone splenectomy are at increased risk of arterial and venous thromboembolism, requiring appropriate prophylaxis.

Hereditary elliptocytosis. Hereditary elliptocytosis is caused by an abnormality in one of the membrane proteins, spectrin or glycophorin, which makes the erythrocyte less pliable. Hereditary elliptocytosis is inherited as an autosomal dominant disorder and is prevalent in regions where malaria is endemic. In those areas the incidence may reach 3 in 100 people. Hereditary elliptocytosis is most often diagnosed as an incidental finding. The majority of RBCs demonstrate an elliptical or even rodlike appearance. Most patients with hereditary elliptocytosis are heterozygous and only rarely experience hemolysis. In contrast, those with homozygous or compound heterozygous defects may demonstrate greater degrees of hemolysis and more severe anemia.

Acanthocytosis. Acanthocytosis is another defect in membrane structure found in patients with a congenital lack of β lipoprotein (abetalipoproteinemia) and infrequently in patients with cirrhosis or severe pancreatitis. It results from cholesterol or sphingomyelin accumulation on the outer membrane of the erythrocyte. This accretion gives the membrane a spiculated appearance and signals the splenic macrophages of the reticuloendothelial system to remove the red cell from the circulation, which produces hemolysis.

Paroxysmal nocturnal hemoglobinuria. Paroxysmal nocturnal hemoglobinuria (PNH) is a stem cell disorder that may arise in hematopoietic cells any time from the second to the eighth decade of life, with a median onset in the third decade of life. Classically, hemolysis is suspected when patients pass dark-colored urine in the morning due to the presence of hemosiderin. PNH causes complement-activated hemolysis in RBCs deficient in surface-bound complement-regulating proteins such as CD55 and CD59. Hemolytic anemia can be either intravascular (mediated by reduced CD59) or extravascular (mediated by reduced CD55). This is caused by a mutation in the *PIGA* gene located on the X chromosome, thus affecting both males and females equally. Besides hemolytic anemia, patients are at risk for other complications of Hb release such as smooth muscle dystonia, pulmonary hypertension, renal insufficiency, and hypercoagulability. Thromboses occur in approximately 40% of patients and can involve the hepatic and portal veins as well as other veins. The basis of the tendency to develop thromboses is unclear. In the absence of protectin, a critical glycosylphosphatidyl inositol–linked protein, patients can develop a dysplastic or aplastic bone marrow suggestive of damage to all hematopoietic precursor cells, manifesting as aplastic anemia or thrombocytopenia.

Treatment of PNH. Mildly symptomatic patients can be managed with surveillance only, whereas those who are transfusion dependent or with disabling symptoms such as fatigue, smooth muscle dystonia, thrombosis, and significant renal insufficiency benefit from eculizumab. Eculizumab is a monoclonal antibody against complement factor C5, which is essential for the complement system to develop membrane attack complexes. In addition, iron therapy should be supplemented and patients with thromboses should be anticoagulated. Patients with severe aplastic anemia, with bone marrow failure, and patients unresponsive to eculizumab are candidates for allogeneic bone marrow transplantation as a definitive treatment.

Management of anesthesia. The nocturnal manifestation of hemolysis is thought to result from carbon dioxide retention and the subsequent respiratory acidosis. Therefore during anesthesia, predisposing factors such as hypoxemia, hypoperfusion, and hypercarbia that can lead to acidosis and complement activation must be avoided. Inhalational agents and propofol may have a theoretical advantage over thiopental, which can be associated with complement-activated anaphylactoid reactions. Prophylaxis against venous thrombosis should be administered perioperatively. If perioperative transfusion is deemed necessary, washed RBCs should be administered to decrease the risk of complement activation. Use of salvaged autologous RBCs in patients with PNH should be limited to critical situations, such as massive bleeding, as a hemolytic reaction may be present inside the transfer bag even after the wash process.

Disorders of red cell metabolism. Lacking a nucleus and having a limited life expectancy, the erythrocyte maintains only the very narrow spectrum of activities necessary to carry out its oxygen transport function. The stability of the RBC membrane and the solubility of intracellular Hb depend on four glucose-supported metabolic pathways. These four pathways are illustrated in Fig. 23.1. The most clinically relevant pathways are described in the following sections.

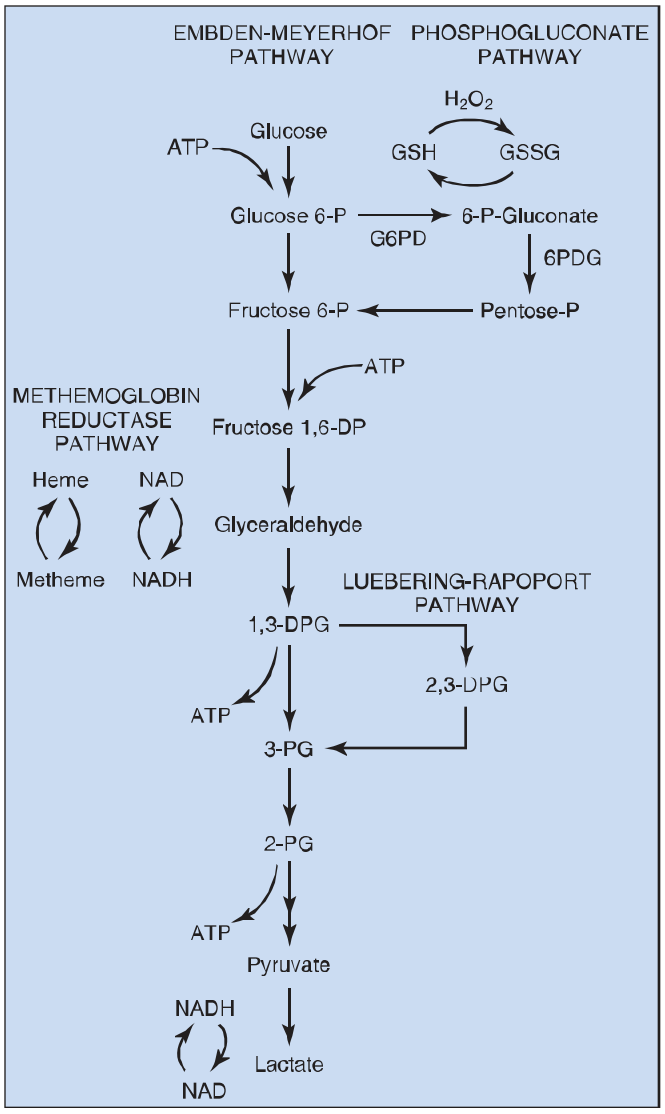

Fig. 23.1 Diagrammatic representation of the four pathways involved in the most common disorders affecting red blood cell metabolism. *1,3-DPG,* 1,3-diphosphoglycerate; *1,6-DP,* 1,6-diphosphate; *2,3,-DPG,* 2,3-diphosphoglycerate; *2-PG,* 2-phosphoglycerate; *3-PG,* 3-phosphoglycerate; *6-P,* 6-phosphate; *6PDG,* 6-phosphogluconate dehydrogenase; *6-P-Gluconate,* 6-phosphogluconate; *ATP,* adenosine triphosphate; *G6PD,* glucose-6-phosphate dehydrogenase; *GSH,* glutathione reductase; *GSSG,* oxidized glutathione; *NAD,* nicotinamide adenine dinucleotide; *NADH,* reduced form of nicotinamide adenine dinucleotide; *Pentose-P,* pentose phosphate.

Embden-Meyerhof pathway. The Embden-Meyerhof pathway (nonoxidative or anaerobic pathway) is responsible for generation of the ATP necessary for membrane function and the maintenance of cell shape and pliability. Defects in anaerobic glycolysis are associated with increased red cell rigidity and decreased survival, which produces a hemolytic anemia. Deficiencies of the glycolytic pathway are not associated with any typical morphologic red cell changes, nor do they lead to hemolytic crisis after exposure to oxidants. The severity of hemolysis is highly variable and largely unpredictable.

Phosphogluconate pathway. The phosphogluconate pathway couples oxidative metabolism with nicotinamide adenine dinucleotide phosphate (NADP) and glutathione reduction. It counteracts environmental oxidants and prevents globin denaturation. When patients lack either glucose-6-phosphate dehydrogenase (G6PD) or glutathione reductase, denatured Hb precipitates on the inner surface of the RBC membrane. This is visible on the peripheral blood smear as Heinz bodies and results in membrane damage and hemolysis.

Glucose-6-phosphate dehydrogenase deficiency. G6PD deficiency is an X-linked genetic disease and is the most common enzymatic disorder of RBCs, with more than 400 million people affected worldwide. G6PD activity is normally highest in young red cells and declines with the age of these cells. The half-life of erythrocytes in G6PD deficiency is approximately 60 days. Clinical manifestations depend on the amount of the enzyme present, with five classes described by the WHO. Patients can have chronic hemolytic anemia (class I, <10% G6PD activity), intermittent hemolysis (class II, 10% G6PD activity), and hemolysis only with stressors (class III, 10–60% G6PD activity). Classes IV and V have increased G6PD activity. There is no hemolysis in class IV or V.

Hemolysis is the result of the inability of a G6PD-deficient RBC to protect itself from oxidative damage. Events that can precipitate new or aggravate preexisting hemolysis include infection, certain metabolic conditions such as diabetic ketoacidosis, certain drugs, and ingestion of fava beans.

Anesthetic risk is largely a function of the severity and acuity of this anemia. The goal is to avoid the risk of hemolysis by not exposing the patient to oxidative drugs. Benzodiazepines (except for diazepam) are safe and beneficial preoperatively, to decrease the anxiety and risk of hemolysis. Codeine, propofol, fentanyl, and ketamine have been proven safe, but it might be wise to avoid isoflurane, sevoflurane, metoclopramide, and penicillin, all of which depress G6PD activity in vitro. Methylene blue is a particular concern. If a patient with methemoglobinemia (with already compromised oxygen delivery) is also G6PD deficient, methylene blue administration may be life threatening. Drugs that can induce methemoglobinemia (e.g., lidocaine, prilocaine, silver nitrate) should be avoided. Many antibiotics and vitamin K should also be avoided. Hypothermia, acidosis, hyperglycemia, and infection can precipitate hemolysis in the G6PD-deficient patient, and these conditions need to be aggressively treated in the perioperative period.

Pyruvate kinase deficiency. Pyruvate kinase deficiency, an autosomal recessive disorder, is the most common erythrocyte enzyme defect causing congenital hemolytic anemia. Pyruvate kinase deficiency is found worldwide but shows a higher prevalence among people of Northern European extraction and individuals from some regions of China. Although less prevalent than G6PD deficiency, pyruvate kinase deficiency is much more likely to produce a chronic hemolytic anemia. The severity of the clinical presentation ranges from a mild fully compensated process without anemia to life-threatening, transfusion-requiring hemolytic anemia at birth. Severely affected individuals may have chronic jaundice, develop pigmented gallstones, and manifest splenomegaly. Splenectomy does not totally prevent hemolysis but does decrease the rate of RBC destruction and may even eliminate the need for transfusion.

Methemoglobin reductase pathway. The methemoglobin reductase pathway uses the pyridine nucleotide–reduced NADP generated from anaerobic glycolysis to maintain heme iron in its ferrous state. An inherited mutation of the methemoglobin reductase enzyme results in an inability to counteract oxidation of Hb to methemoglobin. The ferric form of Hb does not transport oxygen. Patients with type I enzyme deficiency accumulate small amounts of methemoglobin in circulating red cells, whereas patients with type II disease have severe cyanosis and intellectual disability.

Luebering-Rapoport pathway. The Luebering-Rapoport pathway is responsible for production of 2,3-DPG. A single enzyme—2,3-bisphosphoglycerate mutase—mediates both the synthesis of 2,3-DPG and the phosphatase activity that then converts 2,3-DPG to 3-phosphoglycerate, returning it to the glycolytic pathway. The balance of formation versus metabolism of 2,3-DPG is pH sensitive, with alkalosis favoring synthetic activity and acidosis favoring metabolic breakdown. The 2,3-DPG response is also influenced by the supply of phosphate. Severe phosphate depletion in patients with diabetic ketoacidosis or nutritional deficiency can result in reduced 2,3-DPG production.

Disorders of hemoglobin. Inherited defects in Hb structure can interfere with its affinity for oxygen and the process of binding/unloading oxygen. Most defects are substitutions of a single amino acid in either the α- or β-globin chains. Some interfere with molecular movement, restricting the molecule to either a low- or high-affinity state, whereas others change the valency of heme iron from ferrous to ferric or reduce the solubility of the Hb molecule. HbS (the abnormal Hb in sickle cell disease) is an example of an Hb with a single amino acid substitution that results in reduced solubility, which causes precipitation of the abnormal Hb.

Sickle S hemoglobin. Sickle cell disease is a disorder caused by the substitution of valine for glutamic acid in the β-globin subunit. In the deoxygenated state, HbS undergoes conformational changes that expose a hydrophobic region of the molecule. In states of severe deoxygenation the hydrophobic regions aggregate, and this results in distortion of the erythrocyte membrane, oxidative damage to the membrane, impaired deformability, and a shortened life span of only 10 to 20 days.

Sickle cell anemia, the homozygous form of HbS disease, presents early in life with severe hemolytic anemia and progresses to significant end-organ damage involving the bone marrow, spleen, kidneys, and central nervous system. Patients experience episodic painful crises (vasoocclusive crises) characterized by bone and joint pain that may or may not be associated with concurrent illness, stress, or dehydration. The severity and progression of the disease can vary remarkably. Organ damage can start early in childhood, with recurrent splenic infarction culminating in loss of splenic function in the first decade of life. The kidney can demonstrate painless hematuria and loss of concentrating ability as an early feature and then progress to chronic renal failure in the third or fourth decade of life. Pulmonary and neurologic complications are the major causes of morbidity and mortality. Lung damage results from chronic persistent inflammation. Acute chest syndrome, a pneumonia-like complication, is characterized by the presence of a new pulmonary infiltrate involving at least one entire lung segment plus at least one of the following: chest pain, fever, tachypnea, wheezing, or cough. Neurologic complications include stroke, usually as a result of arterial disease rather than sickling. Adolescents present with cerebral infarction, whereas adults typically develop hemorrhagic strokes.

Chronic medical management of sickle cell disease relies on administration of hydroxyurea. Through stimulation of HgbF and release of endogenous nitric oxide, it decreases the incidence of acute chest syndrome and vasoocclusive crisis. Symptomatic treatment for vasoocclusive crises includes rehydration, supplemental oxygen therapy, aggressive analgesia, and incentive spirometry. Similar principles apply to the treatment of acute chest syndrome with the addition of blood exchange transfusion. Hematopoietic stem cell transplantation remains an option for young patients with serious complications such as stroke, acute chest syndrome, or refractory pain.

Management of anesthesia. Sickle cell trait does not cause an increase in perioperative morbidity or mortality. However, sickle cell disease is associated with a high incidence of perioperative complications. Risk factors include advanced age, frequent and severe recent episodes of sickling, evidence of end-organ damage (e.g., low baseline oxygen saturation, elevated creatinine level, cardiac dysfunction, history of stroke), and concurrent infection. Risks intrinsic to the type of surgery are also important considerations, with minor procedures considered to be low risk, intraabdominal operations categorized as intermediate risk, and intracranial and intrathoracic procedures classified as high risk. Among orthopedic procedures, hip surgery and hip replacement in particular are associated with a high risk of complications, including excessive blood loss and sickling events.

The goals of preoperative management in patients with sickle cell disease have changed in recent years. Studies examining the effects of aggressive transfusion strategies aimed at increasing the ratio of normal Hb to sickle Hb appear to show no benefit compared with the more conservative goal of achieving an overall preoperative Hct of 30% (HbS combined with HbA or HbF). The aggressive strategy had necessitated significantly more transfusions, and complications from these transfusions have been significant.

Patients undergoing low-risk procedures now rarely require any preoperative transfusion, and patients undergoing moderate- to high-risk operations need only have preoperative anemia corrected to a target Hct (all Hb types) of 30%. However, some suggest that HbS levels below 30% are desirable for major noncardiac surgery, and HbS levels below 5% are desirable for cardiac surgery involving cardiopulmonary bypass, which is associated with several factors that can promote sickling and hemolysis. In such patients, exchange transfusion can be used perioperatively in conjunction with hydroxyurea to achieve the desired low concentration of HbS.

Anesthetic technique does not appear to significantly affect the risk of complications stemming from sickle cell disease. Secondary goals such as avoiding anxiety, emotional stress, dehydration, acidosis, and hypothermia do help reduce the risk of

perioperative sickling events. Use of occlusive orthopedic tourniquets is not contraindicated, but the incidence of perioperative complications is increased with their use. Postoperative pain requires aggressive, typically multimodal, pain management. Patients often have a degree of tolerance to opioids, and a subset of patients may even have opiate addiction, but these facts must not interfere with appropriate perioperative pain management.

Despite concerns that regional anesthesia might have detrimental effects in sickle cell patients, it is not contraindicated and may offer an advantage in pain control.

Procedures requiring administration of intravenous contrast merit special consideration. Hyperosmolar solution may result in RBC polymerization and sickling, therefore hypo- or isoosmolar products are recommended.

Acute chest syndrome may develop 2 to 3 days postoperatively and requires treatment of hypoxemia, pain, hypovolemia, anemia, likely infection, and possible venous thrombosis. Excessive intravenous volume is a risk factor and should be avoided. Mild cases may respond to simple transfusion. Exchange transfusion may be needed in severely affected patients.

Sickle C hemoglobin. The prevalence of HbC is about one-fourth that of HbS. HbC causes the erythrocyte to lose water via enhanced activity of the potassium chloride cotransport system. This results in cellular dehydration that in the homozygous state may produce a mild to moderate hemolytic anemia. HbS trait or HbC trait in isolation causes no symptoms. However, when they are present together (HbSC disease) they can produce sickling and complications similar to those of HbSS disease. It appears that the dehydration produced by HbC increases the concentration of HbS within the erythrocyte, exacerbating its insolubility and tendency to polymerize.

Management of anesthesia. The anesthetic risks of HbSC disease have not been as well studied as those of HbSS disease. However, one investigation suggested that perioperative transfusion may reduce the incidence of sickling complications.

Sickle hemoglobin–β thalassemia. Among the black population, the frequency of the β thalassemia gene is only one-tenth that of the gene for HbS. The clinical presentation of this compound heterozygous state is largely determined by whether it is associated with reduced amounts of HbA (sickle cell–β^+ thalassemia) or no HbA whatsoever (sickle cell–β^0 thalassemia). In the absence of any HbA, patients experience acute vasoocclusive crises, acute chest syndrome, and other sickling complications at rates approaching those of patients with HbSS.

Unstable hemoglobins. Hbs are made unstable by structural changes that reduce their solubility or render them more susceptible to oxidation of amino acids within the globin chains. More than 100 unique unstable Hb variants have been documented, most associated with minimal clinical impact. The mutations typically impair the globin folding or heme-globin binding that stabilizes the heme moiety within the hydrophobic globin pocket. Once freed from its cleft, the heme binds nonspecifically to other regions of the globin chains. This causes formation of precipitates (Heinz bodies) that contain globin chains, chain fragments, and heme. Heinz bodies interact with the red cell membrane, reducing its deformability and favoring its removal by macrophages in the spleen. Unstable Hbs vary in their propensity to form Heinz bodies and in the severity of any associated anemia. Hemolysis may be aggravated by the development of additional oxidative stresses, such as infection or ingestion of oxidizing drugs. Patients with recurring bouts of severe hemolysis or significant morbidity from the chronic anemia should be considered candidates for splenectomy, which is usually effective in reducing or even eliminating symptoms and signs.

Management of anesthesia. Anesthetic management of patients with unstable Hbs is largely dictated by the degree of hemolysis. Transfusion during bouts of severe hemolysis and avoidance of oxidizing drugs are important. These patients may have severe anemia and Hb-induced renal injury.

Autoimmune hemolytic anemias. Autoimmune hemolytic anemias result from RBC cell lysis due to warm agglutinins (mostly immunoglobulin G [IgG]–mediated lysis at body temperature) or cold agglutinins (IgM-mediated lysis at lower temperatures). Antibodies against RBCs can be detected by a DAT (Coombs test). Warm autoimmune hemolytic anemia (WAHA) is associated with lupus (10% of lupus patients develop warm agglutinins), hematologic malignancies (non-Hodgkin lymphoma, chronic lymphocytic leukemia), viral infections (HIV), or drugs (penicillins, cephalosporins, quinine, quinidine, nonsteroidal antiinflammatory drugs [NSAIDs]). WAHA episodes are managed supportively and/or with corticosteroids. Patients who are not responsive to steroids are candidates for splenectomy, rituximab, or other cytotoxic drugs.

Cold agglutinin disease manifests as hemolytic episodes that occur at lower temperatures. Pathologic cold agglutinins can be a result of certain infections (*Mycoplasma pneumoniae,* infectious mononucleosis) or of neoplastic/paraneoplastic processes. Avoidance of cold temperatures is the mainstay of therapy in such patients. Although the majority of patients do not require treatment, more severe cases may benefit from treatment with rituximab with or without fludarabine. Glucocorticoids and splenectomy have no value in cold agglutinin disease. Plasmapheresis is an attractive option and could be considered in patients about to undergo high-risk surgery (especially surgery involving cardiopulmonary bypass), since it can remove up to 80% of these antibodies. However, plasmapheresis can lead to fluid overload, infection, and altered hemostasis. Intravenous administration of immunoglobulin has also been described as a viable therapeutic option.

Anemia of Chronic Disease

ACD manifests as a normocytic, normochromic, hypoproliferative anemia due to decreased production of RBCs coupled with somewhat shortened RBC survival. ACD is thought to result from several mechanisms: trapping of iron in macrophages (resulting in a lower level of circulating iron available for hematopoiesis), a decrease in erythropoietin concentrations resulting in a decrease in bone marrow red cell production, and shorter RBC life span due to increased macrophage activity.

Patients with ACD present with low iron levels, normal to low transferrin levels, normal to high ferritin levels, but a normal transferrin saturation. This is in particular contrast to IDA, in which there is a low transferrin saturation. Markers of active

inflammation may be present, such as an elevated sedimentation rate and C-reactive protein level. The CBC may support a diagnosis of infection with a high WBC count.

The diagnosis of ACD is supported by the clinical picture, with most patients already carrying a diagnosis of a chronic inflammatory or infectious disease or malignancy at the time the anemia is discovered.

Treatment. The ideal treatment for ACD is cure of the underlying disease, which unfortunately is not often possible. Preoperative treatment of patients with ACD may involve administration of iron with erythropoiesis-stimulating drugs such as darbepoetin and erythropoietin. Iron alone should never be given to patients with ACD due to malignancy and infection, since iron can worsen the underlying disease(s). Erythropoiesis-stimulating drugs should be avoided in patients with ACD due to cancer (especially during active treatment), but they are approved for treatment of significant anemia due to chemotherapy. The minimum effective dose should be administered to avoid thromboembolic complications. These drugs can also be used in patients with rheumatoid arthritis and HIV with low erythropoietin levels.

Anemia of Chronic Kidney Disease

The anemia of chronic kidney disease results from decreased erythropoietin production. Therefore these patients benefit from administration of erythropoiesis-stimulating drugs. The target Hb should be 10 to 12 g/dL, even with patients on hemodialysis, since these patients benefit with a reduction in their symptoms and a better quality of life. Concurrent iron deficiency should be investigated and treated to ensure optimal red cell production.

Aplastic Anemia

Congenital aplastic anemia (Fanconi anemia) is an autosomal recessive disorder that presents in the first two decades of life with severe pancytopenia that often progresses to acute leukemia. When the gene is fully expressed (as occurs in 1 per 100,000 live births), this disorder is associated with progressive bone marrow failure, a number of physical defects, chromosomal abnormalities, and a predisposition to cancer. Not all patients have the classic physical defects, so the diagnosis should be considered in all children and young adults with acute myelogenous leukemia.

Acquired aplastic anemia is due to bone marrow toxicity, typically from drugs. Anemia due to bone marrow damage is a predictable side effect of chemotherapy, and this anemia is usually mild unless high-dose multidrug chemotherapy that can cause pancytopenia is used. So long as the drugs do not irreversibly damage the bone marrow, recovery is usually complete. High-energy radiation can also produce anemia from bone marrow damage, the degree of which is predictable from the type of radiation, the dose, and the extent of bone marrow exposure. Long-term exposure to low levels of external radiation or ingested radioisotopes can produce aplastic anemia.

Several drugs have been associated with the development of severe, often irreversible, aplastic anemia. Table 23.1 lists many classes of these drugs. Some (e.g., chloramphenicol) can produce severe irreversible aplastic anemia after only a few doses, but most (e.g., phenylbutazone, propylthiouracil, tricyclic antidepressants) are associated with a more gradual onset of pancytopenia, which is reversible if the offending drug is withdrawn.

TABLE 23.1 Classes of Drugs Associated With Marrow Damage

Antibiotics (chloramphenicol, penicillin, cephalosporins, sulfonamides, amphotericin B, streptomycin)
Antidepressants (lithium, tricyclics)
Antiepileptics (phenytoin, carbamazepine, valproic acid, phenobarbital)
Antiinflammatory drugs (phenylbutazone, nonsteroidals, salicylates, gold salts)
Antidysrhythmics (lidocaine, quinidine, procainamide)
Antithyroidal drugs (propylthiouracil)
Diuretics (thiazides, pyrimethamine, furosemide)
Antihypertensives (captopril)
Antiuricemics (allopurinol, colchicine)
Antimalarials (quinacrine, chloroquine)
Hypoglycemics (tolbutamide)
Platelet inhibitors (ticlopidine)
Tranquilizers (prochlorperazine, meprobamate)

Immunosuppression of stem cell growth can also produce anemia, even aplastic anemia. This can be seen following viral illnesses such as viral hepatitis, Epstein-Barr virus infection, HIV infection, and rubella. Parvovirus B19 infection can cause an acute reversible pure red cell aplasia in patients with congenital hemolytic anemia. Although most of these anemias are reversible, some infections can produce fatal aplastic anemia.

Management of anesthesia. Patients may come for surgery with anemia and thrombocytopenia severe enough that transfusion is necessary preoperatively. The severity of the neutropenia will affect the need for and choice of antibiotic coverage. The use of granulocyte colony-stimulating factor preoperatively to increase neutrophil counts is controversial.

Macrocytic/Megaloblastic Anemias

Disruption of the erythroid precursor maturation sequence can result from deficiencies in vitamins such as folic acid and vitamin B_{12}, exposure to chemotherapeutic agents, or a preleukemic state. Since these are all defects in nuclear maturation, patients have macrocytic anemia and megaloblastic bone marrow morphology.

Folate and Vitamin B_{12} Deficiency Anemia

Folic acid and vitamin B_{12} deficiency are primary causes of macrocytic anemia in adults. Both vitamins are essential for normal DNA synthesis, and high-turnover tissues such as bone marrow are the first to be affected when these vitamins are in short supply. In deficiency states the marrow precursors appear much larger than normal and are unable to complete cell division. Therefore the marrow becomes megaloblastic, and macrocytic red cells are released into the circulation. The prevalence of deficiency of these vitamins varies considerably in different parts of the world. In developed countries, alcoholism is a frequent cause of folate deficiency, both because of the poor

dietary habits of alcoholic individuals and because of alcohol's interference with folate metabolism. In developing countries where tropical and nontropical sprue are more widespread, malabsorption may increase the frequency of vitamin B_{12} deficiency.

Sustained exposure to nitrous oxide can produce an impairment of vitamin B_{12} activity. Nitrous oxide can oxidize the cobalt atom of the vitamin, which reduces its cofactor activity and causes impairment in both methionine synthesis and *S*-adenosylmethionine synthesis. This action requires long exposure to high concentrations of nitrous oxide and pertains only to situations in which scavenging systems are inadequate or there is recreational use of this gas.

The macrocytic anemia caused by folate or vitamin B_{12} deficiency may result in Hb levels below 8 to 10 g/dL, a mean red cell volume of 110 to 140 fL (normal, 90 fL), a normal reticulocyte count, and increased levels of LDH and bilirubin. In addition to causing megaloblastic anemia, vitamin B_{12} deficiency is associated with peripheral neuropathy due to degeneration of the lateral and posterior columns of the spinal cord. There are symmetric paresthesias with loss of proprioceptive and vibratory sensations, especially in the lower extremities. Gait is unsteady, and deep tendon reflexes are diminished. Memory impairment and depression may be prominent. These neurologic deficits are progressive unless vitamin B_{12} is provided. Abuse of nitrous oxide may be associated with neurologic findings similar to those that accompany vitamin B_{12} deficiency and pernicious anemia.

Folate and/or vitamin B_{12} deficiency can be corrected by vitamin administration. In cases of intestinal malabsorption, the parenteral route is preferred. Emergency correction of life-threatening anemia or preparation for urgent surgery requires red cell transfusion. The presence of neurologic changes present in severe B_{12} deficiency may preclude the use of regional anesthetic techniques. Moreover, the use of nitrous oxide would not be prudent.

OTHER HEMOGLOBIN-RELATED DISORDERS

Hemoglobins With Increased Oxygen Affinity

Hb mutations that increase the oxygen-binding avidity of the heme moiety cause the oxyhemoglobin dissociation curve to shift to the left, which reduces the P_{50}, the partial pressure of oxygen at which Hb is 50% saturated with oxygen. Many types of mutations can increase oxygen affinity. These Hbs bind oxygen more readily than normal and retain more oxygen at lower Po_2 levels. Accordingly, they deliver less oxygen to tissues at normal capillary Po_2, and blood returns to the lungs still partially saturated with oxygen. The net result is mild tissue hypoxia that triggers increased erythropoietin production, leading to polycythemia.

Management of Anesthesia

Tissue oxygen delivery at baseline may be barely adequate, so even a modest decrease in Hct is potentially dangerous. Patients with only mild erythrocytosis do not require intervention. Patients with high Hcts (>55–60%), whose blood viscosity may further compromise oxygen delivery, will require hydration and possibly preoperative exchange transfusion.

Hemoglobins With Decreased Oxygen Affinity

Methemoglobinemia

Methemoglobin (HbM) is formed when the iron moiety in Hb is oxidized from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. Normal Hb, when bound to oxygen, partially transfers an electron from the iron to the oxygen, which moves the iron close to its ferric state, and the oxygen resembles a superoxide. Deoxygenation ordinarily returns the electron to the iron, but methemoglobin forms if the electron is not returned. The normal erythrocyte maintains methemoglobin levels at 1% or less by the methemoglobin reductase enzyme system. Methemoglobin moves the oxyhemoglobin dissociation curve markedly to the left and therefore delivers little oxygen to the tissues. Methemoglobin levels below 30% of total Hb content may cause no compromise in tissue oxygenation. However, levels between 30% and 50% do cause symptoms and signs of oxygen deprivation, and levels above 50% can result in coma and death.

Methemoglobinemia of clinical importance can arise from three mechanisms: globin chain mutations favoring the formation of methemoglobin (HbM disease), mutations impairing the efficacy of the methemoglobin reductase system (cytochrome b5 reductase deficiency), and toxic exposure to substances that oxidize normal Hb iron at a rate that exceeds the capacity of the normal reducing mechanisms.

In congenital methemoglobinemia, an autosomal recessive disorder, the enzyme responsible for the reduction of ferric methemoglobin to ferrous oxyhemoglobin, cytochrome b5 reductase, is deficient. This deficiency can be present in all cells, as seen in type II congenital methemoglobinemia or absent only in RBCs as seen in type I congenital methemoglobinemia.

Patients with cytochrome b5 reductase deficiency can be treated with either methylene blue or ascorbic acid as chronic therapy.

HbM disease is an autosomal dominant genetic disorder resulting in hemoglobin that resists reduction from the oxidized ferric state back to the ferrous state. This causes a permanent increase in levels of methemoglobin ranging between 15% and 30%, and these patients are usually asymptomatic. The methemoglobin has a brownish-blue color that does not change to red on exposure to oxygen, which gives patients a cyanotic appearance independent of their Pao_2.

There is no treatment for HbM disease, as it does not respond to either methylene blue or ascorbic acid.

Exposure to chemical materials that directly oxidize Hb or produce reactive oxygen intermediates that oxidize Hb may produce an acquired methemoglobinemia in which life-threatening amounts of methemoglobin accumulate. Since infants have lower levels of methemoglobin reductase in their erythrocytes, they manifest greater susceptibility to oxidizing agents. Treatment entails withdrawal of causing agent, supportive treatment, and methylene blue. The dosage is 1 to 2 mg/kg infused over 3 to 5 minutes. A single treatment is usually effective but might need to be repeated after 30 minutes. Methylene blue acts through the methemoglobin reductase system and requires

the activity of G6PD. Patients who are G6PD deficient and patients severely affected by methemoglobin may require exchange transfusion instead.

Management of anesthesia. Management of anesthesia in patients with methemoglobinemia focuses on avoiding any tissue hypoxia. Certain comorbidities, such as cardiovascular disease, place these patients at an increased risk of exhibiting symptoms of hypoxia in the perioperative setting. It is recommended that patients who cannot tolerate a reduction in oxygen-carrying capacity be treated when methemoglobin levels reach 10%, regardless of presence or absence of symptoms. Furthermore, all patients with methemoglobin levels of 30% are also candidates for treatments, regardless of symptoms.

Pulse oximetry is unreliable in the perioperative setting because most pulse oximeters cannot detect methemoglobin. An intraarterial catheter should be inserted to be able to measure blood pressure, methemoglobin levels, and arterial blood gas concentrations. Any acidosis should be corrected, and the electrocardiogram must be closely monitored for signs of ischemia. Patients with HbM may be very sensitive to exposure to oxidizing agents. Therefore local anesthetics (benzocaine and prilocaine), nitrates, and nitric oxide should be avoided.

POLYCYTHEMIA

Sustained hypoxia usually results in a compensatory increase in RBC mass and Hct. Although this increases the oxygen-carrying capacity of the blood, it also increases blood viscosity. Tissue oxygen delivery is maximal at a Hct of 33% to 36% (Hb concentration, 11–12 g/dL), assuming no changes occur in cardiac output or regional blood flow. With higher Hcts there is an increase in blood viscosity that will tend to slow blood flow and decrease oxygen delivery. This effect is relatively minor until the Hct exceeds 55% to 60%, at which time blood flow to vital organs can be significantly reduced.

Physiology of Polycythemia

Polycythemia and erythrocytosis are terms that describe an abnormally high Hct. Even modest increases in the Hct can have a major impact on whole-blood viscosity. An increase in Hct can result from a reduction in plasma volume (relative polycythemia) without an actual increase in red cell mass. An acute decrease in plasma volume, as may be seen with preoperative fasting, can convert an asymptomatic polycythemia into one in which hyperviscosity threatens tissue perfusion. When the Hct rises to levels above 55% to 60%, whole-blood viscosity increases exponentially, affecting blood flow especially in small blood vessels such as capillaries with low flow/shear rates. The cerebral circulation is particularly vulnerable to reductions in blood flow resulting from increased viscosity (Figs. 23.2 and 23.3).

The signs and symptoms of a high Hct vary depending on the underlying disease process and the rate of development of the erythrocytosis. Patients with modest chronic polycythemia have few complaints until the Hct exceeds 55% to 60%. Headaches and easy fatigability then occur. Hct levels above 60% can be life threatening because the increase in viscosity

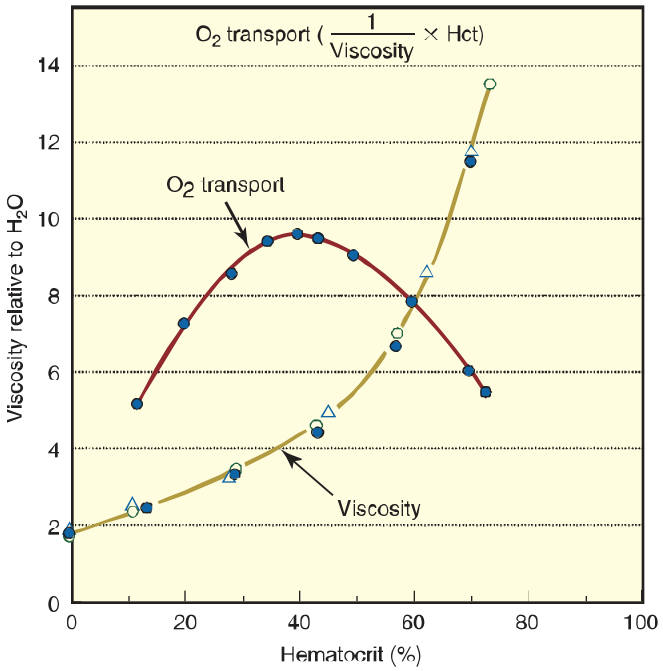

Fig. 23.2 Viscosity of heparinized normal human blood as a function of hematocrit (Hct). Viscosity is measured with an Ostwald viscosimeter at 37°C and expressed in relation to the viscosity of saline solution. Oxygen transport is computed from Hct and oxygen flow (1/viscosity) and is recorded in arbitrary units. (Data from Murray JF, Gold P, Johnson Jr BL, et al. Clinical manifestations and classification of erythrocyte disorders. In: Kaushansky K, Lichtman M, Beutler E, et al., eds. *Williams Hematology.* ed 8. New York, NY: McGraw-Hill Medical; 2010.)

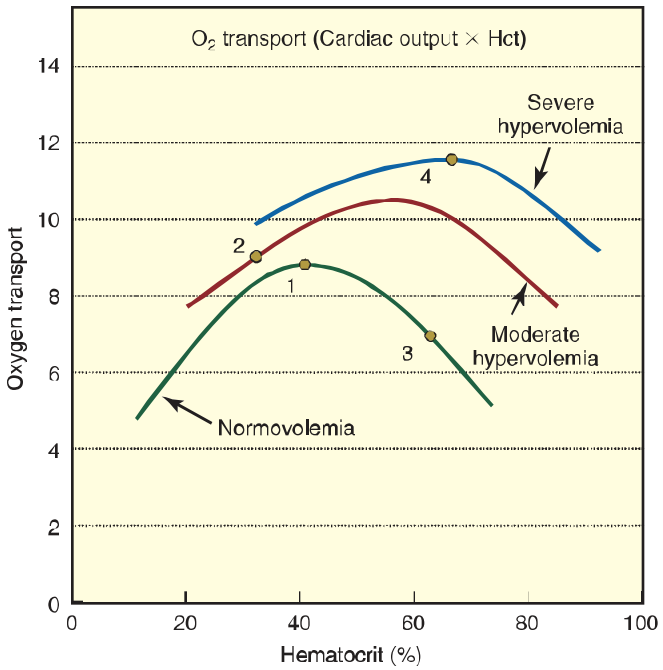

Fig. 23.3 Oxygen transport at various hematocrit (Hct) levels in normovolemia, moderate hypervolemia, and severe hypervolemia. Oxygen transport is estimated by multiplying Hct by cardiac output. (Data from Murray JF, Gold P, Johnson Jr BL, et al. Clinical manifestations and classification of erythrocyte disorders. In: Kaushansky K, Lichtman M, Beutler E, et al., eds. *Williams Hematology.* ed 8. New York, NY: McGraw-Hill Medical; 2010.)

threatens vital organ perfusion. Patients with such high Hcts are also at significant risk of venous and arterial thromboses.

Polycythemia Vera

Primary polycythemia, also known as polycythemia vera (PV), is a stem cell disorder characterized by proliferation of a clone of hematopoietic precursors, nearly all of which arise from a mutation in the *JAK2* (Janus kinase 2) gene. This clonal expansion most commonly produces an excess of erythrocytes, but the number of platelets and leukocytes may also be increased. The criteria for a diagnosis of PV include an elevated Hb level (>16.5 g/dL in men, >16 g/dL in women) or Hct (>49 in men, >48 in women), trilineage hypercellularity of bone marrow, and the presence of the *JAK2* mutation. Alternatively, the first two criteria in the presence of a subnormal serum erythropoietin level are sufficient for diagnosis. PV may appear at any age, but most patients develop the disease in their sixth or seventh decade. Patients can have a number of symptoms. Budd-Chiari syndrome (hepatic vein occlusion) is a common presentation, as are generalized pruritus, transitory visual disturbances, and erythromelalgia. Coronary or cerebral thrombosis is also a common presenting sign. Pulmonary hypertension occurs with increased frequency in this population. Patients with low-grade PV (age <60 and no thromboses) generally require regular phlebotomy to maintain a Hct below 45 and low-dose aspirin. More severe patients may require treatment with myelosuppressive drugs such as hydroxyurea, interferon, or busulfan, to control the Hct. Ruxolitinib, a JAK1/JAK2 inhibitor, is used to treat refractory PV. Approximately 30% of patients with PV will die of thrombotic complications and another 30% will succumb to cancer, most commonly myelofibrosis and acute leukemia.

Patients with PV who are undergoing surgery are at risk of perioperative thrombosis and (paradoxically) hemorrhage. This increased risk of thrombosis is due to the combination of baseline hypercoagulability augmented by the prothrombotic state of surgery. Hemorrhage is attributable to an acquired von Willebrand syndrome caused by abnormally low amounts of the ultralarge von Willebrand factor (vWF) multimers essential to normal platelet adhesion. The hyperviscosity associated with a high Hct favors a conformational change in vWF that renders it vulnerable to enzymatic cleavage. Therefore the most hemostatically effective large multimers become depleted, which then creates the risk of bleeding. Phlebotomy and absolute avoidance of dehydration lower the risk of both thrombosis and hemorrhage during the perioperative period.

Management of Anesthesia

Polycythemia vera patients are at risk for perioperative thromboses and hemorrhage. Reducing the Hct before surgery to 45% via phlebotomy and hydration may reduce the risk of thrombohemorrhagic complications. Thrombocytosis, if present, should be decreased to below 400,000 platelets/mm^3. Cytoreduction with hydroxyurea is recommended in patients older than 60 years or with a prior history of thrombosis. Hydroxyurea can often resolve the acquired vWF syndrome. Aspirin therapy should be withheld for 7 days before surgery. Factor VIII/vWF concentrates can be beneficial in improving levels of vWF and thus in reducing bleeding. Desmopressin could also be used, although there is a risk of tachyphylaxis with repeated use.

Secondary Polycythemia Due to Hypoxia

An increase in the RBC mass without evidence of a change in other hematopoietic cell lines is a normal physiologic response to hypoxia, regardless of cause. Individuals living at high altitudes develop a compensatory polycythemia that is physiologically appropriate and not associated with clinical abnormalities. At altitudes over 7000 feet, humans are at risk of both acute and chronic mountain sickness.

Significant cardiopulmonary disease can also result in enough tissue hypoxia to induce polycythemia. Congenital heart disease with a significant right-to-left shunt and cyanosis is a good example. Extremely low cardiac output, whether congenital or acquired, may stimulate release of erythropoietin and be associated with an increased Hct. Pulmonary disease can result in hypoxia-induced polycythemia. Extreme obesity with development of the obesity-hypoventilation syndrome (Pickwickian syndrome) is another classic example. Inherited defects of Hb, such as Hbs with a high affinity for oxygen and defects in the amount or function of 2,3-DPG, may cause polycythemia due to reduced tissue oxygen delivery and a leftward shift in the oxyhemoglobin dissociation curve. Defects or drugs producing significant methemoglobinemia can also lead to a compensatory polycythemia.

Secondary Polycythemia Due to Increased Erythropoietin Production

Renal disease and several erythropoietin-secreting tumors have been associated with secondary polycythemia. Hydronephrosis, polycystic kidney disease, renal cysts, and both benign and malignant renal tumors can result in increased erythropoietin production. Uterine myomas, hepatomas, and cerebellar hemangiomas have also been shown capable of secreting erythropoietin. After renal transplantation, patients can develop erythrocytosis that is unrelated to erythropoietin production. Angiotensin-converting enzyme inhibitors will reverse this particular form of polycythemia. Surreptitious use of erythropoietin by high-performance athletes may also produce polycythemia.

Management of Anesthesia in Secondary Polycythemia

Management of patients with secondary polycythemia depends on the specific cause of the polycythemia. Patients with mild hypoxic polycythemia require no specific treatment. Patients with a very high Hct may require phlebotomy to reduce the potential for perioperative thrombotic and hemorrhagic complications.

DISORDERS OF HEMOSTASIS

Normal Hemostasis

Any disruption of vascular endothelium is a potent stimulus to clot formation. As a localized process, clotting acts to seal the break in vascular continuity, limit blood loss, and begin the process of wound healing. Prevention of an exuberant response

that would result in pathologic thrombosis relies on several counterbalancing mechanisms, including the anticoagulant properties of intact endothelial cells, circulating inhibitors of activated coagulation factors, and localized fibrinolytic enzymes. Most abnormalities in hemostasis involve a defect in one or more of the steps in the coagulation process, so it is important to understand the physiology of hemostasis.

Cascade Coagulation Model

The cascade model of coagulation was described during the 1960s and consists of an extrinsic and an intrinsic pathway (Fig. 23.4). The extrinsic system was represented by factor VIIa and tissue factor. By contrast, the intrinsic system was thought to be entirely intravascular. Both pathways could activate factor X, which, when complexed with factor Va, could convert prothrombin to thrombin. The prothrombin time (PT) used to guide warfarin therapy reflects the extrinsic pathway, whereas the activated partial thromboplastin time (aPTT) used to guide heparin therapy reflects the intrinsic pathway. Although this model correlates well with clotting measurements, it does not accurately represent in vivo clotting.

New Coagulation Model

In vivo coagulation follows exposure of blood to a source of tissue factor, typically from subendothelial cells, following damage to a blood vessel. The intrinsic, or contact, pathway of

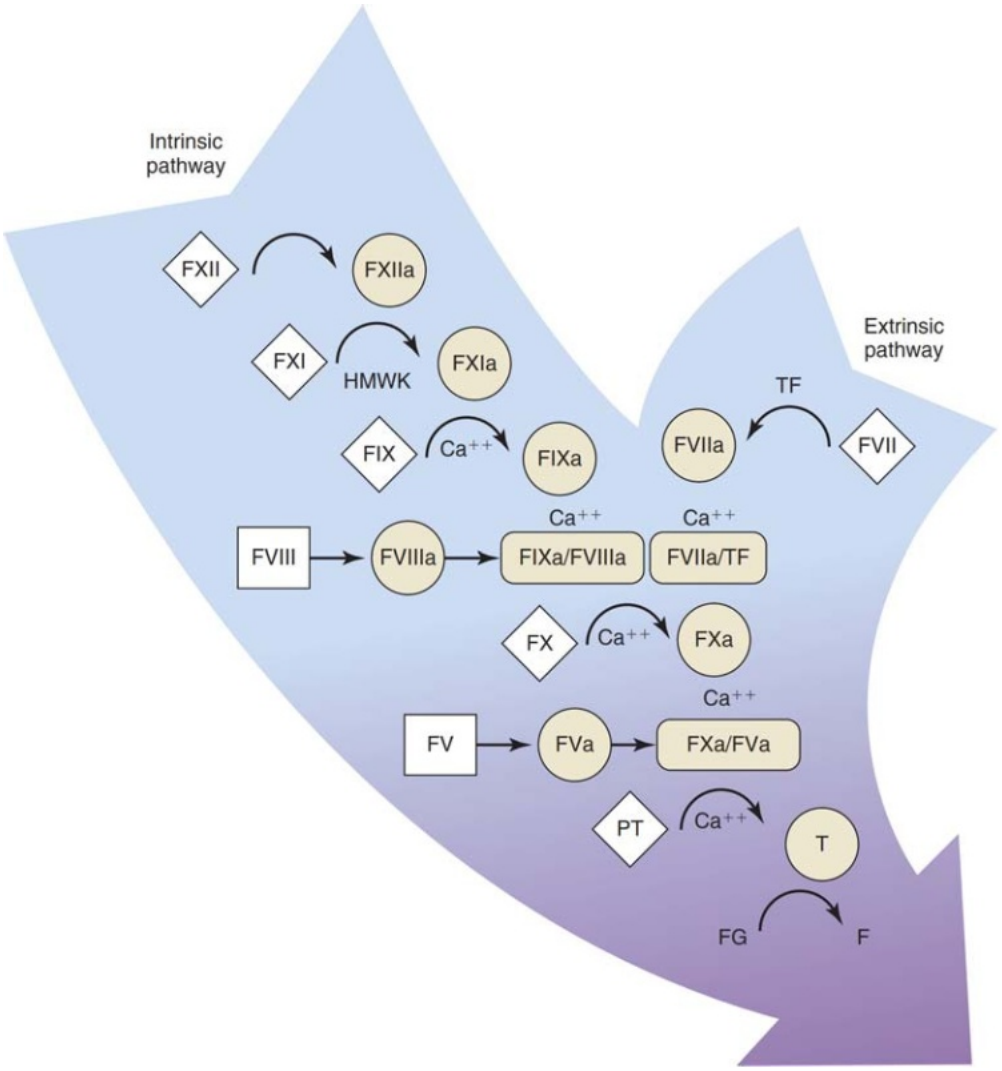

Fig. 23.4 Coagulation cascade. Glycoprotein components of the intrinsic pathway include factors XII, XI, IX, VIII, X, and V; prothrombin; and fibrinogen. Glycoprotein components of the extrinsic pathway, initiated by the action of tissue factor located on cell surfaces, include factors VII, X, and V; prothrombin; and fibrinogen. Cascade reactions culminate in conversion of fibrinogen to fibrin and formation of a fibrin clot. Certain reactions, including activation of factor X and prothrombin, take place on membrane surfaces. Diamonds indicate proenzymes; squares indicate pro-cofactors; circles indicate enzymes and cofactors; shaded rectangles indicate macromolecular complexes on membrane surfaces. *F,* Fibrin; *FG,* fibrinogen; *HMWK,* high-molecular-weight kininogen; *PT,* prothrombin; *T,* thrombin; *TF,* tissue factor. (From Furie B, Furie BC. Molecular basis of blood coagulation. In: Hoffman R, Benz EJ, Shattil SJ, et al., eds. *Hematology: Basic Principles and Practice.* ed 5. Philadelphia, PA: Churchill Livingstone; 2009, fig. 118.1.)

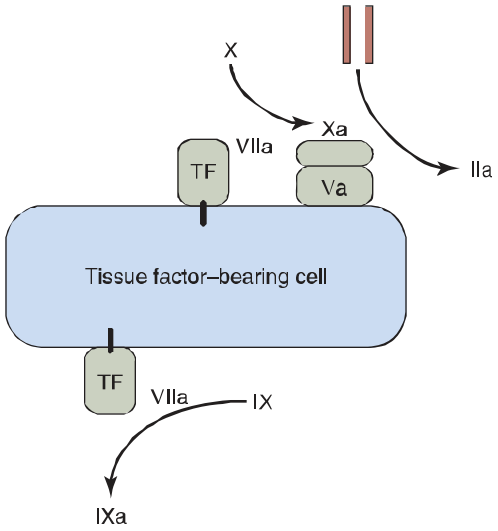

Fig. 23.5 Initiation phase of the blood coagulation cascade. *TF,* Tissue factor. (From Hoffmann M. Remodeling the blood coagulation cascade. *J Thromb Thrombolysis.* 2003;16:17-20, fig. 2.)

coagulation has no role in this earliest clotting event. Tissue factor–initiated coagulation has three phases: an initiation phase, an amplification phase, and a propagation phase.

The initiation phase begins as exposed tissue factor binds to factor VIIa (Fig. 23.5). This factor VIIa–tissue factor complex catalyzes the conversion of small amounts of factor X to Xa, which in turn generates similarly small amounts of thrombin. During the amplification phase, platelets, factor V, and factor XI are activated by the small amount of thrombin (Fig. 23.6). The propagation phase is initiated by the activation of factor X by factors VIII and IX and calcium on the platelet surface (Fig. 23.7). During this phase, thrombin increases its own formation by activating platelets and factors V and VIII. This sets the stage for formation of the factor VIIIa-IXa complex. Formation of this complex allows factor Xa generation to switch from a reaction catalyzed by the factor VIIa–tissue factor complex to one produced by the intrinsic Xase pathway. This switch is of enormous kinetic advantage, since the intrinsic Xase complex is 50 times more efficient at factor Xa generation. The bleeding diathesis associated with hemophilia, with its intact initiation phase and absent propagation phase, is evidence of the hemostatic importance of the propagation phase.

Commonly used laboratory tests of soluble coagulation factors measure only the kinetics of the initiation phase. The PT and aPTT both have as end points the first appearance of fibrin gel. This occurs after completion of less than 5% of the total reaction. These tests are sensitive in detecting severe deficiencies in clotting factors such as hemophilia and in guiding warfarin or heparin therapy. However, they do not model the sequence of events necessary for actual hemostasis and do not necessarily predict the risk of intraoperative bleeding.

In the venous circulation the kinetic advantage of the coagulation cascade assembly on the platelet surface is readily apparent. However, relatively small numbers of platelets are needed to perform this function. To increase the risk of venous bleeding, the platelet count must decrease to very low levels (i.e., $<10{,}000/mm^3$). This contrasts sharply with the arterial circulation, in which the minimum platelet count needed to ensure hemostasis for surgery is at least five times higher.

Hemostatic Disorders Affecting Coagulation Factors of the Initiation Phase

Table 23.2 lists both inherited and acquired hemostatic disorders.

Factor VII Deficiency

Hereditary deficiency of factor VII is a rare autosomal recessive disease with highly variable penetrance and clinical severity. Only patients with a homozygous deficiency have factor VII

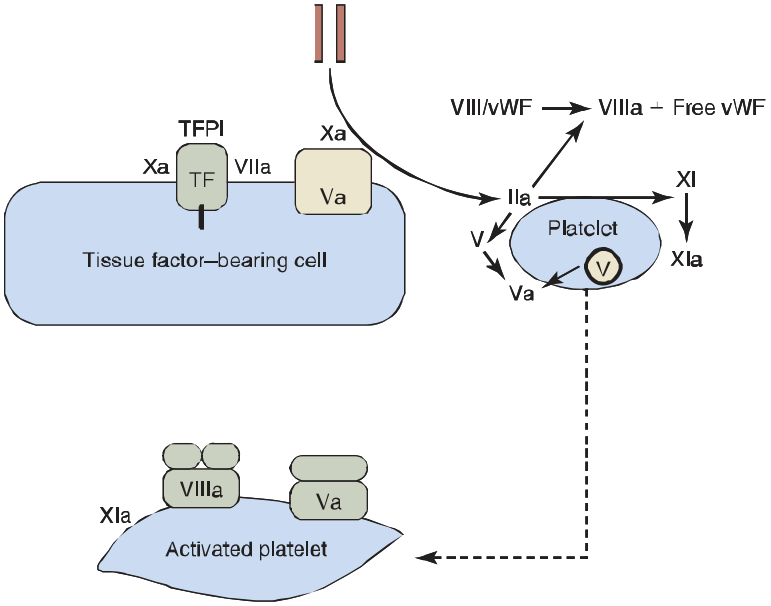

Fig. 23.6 Amplification phase of the blood coagulation cascade. *TF,* Tissue factor; *TFPI,* tissue factor pathway inhibitor; *vWF,* von Willebrand factor. (From Hoffmann M. Remodeling the blood coagulation cascade. *J Thromb Thrombolysis.* 2003;16:17-20, fig. 3.)

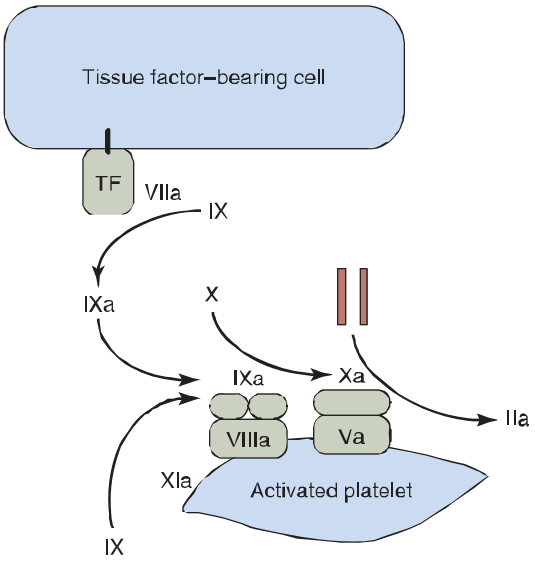

Fig. 23.7 Propagation phase of the blood coagulation cascade. *TF*, Tissue factor. (From Hoffmann M. Remodeling the blood coagulation cascade. *J Thromb Thrombolysis*. 2003;16:17-20, fig. 4.)

TABLE 23.2 Categorization of Coagulation Disorders

Hereditary Causes
- Hemophilia A
- Hemophilia B
- Von Willebrand disease
- Afibrinogenemia
- Factor V deficiency
- Hereditary hemorrhagic telangiectasia
- Protein C deficiency
- Antithrombin III deficiency

Acquired Causes
- Disseminated intravascular coagulation
- Perioperative anticoagulation
- Intraoperative coagulopathies
- Dilutional thrombocytopenia
- Dilution of procoagulants
- Massive blood transfusion
- Certain types of surgery (cardiopulmonary bypass, brain surgery, orthopedic surgery, urologic surgery, obstetric delivery)
- Drug-induced hemorrhage
- Drug-induced platelet dysfunction
- Idiopathic thrombocytopenic purpura
- Thrombotic thrombocytopenic purpura
- Catheter-induced thrombocytopenia
- Vitamin K deficiency

levels low enough (<15%) to have symptomatic bleeding. These patients are easily recognized by their laboratory testing: They have a prolonged PT but normal PTT.

Management of anesthesia. The treatment of a single-factor deficiency depends on the severity of the deficiency. For surgery, individual clotting factor levels of 20% to 25% provide adequate hemostasis. Several products are available to treat factor VII deficiency. Patients with factor VII levels below 3% and patients with a history of major bleeds require treatment with a concentrated source of factor VII. For prophylaxis, factor VII concentrate (30–40 international units [IU]/kg) and recombinant factor VIIa (NovoSeven, 15–30 μg/kg) are preferred. The concentrates consist of a low-volume infusion and have a low risk of infection. Factor repletion needs to continue for 2 to 3 days for minor procedures and until healing has occurred for major surgeries. Actively bleeding patients can be treated with factor VII concentrates, recombinant factor VIIa, prothrombin complex concentrates, or fresh frozen plasma.

Congenital Deficiencies in Factor X, Factor V, and Prothrombin (Factor II)

Congenital deficiencies in factor X, factor V, and prothrombin are inherited as autosomal recessive traits. Severe deficiencies are quite rare. However, patients with a severe deficiency in any of these factors will demonstrate prolongation of both the PT and PTT.

Deficiencies in factor X, factor V, and prothrombin could be corrected with fresh frozen plasma. However, to obtain a significant increase in the level of any factor, a considerable volume of fresh frozen plasma must be infused. As a rule of thumb, 15 to 20 mL/kg of fresh frozen plasma is needed to obtain a 20% to 30% increase in the level of any clotting factor. This may present a significant cardiovascular challenge to some patients. The duration of effect of this replacement therapy depends on the turnover time of each factor, which then dictates how often another infusion of fresh frozen plasma will be needed.

For factor X and prothrombin deficiency in patients about to undergo surgery with a significant risk of blood loss, several prothrombin complex concentrates are available. Some of these concentrates contain three clotting factors and some contain four. The advantage of these products is that factor levels of 50% or more can be achieved without the risk of volume overload. The disadvantages of prothrombin complex concentrates are significant, however, and include the risk of inducing widespread thrombosis, thromboembolism, and disseminated intravascular coagulation (DIC). It is also important to recognize that factor levels in the different products vary considerably.

Factor X deficiency can also be corrected with factor X concentrate. There is no recombinant factor V or plasma-derived concentrate available to treat factor V deficiency.

Hemostatic Disorders Affecting Coagulation Factors of the Propagation Phase

Defects in the propagation phase of coagulation are associated with a significant bleeding tendency. Some of these propagation phase defects are detected by an isolated prolongation of the aPTT. The X-linked recessive disorders hemophilia A and B are the principal examples of this type of abnormality. A marked reduction in either factor VIII or factor IX is associated with spontaneous and/or excessive hemorrhage, commonly presenting as hemarthroses and muscle hematomas. A deficiency in factor XI also prolongs the aPTT but typically results in a less severe bleeding tendency.

Not all factor deficiencies causing prolongation of the aPTT are associated with bleeding. The initial activation stimulus for this laboratory test is surface contact activation of factor XII (Hageman factor) to produce XIIa. This reaction is facilitated by the presence of high-molecular-weight kininogen and the conversion of prekallikrein to the active protease kallikrein. Deficiency in any of these chemicals causes prolongation of the aPTT. However, these contact activation factors play no role in either the initiation phase or the propagation phase of clotting in vivo. Thus deficiencies of factor XII, high-molecular-weight kininogen, and prekallikrein are not associated with clinical bleeding. Patients with deficiencies of these particular factors require no special management.

Congenital Factor VIII Deficiency: Hemophilia A

The factor VIII gene is a very large gene on the X chromosome. Patients with very severe hemophilia generally have an inversion or deletion of major portions of the X chromosome genome or a missense mutation resulting in factor VIII activity below 1% of normal. Other mutations, including point mutations and minor deletions, generally result in milder disease with factor VIII levels above 1%. In some patients a functionally abnormal protein is produced that causes a discrepancy between results on the immunologic assay of factor VIII antigen and results on the coagulation test of factor VIII activity.

The clinical severity of hemophilia A is best correlated with the factor VIII activity level. Patients with severe hemophilia have factor VIII activity levels below 1% of normal and are usually diagnosed during childhood because of frequent spontaneous hemorrhage into joints, muscles, and vital organs. They require frequent treatment with factor VIII concentrates.

Factor VIII levels as low as 1% to 5% of normal are enough to reduce the severity of hemophilia in everyday life, but such patients are at increased risk of hemorrhage with surgery or trauma. Patients with factor levels of 6% to 30% have only mild disease that may go undiagnosed until adulthood. Nevertheless, they are at risk for excessive bleeding when undergoing a major surgical procedure. Female carriers of hemophilia A can also be at risk of excessive surgical bleeding. About 10% of female carriers have factor VIII activity below 30%.

Patients with severe hemophilia A have a significantly prolonged aPTT, whereas those with milder disease may an aPTT that is only a few seconds longer than normal. The PT is normal.

In the outpatient setting, hemophilia A is treated with either prophylactic factor VIII concentrates or emicizumab. Emicizumab is a recombinant humanized bispecific monoclonal antibody that binds to factors IXa and X simultaneously, bringing these two molecules together and essentially substituting factor VIIIa as a cofactor for factor IXa in activating factor X. When recommended, therapy is started with a loading dose of 3 mg/kg subcutaneously once weekly for 4 weeks. Subsequent maintenance dosing can be done using 1.5 mg/kg subcutaneously once per week, 3 mg/kg subcutaneously once every 2 weeks, or 6 mg/kg subcutaneously once every 4 weeks.

Management of anesthesia. Whenever surgery is necessary in a patient with hemophilia A, the factor VIII level must be brought to 80% to 100% prior to the major procedures and to 50% to 80% prior to minor procedures. There should also be preoperative assessment for the presence of factor VIII inhibitors, since up to 30% of patients with severe hemophilia A who have been exposed to factor VIII concentrate or recombinant factor VIII product will develop inhibitor antibodies that render administration of concentrate ineffective.

For patients with mild hemophilia A, an infusion of desmopressin (DDAVP) may be sufficient. This should be administered 30 to 90 minutes prior to surgery. DDAVP increases the level of factor VIII three- to fivefold, which may restore normal hemostasis. Preoperative use of DDAVP is only appropriate in patients who have had a trial demonstrating an adequate response to DDAVP infusion.

For patients with moderate to severe hemophilia A, correction of the coagulopathy requires an infusion of factor VIII concentrate preoperatively. Factor VIII concentrate should be administered 30 to 60 minutes preoperatively, and repeated infusions every 8 to 12 hours will be needed to keep the factor VIII level above 50% (given the half-life of factor VIII: ~12 hours). In children the half-life of factor VIII may be as short as 6 hours, which requires more frequent factor VIII infusions and laboratory assays to confirm efficacy. Peak and trough factor VIII levels should be measured to confirm the appropriate amount of factor VIII to be infused and the dosing interval. Therapy must be continued for up to 2 weeks postoperatively to avoid bleeding that could disrupt wound healing. Even longer periods of therapy may be required in patients who undergo bone or joint surgery. In this situation, 4 to 6 weeks of replacement therapy may be needed.

Patients on emicizumab should be treated with factor VIII concentrate if no inhibitors are present, while monitoring factor VIII levels.

Fresh frozen plasma and cryoprecipitate can also correct factor VIII levels. Fibrinolytic inhibitors such as ε-aminocaproic acid (EACA) and tranexamic acid can be given as adjunctive therapy for bleeding from mucous membranes and are particularly useful for dental procedures.

Congenital Factor IX Deficiency: Hemophilia B

Patients with hemophilia B have a clinical spectrum of disease similar to that found in hemophilia A. Factor IX levels below 1% of normal are associated with severe bleeding, whereas more moderate disease is seen in patients with levels of 1% to 5%. Patients with factor IX levels between 5% and 40% generally have very mild disease. Mild hemophilia (>5% factor IX activity) is often not detected until surgery is performed or the patient has a dental extraction. Similar to the laboratory findings in hemophilia A, patients with hemophilia B have a prolonged aPTT and a normal PT.

Management of anesthesia. General guidelines for management of patients with hemophilia B do not differ significantly from those for management of hemophilia A patients. Recombinant or purified factor IX product or factor IX–prothrombin complex concentrate is used to treat mild bleeding episodes or administered as prophylaxis for minor surgery. Caution is needed when using factor IX–prothrombin complex concentrates. These concentrates

can contain activated clotting factors. When given in amounts sufficient to increase factor IX levels to above 50%, there is an increased risk of thromboembolic complications, especially in patients undergoing orthopedic procedures. Therefore it is essential to use only purified factor IX or recombinant factor IX to treat patients undergoing major or orthopedic surgery and those with severe traumatic injuries or liver disease.

Purified factor IX concentrates or recombinant factor IX is used for several days to treat bleeding in patients with hemophilia B. Because of absorption into collagen sites in the vasculature, factor IX is less available than factor VIII, so dosing is approximately double that for factor VIII concentrates. Factor IX has a half-life of 18 to 24 hours, so repeat infusion of half of the original dose every 12 to 24 hours is usually sufficient to keep the factor IX plasma level above 50%.

Acquired Factor VIII or IX Inhibitors

Patients with hemophilia A are at significant risk of developing circulating inhibitors to factor VIII. This occurs in 30% to 40% of patients with severe hemophilia A. Patients with hemophilia B are less likely to develop inhibitors to factor IX, with only 3% to 5% of patients with hemophilia B developing inhibitors. A severe hemophilia-like syndrome can occur in genetically normal individuals because of the appearance of an acquired autoantibody to either factor VIII or factor IX. Such patients are usually middle-aged or older, with no personal or family history of abnormal bleeding, who experience sudden onset of severe spontaneous hemorrhage.

The diagnosis of an inhibitor is made using a Bethesda assay, which both identifies the inhibitor and quantifies it. The assay principle uses serial dilutions of patient plasma incubated at 37°C with pooled normal plasma and measures factor activity using an aPTT-based assay. Importantly, this type of aPTT-based assay cannot be used to diagnose or quantify inhibitors in individuals receiving emicizumab. Emicizumab will normalize the aPTT despite the presence of an inhibitor, making it appear that the inhibitor is absent or of markedly lower titer than it actually is. For individuals receiving emicizumab, inhibitor titer must be measured with a chromogenic assay specific for factor VIIIa activity, similar to testing factor VIII levels on emicizumab.

Management of anesthesia. Management of a hemophilia A patient with circulating factor VIII inhibitors will vary depending on whether the patient is a high or low responder. Low responders have low titers of inhibitors (<5 Bethesda units [BU]) and do not show anamnestic responses to factor VIII concentrates. High responders (>5 BU) have high titers of inhibitors and have dramatic anamnestic responses to therapy. Patients in the low-responder category can usually be managed with factor VIII concentrates. Larger initial and maintenance doses of factor VIII will be required, and frequent assays of factor VIII levels will be essential to guide therapy.

High responders cannot be treated with factor VIII concentrate. These patients represent a clinical challenge, and the use of inhibitor bypassing drugs is required. Such inhibitor bypassing drugs include activated prothrombin complex concentrates and recombinant factor VIIa (NovoSeven). NovoSeven (90–120 μg/kg preoperatively, then every 2 hours for the first 28 hours) and factor VIII inhibitor bypassing agent (FEIBA) in doses of 75 to 100 units/kg, then 70 units/kg every 6 to 8 hours for 3 days, are FDA approved for use in patients with factor VIII antibodies.

Although the thrombin formed via factor VIIa is not as strong as that seen with factor VIII therapy, recombinant factor VIIa therapy is successful in controlling bleeding in more than 80% of patients with factor VIII inhibitors.

Patients on emicizumab with inhibitors should be treated with FEIBA. Doses of FEIBA should be kept below 100 units/kg in a 24-hour period, and patients should be monitored closely for thrombotic events and thrombotic microangiopathy (TMA), possible in the setting of emicizumab use.

Hemophilia B patients with factor IX inhibitors can be managed in acute situations using recombinant VIIa (preferred) or a prothrombin complex concentrate.

Patients without a history of hemophilia can develop an acquired autoantibody to factor VIII or IX and experience life-threatening hemorrhage. Often they exhibit very high inhibitor levels. Treatment with recombinant factor VIIa or an activated prothrombin concentrate is the recommended approach as administration of factor VIII or IX alone may be effective.

Another option for a patient with or without hemophilia A and a high titer inhibitor is recombinant porcine factor VIII (susoctocog alfa). High factor infusion could be used temporarily, as a last resort, in cases of life-threatening bleeding if the current inhibitor titer is less than 5 BU or after plasmapheresis.

Factor XI Deficiency

The only other coagulation factor defect causing an isolated prolongation of the PTT and a bleeding tendency is factor XI deficiency. It is inherited as an autosomal recessive trait. Factor XI deficiency is much rarer than either hemophilia A or B, but it affects up to 5% of Jews of Ashkenazi descent from Eastern Europe. Generally the bleeding tendency is mild and may be apparent only during a surgical procedure. Hematomas and hemarthroses are very unusual, even in patients with factor XI levels below 5%.

Management of anesthesia. The treatment of factor XI deficiency depends on the severity of the deficiency and the bleeding history. Patients undergoing dental procedures can be treated exclusively with antifibrinolytic agents (tranexamic acid or EACA). Factor XI concentrates are reserved for patients with severe deficiency or history of major bleeding who are undergoing surgical procedures. An expectant management is acceptable also in patients where a bleeding risk is not deemed to be very high. Inhibitors are not routinely screened for preoperatively, given that most patients are not exposed to factor XI concentrates. However, in patients with known inhibitors, activated factor VII is required to treat bleeding.

Congenital Abnormalities in Fibrinogen

Hypofibrinogenemia and afibrinogenemia. Congenital abnormalities in fibrinogen production interfere with the final step in the generation of a fibrin clot. Disorders with decreased fibrinogen levels, either hypofibrinogenemia or afibrinogenemia,

are relatively rare conditions inherited as autosomal recessive traits. Patients with afibrinogenemia have a severe bleeding diathesis with both spontaneous and posttraumatic bleeding. The bleeding can begin during the first few days of life, and this condition may initially be confused with hemophilia. Hypofibrinogenemic patients usually do not have spontaneous bleeding but may have bleeding with surgery. Severe bleeding can be anticipated in patients with plasma fibrinogen levels below 50 to 100 mg/dL.

Dysfibrinogenemia. Production of an abnormal fibrinogen is a more common defect than very low levels of fibrinogen. Fibrinogen is synthesized in the liver under the control of three genes on chromosome 4. More than 300 different mutations producing dysfunctional and/or reduced amounts of fibrinogen have been reported. Many of these mutations are inherited as autosomal dominant traits. The clinical presentation of dysfibrinogenemia is highly variable. Patients who have both a reduced amount of fibrinogen and a dysfunctional fibrinogen (hypodysfibrinogenemia) usually have excessive bleeding. Most dysfibrinogenemic patients have abnormal coagulation tests but do not have clinical bleeding. Overall, approximately 60% of dysfibrinogenemias are clinically silent. The remainder can present as either a bleeding diathesis or, paradoxically, a thrombotic tendency. A small number of dysfibrinogenemias have been associated with spontaneous abortion and poor wound healing.

Laboratory evaluation of fibrinogen involves measurement of both the concentration and function of fibrinogen. The most accurate quantitative measurement of total fibrinogen is provided by immunoassay or a protein precipitation technique. Screening tests for fibrinogen dysfunction include the thrombin time and clotting time using a venom enzyme such as reptilase.

Management of anesthesia. Most patients with dysfibrinogenemia have no clinical disease. Patients with hypo- or afibrinogenemia who are symptomatic and at risk of bleeding during or after surgery require treatment with fibrinogen concentrates or cryoprecipitate. Fibrinogen concentrates are preferred, and target fibrinogen levels of >100 mg/dL for major surgery and >50 mg/dL for minor surgery are reasonable. Cryoprecipitate can be used if fibrinogen concentrate is not available and dosed 1 unit/10 kg of body weight for procedures with a minor risk of bleeding and 1 unit/5 kg of body weight for procedures with a higher risk of bleeding. Human fibrinogen concentrates are indicated for treating hypofibrinogenemia but not dysfibrinogenemia.

Antifibrinolytic agents such as tranexamic acid or EACA may be used to treat or prevent mucosal bleeding.

Factor XIII Deficiency

The stability of the fibrin clot is very important in hemostasis. Deficiency of factor XIII (fibrin-stabilizing factor) is a rare autosomal recessive disorder, with patients manifesting either A subunit or B subunit deficiency. Newborns may have persistent umbilical cord or circumcision-related bleeding. Others may demonstrate a severe bleeding diathesis characterized by recurrent soft tissue bleeding, poor wound healing, and a high incidence of intracranial hemorrhage. Blood clots form but are weak and therefore unable to maintain hemostasis. Fetal loss in women with factor XIII deficiency approaches 100% without replacement therapy.

Factor XIII deficiency should be considered in patients with a severe bleeding diathesis who have normal results on coagulation screening tests, including PT, PTT, fibrinogen level, platelet count, and platelet function assay. Clot dissolution in urea can be used as a screening test. Patients at risk of severe hemorrhage have factor XIII levels only 1% of normal. Those with factor XIII levels of 50% or more usually have no bleeding tendency.

Management of anesthesia. Several factor XIII concentrates are available for use as prophylaxis or treatment of these patients. Recombinant A subunit factor XIII (Tretten) and factor XIII concentrated and purified from plasma (Corifact) are available in the United States. The long half-life of factor XIII (11–14 days) allows it to be used once a month. Patients who have no access to factor XIII concentrate can be treated with fresh frozen plasma or cryoprecipitate. As with other factor deficiencies, antifibrinolytics can be used alone (minor bleeding) or in combination with factor replacement (major bleeding).

ARTERIAL COAGULATION

Disorders Affecting Platelet Number

The normal circulating platelet count is maintained within relatively narrow limits. Approximately one-third of platelets are sequestered in the spleen at any given time. Since a platelet has a life span of about 9 to 10 days, some 15,000–45,000 platelets/mm^3 must be produced each day to maintain a steady state.

General Concepts for Treating Thrombocytopenia

Regardless of the cause of thrombocytopenia, platelet transfusion is appropriate if the patient is experiencing a life-threatening hemorrhage, is bleeding into a closed space such as the cranium, or requires emergency surgery. Long-term management of the thrombocytopenia may require other therapeutic maneuvers to either improve platelet production or decrease platelet destruction.

Platelet transfusion therapy must be tailored to the severity of the thrombocytopenia, the presence of bleeding complications, and the patient's underlying disease. For minor surgery a platelet count as low as 20,000 to 30,000/mm^3 may be adequate. For major surgery the platelet count should be increased to 50,000/mm^3. However, for neurosurgical, eye, and neuraxial procedures, platelets should be approximately 100,000/mm^3. Each unit of single-donor apheresis platelets or 6 units of random-donor platelets increases the platelet count in a normal-sized adult by about 50,000/mm^3. If there is alloimmunization or increased platelet consumption, measurement of platelet counts 1 hour after transfusion and at frequent intervals thereafter is important in planning further platelet transfusion needs.

One unit of single-donor apheresis platelets is equivalent to a random-donor pool of 4 to 8 units of platelets. For patients who become alloimmunized to random-donor platelets, blood banks can provide HLA-matched, single-donor platelets. Random- and single-donor platelets do not need to be ABO compatible.

However, sufficient RBCs are transfused in the platelet pool to increase the risk of sensitization in Rh-negative patients. Therefore such patients, particularly women of childbearing age, should receive platelets from Rh-negative donors or be treated with $Rh_0(D)$ immunoglobulin (RhoGAM) after transfusion of Rh-positive product.

Patients with very low platelet counts (<15,000/mm^3) can experience significant bleeding from multiple sites, including the nose, mucous membranes, GI tract, skin, and vessel puncture sites. One sign that strongly suggests thrombocytopenia is the appearance of a petechial rash involving the skin or mucous membranes. This condition is most pronounced in the lower extremities because of the increased hydrostatic pressure in the legs. The differential diagnosis of thrombocytopenia is best organized according to the physiology of (1) platelet production, (2) distribution in the circulation, and (3) platelet destruction.

Congenital Disorders Resulting in Platelet Production Defects

Platelet production disorders may be caused by megakaryocyte hypoplasia or aplasia in the bone marrow.

Congenital hypoplastic thrombocytopenia with absent radii (TAR syndrome) is inherited in an autosomal recessive manner. Thrombocytopenia develops in the third trimester or soon after birth. The thrombocytopenia is initially severe (<30,000 platelets/mm^3) but gradually improves, approaching the normal range by age 2. These patients often have bilateral radial anomalies, and abnormalities of other bones may also occur.

The hematologic manifestations of Fanconi anemia do not usually appear until about age 7. Bone marrow shows reduced cellularity and reduced numbers of megakaryocytes. Stem cell transplantation is curative in the majority of children once severe bone marrow failure has developed.

Patients with May-Hegglin anomaly typically have giant platelets in the circulation and Döhle bodies (basophilic inclusions) in WBCs. Platelet production is variably ineffective, with one-third of patients having significant thrombocytopenia.

Wiskott-Aldrich syndrome is an X-linked disorder that presents with a combination of eczema, immunodeficiency, and thrombocytopenia. Circulating platelets are smaller than normal, function poorly because of granule defects, and have a reduced survival. Ineffective thrombopoiesis is the principal abnormality.

Patients with autosomal dominant thrombocytopenia have an increased megakaryocyte mass but ineffective platelet production and release macrocytic platelets into the circulation. Many of these patients also have nerve deafness and nephritis (Alport syndrome).

Acquired Disorders Resulting in Platelet Production Defects

A failure in platelet production can result from bone marrow damage. All aspects of normal hematopoiesis can be depressed, even to the point of bone marrow aplasia (aplastic anemia). A reduction in the marrow megakaryocyte mass can be seen in response to radiation therapy or cancer chemotherapy, as a result of exposure to toxic chemicals (benzene, insecticides) or alcohol, and as a complication of viral hepatitis. Infiltration of bone marrow by a malignant process can also disrupt thrombopoiesis. Hematopoietic malignancies, including multiple myeloma, acute leukemia, lymphoma, and myeloproliferative disorders, frequently produce platelet production defects.

Ineffective thrombopoiesis is also seen in patients with vitamin B_{12} or folate deficiency (caused by alcoholism) and defective folate metabolism. Marrow megakaryocyte mass is increased, but effective platelet production is reduced. This failure of platelet production is rapidly reversed by appropriate vitamin therapy. Recovery of the platelet count to normal occurs within days of initiating vitamin therapy, which makes platelet transfusion unnecessary in all but the most acute situations.

Management of Anesthesia

Platelet transfusions are the mainstay in management of patients with platelet production disorders. Patients with ineffective thrombopoiesis due to an intrinsic abnormality of megakaryocytes are treated like those with a production disorder when there is need for urgent surgery.

Nonimmune Platelet Destruction Disorders

Platelet consumption as a part of intravascular coagulation can be seen in several clinical settings. If the entire coagulation pathway is activated, the process is referred to as disseminated intravascular coagulation. DIC can be fulminant, with severe thrombocytopenia and markedly abnormal coagulation factor assays accompanied by bleeding, or it can be low grade with little or no thrombocytopenia and less tendency for bleeding. Platelet consumption can also occur as an isolated process, so-called platelet DIC. Viral infection, bacteremia, malignancy, high-dose chemotherapy, and vasculitis can result in sufficient endothelial cell damage to dramatically increase the rate of platelet clearance without full activation of the coagulation pathway. Basically this is an accentuation of the normal blood vessel repair process in which platelets adhere to exposed subendothelial surfaces and then aggregate with fibrinogen binding. With marked endothelial disruption, enough platelets can be consumed to result in thrombocytopenia. Blood vessel occlusion by platelet thrombi is unusual but can occur with severe vasculitis. Patients with acquired immunodeficiency syndrome (AIDS) can develop a consumptive thrombocytopenia with end-organ damage due to arterial thrombosis.

In addition to DIC, TMA is the most common cause of nonimmune platelet destruction. TMA can have several etiologies such as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), drug induced, or complement activated. HELLP syndrome is a common nonimmune cause of thrombocytopenia encountered in pregnancy. Although the underlying pathophysiology of each of these disorders is distinctly different, all of these entities can lead to thrombus formation and end-organ damage.

Thrombotic Thrombocytopenic Purpura

TTP is characterized by formation of platelet-rich thrombi in the arterial and capillary microvasculature, leading to

thrombocytopenia and microangiopathic hemolytic anemia. TTP is caused by a deficiency of ADAMTS 13 protease, whose usual function is to cut ultralarge vWF multimers into smaller pieces and prevent them from triggering formation of unnecessary blood clots. Its deficiency leads to accumulation of large vWF multimers and development of a microvasculopathy. Although this disease was classically described as a complex of five signs—fever, renal failure, thrombocytopenia, microangiopathic hemolytic anemia, and neurologic abnormalities—not all patients with TTP have all five signs. The presence of at least thrombocytopenia and microangiopathic hemolytic anemia suggest the diagnosis of TTP. TTP is caused either by presence of autoantibodies to the vWF protease ADAMTS 13 (acquired form) or a mutation leading to decreased levels of the same enzyme (hereditary form). The diagnosis is confirmed by measuring a reduced ADAMTS 13 activity level (<10% of normal).

TTP is a medical emergency, and plasma exchange should be initiated as soon as the diagnosis is suspected based on a specific scoring system, without waiting for ADAMTS 13 levels. Glucocorticoids and rituximab are also administered in conjunction with plasma exchange in patients with high score and/or proven ADAMTS 13 deficiency. Patients with neurologic findings or high presenting troponin levels are candidates for caplacizumab. Caplacizumab is a humanized monoclonal antibody fragment (a bivalent, variable-domain-only fragment) that binds vWF and blocks its interaction with platelet glycoprotein Ib-IX-V, therefore decreasing the risk of microthrombi formation. Plasma exchange can be discontinued as soon as clinical improvement occurs; however, medical therapies should be continued until ADAMTS activity recovers to 20% to 30%.

Drug-Induced TMA

Therapy with certain drugs such as quinine, trimethoprim-sulfamethoxazole, oxaliplatin, gemcitabine, and quetiapine can result in an immune-mediated TMA. Other drugs, such as mitomycin C, cyclosporin A, tacrolimus, interferon and ecstasy cause a non-immune mediated TMA. Treatment relies on discontinuing the offending agent and supportive measures.

Hemolytic Uremic Syndrome

HUS is a disorder similar to TTP that can be either hereditary (complement deficiency mediated) or acquired (infectious etiology). Historically it was seen in children who come for treatment of bloody diarrhea due to infection with a particular strain of *Escherichia coli* that produces a Shiga-like toxin. However, other agents such as *Streptococcus pneumoniae*, HIV, and influenza virus H1N1 can lead to HUS. Acute renal failure dominates the presentation. Thrombocytopenia and anemia are less severe than with TTP, and neurologic signs are absent. Patients are treated with fluids and RBC and platelet transfusion as necessary. Most children recover spontaneously but may require hemodialysis for a period. The mortality rate is less than 5%. HUS generally requires supportive treatment (IV fluids, RBC or platelet transfusions) and, rarely, temporary hemodialysis.

HELLP Syndrome

Thrombocytopenia is a frequent complication of pregnancy. Mild thrombocytopenia (platelet counts between 70,000 and 150,000/mm^3) is seen in about 6% of women nearing delivery, and this represents a physiologic change similar to the dilutional anemia of pregnancy. Thrombocytopenia associated with hypertension is observed in 1% to 2% of pregnancies, and about half of these women with preeclampsia will develop a DIC-like condition with severe thrombocytopenia (platelet counts of 20,000–40,000/mm^3) at the time of delivery. This is referred to as HELLP syndrome when the combination of red cell hemolysis (H), elevated liver enzyme levels (EL), and low platelet count (LP) is present. Physiologically, HELLP syndrome resembles TTP. Control of the hypertension and delivery of the child are usually enough to bring this process to a halt. However, a few patients will go on to develop TTP following delivery. Postpartum TTP is a life-threatening illness with a poor prognosis. Treatment with both plasma exchange and IV immunoglobulin has yielded variable results.

Management of Anesthesia in Nonimmune Platelet Destruction Disorders

Proper management of patients with platelet destruction disorders depends on the diagnosis of the hematologic disorder. Individuals who have nonimmune destruction as a part of DIC may require supportive therapy with platelet and plasma transfusions, but the only truly effective therapy is treatment of the underlying cause of DIC. If the primary condition causing DIC can be corrected, the levels of coagulation factors and the platelet count will return to normal.

Patients with TTP should receive platelet transfusions only for life-threatening bleeding. There is potential for significant harm from platelet transfusion with these conditions. Platelet transfusion may cause further thrombosis and end-organ damage due to marked platelet activation and aggregation. Surgery should be delayed whenever possible until the underlying disorder is controlled.

HUS and HELLP syndrome present a different therapeutic challenge. HUS in children can usually be managed without plasmapheresis, although dialysis may be necessary if renal failure is severe. HELLP syndrome, like preeclampsia, typically resolves with delivery of the baby. However, a small number of women will develop a TTP-like syndrome postpartum.

Autoimmune Platelet Destruction Disorders

Thrombocytopenia is a common manifestation of autoimmune disease. The severity of this thrombocytopenia is highly variable. In some conditions the platelet count can be as low as 1000 to 2000/mm^3. In other conditions the ability of megakaryocytes to increase platelet production can result in a compensated state, with platelet counts ranging from 20,000/mm^3 to near-normal levels.

The diagnosis of immune platelet destruction is usually made from the clinical presentation, the finding of an increased number of reticulated (RNA-containing) platelets in the peripheral blood smear, and demonstration of an increase in both the marrow megakaryocyte number and the number of

chromosome sets in these megakaryocytes (ploidy). Expansion of the megakaryocyte mass in the marrow is evidence that platelet production has increased markedly in an attempt to compensate for shortened platelet survival in the circulation.

Thrombocytopenic Purpura in Adults

The differential diagnosis of autoimmune thrombocytopenia in adults includes exposure to potentially toxic drugs, receipt of blood products, and viral infection.

Posttransfusion purpura. Adults can develop posttransfusion purpura (PTP) after exposure to a blood product, usually RBCs or platelets. Multiparous women negative for platelet antigen A1 (PlA1) are at greatest risk. A potent alloantibody with PlA1 specificity is detected in the plasma. The antibody destroys both the PlA1-positive transfused platelets and bystander destruction of the patient's own PlA1-negative platelets, leading to thrombocytopenia. PTP has been reported in both men and women; the female-to-male ratio is approximately 26:1. The preferred therapy for PTP is intravenous immunoglobulin (IVIG).

Drug-induced autoimmune thrombocytopenia. Several drugs can produce immune thrombocytopenia. Quinine and quinidine are the best known and studied. Clinically, patients show severe thrombocytopenia, with platelet counts below 20,000/mm^3. These drugs act as haptens to trigger antibody formation and then serve as obligate molecules for antibody binding to the platelet surface. Thrombocytopenia can also occur within hours of a first exposure to a drug because of preformed antibodies. This has been reported with varying frequency with abciximab (ReoPro) and other glycoprotein IIb/IIIa inhibitors. Other drugs, such as α methyldopa, sulfonamides, and gold salts also stimulate autoantibody production.

Heparin-induced thrombocytopenia. The association of heparin with thrombocytopenia deserves special discussion. Heparin-induced thrombocytopenia (HIT) can take one of several forms. A modest decrease in the platelet count, HIT type 1 (nonimmune HIT) may be observed in most patients during the first day of therapy with full-dose unfractionated heparin. This condition is caused by passive heparin binding to platelets, which results in a modest shortening of the platelet life span. The effect is transient and clinically insignificant.

A second form of HIT, type 2 (immune-mediated HIT), is much more important. In this type of HIT, antibodies form to the heparin–platelet factor 4 complex, and these antibodies are capable of binding to platelet receptors and inducing platelet activation and aggregation. Platelet activation results in further release of heparin–platelet factor 4 and the appearance of platelet microparticles in the circulation. These exacerbate this procoagulant state. In addition, heparin–platelet factor 4 complex binds to endothelial cells and stimulates thrombin production. This leads to both an increased clearance of platelets, with resultant thrombocytopenia, and venous and/or arterial thrombus formation, with the potential for both severe end-organ damage and thromboses in unusual sites such as the adrenal gland, portal vein, and skin.

The incidence of HIT type 2 varies with the type and dose of heparin and the duration of heparin therapy. Between 10% and 15% of patients receiving bovine unfractionated heparin develop an antibody. Fewer than 6% of patients receiving porcine heparin develop antibodies. The risk of heparin-induced thrombosis is lower than the incidence of antibody formation. Fewer than 10% of those who develop an antibody to the heparin–platelet factor 4 complex will experience a thrombotic event. However, the risk varies considerably with the clinical situation and can exceed 40% in the period after orthopedic surgery. Some studies have suggested that the presence of the HIT antibody has a negative impact on clinical outcome even in the absence of overt thrombosis. HIT antibody–positive patients undergoing coronary artery bypass surgery or receiving heparin therapy for unstable angina have been reported to have a significantly higher incidence of adverse events, including stroke, myocardial infarction, prolonged hospitalization, and death.

Immune-mediated HIT occurs between days 5 and 10 of heparin use. There are two variants: an early-onset HIT that occurs in patients exposed to heparin within the previous 3 months and a delayed-onset HIT that appears after heparin is discontinued. The diagnosis of HIT is based on a scoring method called the 4Ts system that considers the degree of thrombocytopenia, the timing of the platelet reduction, the presence of thrombosis or other sequelae, and the presence of other causes of thrombocytopenia (Table 23.3). A high index of suspicion should prompt performance of an antiplatelet factor 4–heparin enzyme immunoassay and a platelet function assay.

Patients who receive full-dose unfractionated heparin for longer than 5 days or who have previously received heparin should be routinely monitored with measurement of the platelet count every other day. A decrease in the platelet count of more than 50%, even if the absolute platelet count remains within the normal range, can signal the appearance of HIT type 2 antibodies. These significant decreases in platelet count mandate discontinuation of heparin therapy and substitution of a direct thrombin inhibitor for continued anticoagulation. If heparin is continued, even at low doses, or even if a low-molecular-weight heparin (LMWH) were to be substituted, there is still significant risk of a major thrombotic event. To prevent life-threatening thromboembolic events in patients with HIT type 2, all forms of heparin must be stopped immediately. Any delay can put a patient at increased risk of thrombosis. Substitution of LMWH for unfractionated heparin is not an option because there is significant antibody cross-reactivity. Patients with a suspected or confirmed episode of HIT should be started immediately on a direct thrombin inhibitor (IV bivalirudin or argatroban, or oral dabigatran) or anti-Xa inhibitor (subcutaneous fondaparinux or oral agents [apixaban, rivaroxaban, edoxaban]) even in the absence of a thrombotic event. Patients with confirmed HIT (positive antibodies) should have a lower extremity venous thromboembolism ruled out, even in the absence of symptoms. Warfarin is an option for the outpatient setting but should be started only after full anticoagulation with a different agent is established and the platelet count is greater than 100,000/mL. Another option is continuing the direct oral anticoagulant (DOAC).

TABLE 23-3 4Ts Scoring System for Heparin-Induced Thrombocytopenia (HIT)

Category	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count decreased >50% from baseline and platelet nadir ≥20,000/mm³	Platelet count decreased 30–50% from baseline or platelet nadir 10,000–13,000/mm³	Platelet count decreased <30% from baseline or platelet nadir <10,000/mm³
Timing of platelet decrease	Clear onset between days 5 and 10 of heparin exposure or platelet decrease in <1 day with heparin exposure within prior 30 days	Decrease in platelet counts consistent with onset between days 5 and 10 of heparin exposure, but timing is not clear because of missing platelet counts or onset after day 10 of heparin exposure or decrease in platelet counts in <1 day with prior heparin exposure between 30 and 100 days earlier	Platelet count decrease within 4 days of heparin exposure
Thrombosis or other sequelae	New thrombosis, skin necrosis, or acute systemic reaction after unfractionated heparin exposure	Progressive/recurrent thrombosis or unconfirmed but clinically suspected thrombosis	No thrombosis or previous heparin exposure
Other causes of Thrombocytopenia	None apparent	Possible other causes present	Probable other causes present

The 4Ts score is assigned by summing the values for each of the four categories. A score of 1, 2, or 3 is considered to indicate low probability of HIT; 4 or 5 indicates intermediate probability of HIT; and 6, 7, or 8 indicates high probability of HIT.
Data from Crowther MA, Cook DJ, Albert M, et al. The 4Ts scoring system for heparin-induced thrombocytopenia in medical-surgical intensive care unit patients. *J Crit Care*. 2010;25:287-293.

Oral anticoagulation with a nonheparin product should be continued at least until the platelet count normalizes (if no thrombosis) or 3 months (if thrombosis is present).

An acute form of HIT type 2 can occur when heparin therapy is restarted within 20 days of a previous exposure. If HIT antibodies are present, the patient in whom heparin therapy is restarted can exhibit an acute drug reaction with abrupt onset of severe dyspnea, rigors, diaphoresis, hypertension, and tachycardia. Such patients are at extreme risk of fatal thromboembolism if heparin administration is continued.

More recently, autoimmune HIT has been described. A delayed onset presents with thrombocytopenia and/or thrombosis 5 or more days after heparin has been withdrawn. Refractory or persistent HIT refers to HIT with persistent thrombocytopenia and/or thrombosis that lasts for weeks after stopping heparin. Spontaneous HIT refers to HIT that occurs in the absence of recent heparin exposure. Patients with persistent thromboses and one of the autoimmune forms of HIT benefit from treatment with IVIG in addition to a nonheparin anticoagulant.

Management of anesthesia. Platelet transfusions are appropriate if a patient with thrombocytopenia is experiencing life-threatening hemorrhage or is bleeding into a closed space. Platelet transfusion therapy must be tailored to the severity of the thrombocytopenia, the presence of bleeding complications, and the patient's underlying disease. Prophylactic platelet transfusion should be avoided in patients with HIT type 2, since transfused platelets can increase the risk of thrombosis. However, platelet transfusions are recommended for patients with type 2 HIT who are bleeding and have platelet counts less than 50,000/mL. In patients with autoimmune thrombocytopenia due to drug ingestion, the most important management step is discontinuation of the offending drug. Corticosteroid therapy may speed recovery in patients with an idiopathic thrombocytopenic purpura–like presentation. The speed of recovery depends on both the clearance rate of the offending drug and the ability of marrow megakaryocytes to proliferate and increase platelet production. Even if the platelet count is very low, bleeding is unlikely, and patients can be allowed to recover without platelet transfusion.

HIV-infected thrombocytopenic patients who require urgent surgery should be given platelet transfusions as appropriate. In preparation for elective surgery in patients who develop thrombocytopenia early in their HIV/AIDS disease course, consideration may be given to treatment with zidovudine for a period before surgery. About 60% of these patients will have a favorable response, and up to 50% will have long-lasting improvement in their platelet counts. The effect, however, is not immediate. It can take up to 2 months before the platelet count improves. If patients do not respond to zidovudine, splenectomy can be helpful in reducing significant thrombocytopenia in more than 85% of patients, especially if done early in the course of the thrombocytopenia. Corticosteroids, IVIG, and IV $Rh_0(D)$ immunoglobulin have also been used in patients with AIDS. Later in their disease progression, HIV-infected patients can develop a platelet production defect that responds only to platelet transfusion therapy.

Cardiac surgery represents a particular challenge for patients with HIT, since heparin is the ideal anticoagulant for use during cardiopulmonary bypass. Cardiac surgery should be delayed until the HIT episode resolves; if this is not possible, bivalirudin, a direct thrombin inhibitor, should be used for anticoagulation during cardiopulmonary bypass. In situations in which the HIT episode has resolved, antibodies have disappeared, and sufficient time has passed since the diagnosis (>100 days), heparin could be safely used just for the cardiopulmonary bypass period, since the likelihood of an anamnestic response is low.

Idiopathic thrombocytopenic purpura. Thrombocytopenia unrelated to drug exposure, infection, or autoimmune disease is generally classified as autoimmune idiopathic thrombocytopenic

purpura (ITP). This diagnosis is made only by excluding all other causes of nonimmune and immune platelet destruction, in a patient with isolated thrombocytopenia. Presence of antiplatelet antibodies is not necessary for diagnosis. Most adults with the disorder proceed to a chronic form of ITP in which a continued high level of marrow platelet production is required to maintain a chronically low to near-normal platelet count in the face of a shortened platelet life span. This condition is characterized by a high level of platelet destruction that is balanced by high marrow production of platelets that have better-than-normal function. Severe bleeding does not occur until the platelet count drops below 10,000/mm^3. Patients with chronic ITP have platelet counts of 20,000 to 100,000/mm^3.

Platelet survival in severely affected patients can be measured in hours rather than days, with destruction occurring mainly in the spleen. Transfused platelets also have a shortened life span. Some patients demonstrate only a modest shortening of platelet survival. Although most ITP patients receiving platelet transfusions rapidly destroy the infused platelets, up to 30% of patients do demonstrate near-normal posttransfusion platelet survival.

Management of anesthesia. Severe ITP (platelet count <30,000/mL) associated with bleeding in adults should be treated as a medical emergency, with administration of high-dose corticosteroids. If there is a need for emergency surgery or clinical evidence of intracranial hemorrhage, the patient should also be given IV immunoglobulin and platelet transfusions at least every 8 to 12 hours, regardless of the effect on the platelet count. Some patients who receive platelet transfusions will show a relatively normal posttransfusion platelet count and reasonable platelet survival. However, even when there is no posttransfusion improvement in the platelet count, sufficient numbers of the transfused platelets may survive and improve hemostasis.

Some adults do not respond to corticosteroids and develop chronic ITP. If ITP persists for longer than 3 to 4 months, it is extremely unlikely the patient will spontaneously recover. Patients with chronic ITP should be monitored only if platelet counts are less than 30,000/mL. Second-line therapies such as splenectomy and rituximab or thrombopoietin receptor agonists can be considered if platelet counts are persistently lower. Splenectomy may result in a permanent remission of the ITP; however, it is important to immunize the patient with pneumococcal, meningococcal, and *Haemophilus influenzae* vaccines before surgery to reduce the risk of postsplenectomy sepsis. Thrombopoietin receptor agonist (romiplostim) can be used as a temporizing measure when an increased platelet count is desired.

Prior to elective surgical procedures, steroids, IVIG, or romiplostim can be used to help raise the platelet count to the desired level preoperatively. Generally the agent is chosen based on its effectiveness in a particular patient.

Management of chronic ITP in pregnancy deserves special attention. Most pregnant women with chronic ITP can be managed with no medication, modest amounts of prednisone, or intermittent use of IVIG. If the thrombocytopenia becomes more severe, a higher daily dose of corticosteroids together with weekly immunoglobulin infusion, especially during the last few weeks of pregnancy, may be needed to prevent maternal bleeding. Even though the mother has severe ITP, most children are born with normal platelet counts. Platelet counts in neonates normally decrease for about 1 week after delivery. Therefore in children at risk, platelet counts should be checked every 2 to 3 days until the platelet count begins to increase.

Qualitative Platelet Disorders

Abnormalities in platelet function are often noted for the first time as a complication of an acute illness or surgery. However, there may be several factors that could play a role in determining the severity of the bleeding tendency. Initial treatment should address as many potential contributing factors as possible and include discontinuation of drugs that inhibit platelet function, empirically replacing vWF or treating with desmopressin, and even transfusing platelets. Although this approach lacks precision, it is usually effective. Then after the acute event is over a precise diagnosis of the cause of the bleeding can be made.

Congenital Disorders Affecting Platelet Function

Von Willebrand disease. Von Willebrand disease (vWD) is the most common inherited abnormality affecting platelet function. It is inherited as either an autosomal dominant or autosomal recessive trait. Severe vWD with life-threatening bleeding is seen in fewer than five individuals per million in Western countries.

Patients with vWD usually experience mucocutaneous bleeding (typically epistaxis), easy bruising, menorrhagia, and gingival and GI bleeding. The number of patients with mild to moderate reductions in vWF activity far exceeds the number of patients with overt clinical bleeding. Hence there will be a marked overdiagnosis of vWD if the measured vWF level is the sole criterion used for diagnosis. The diagnosis of "clinically important" vWD should be limited to those cases in which abnormal bleeding occurs. If vWD is considered to be a contributing factor in a bleeding patient, it should be treated empirically. Laboratory evaluation can be postponed until the patient is in stable condition and has not received blood products or drugs for several weeks.

Screening should be prompted by a positive family history of vWD, personal history of mucocutaneous bleeding, mild thrombocytopenia or prolonged aPTT, or hemophilia A in a female patient. Obtaining an accurate bleeding history is of paramount importance. Screening laboratory evaluation for vWD should include vWF antigen, vWF activity, and factor VIII levels in addition to routine coagulation tests. Patients with vWD generally will have a normal CBC and a normal platelet count, with the exception of those with type 2B vWD, most of whom will have mild thrombocytopenia. The PT is normal and the aPTT may be normal or prolonged, depending on the degree of reduction of the factor VIII level.

Patients with a positive family or personal diagnosis of bleeding are diagnosed with vWD if their vWF (antigen or activity) is less than 30% and "low" vWD if vWF (antigen or activity) is 30% to 50%.

All vWD-diagnosed patients should have additional specialty testing aimed to detect the type (e.g., vWF multimer analysis).

Type 1 disease. Type 1 vWD (80% of cases) represents a quantitative defect in plasma vWF levels. Clinical severity is quite variable but generally correlates with the plasma levels of vWF and factor VIII. In patients/families with a history of repeated and severe bleeding episodes, vWF antigen and vWF activity are usually reduced to less than 15% to 25% of normal. These individuals with a history of severe disease should be treated for any bleeding episode and given prophylactic treatment for even minor surgical procedures.

Type 2 disease. Type 2 vWD is characterized by a qualitative defect in plasma vWF. This can involve a reduction in the number of large vWF multimers or variable changes in vWF antigen and factor VIII binding. The absence of large multimers results in a significant decrease in vWF activity.

Type 3 disease. Type 3 vWD is characterized by the virtual absence of circulating vWF antigen and very low levels of both vWF activity and factor VIII (3–10% of normal). These patients experience severe bleeding with mucosal hemorrhage, hemarthroses, and muscle hematomas reminiscent of those seen in hemophilia A or B.

Management of anesthesia. The type of vWD and its severity, as well as the nature, urgency, and location of the surgical procedure, factor into therapeutic management of a patient with vWD. Treatments for this disorder include desmopressin, a drug that increases plasma levels of endogenous vWF, and vWF concentrates.

DDAVP (desmopressin) is a synthetic analogue of the antidiuretic hormone vasopressin; when given intravenously, it stimulates release of vWF from endothelial cells to produce an immediate increase in plasma vWF and factor VIII activity. This improves platelet function. It can be very effective in correcting the bleeding defect in vWD. Platelet function abnormalities resulting from aspirin, glycoprotein IIb/IIIa inhibitors, uremia, or liver disease can also be partially corrected by desmopressin-stimulated release of very large vWF multimers.

Success in treating vWD patients with desmopressin depends on the disease type and the bleeding risk of the surgical procedures. DDAVP is indicated only for minor procedures. Patients with type 1 vWD show the best response. The value of treatment with desmopressin in patients with type 2 disease is less certain as it can cause thrombocytopenia, but it can be of benefit in patients with type 2A/2M and 2N. Patients with type 3 vWD do not respond to desmopressin because these patients lack endothelial stores of vWF. Both vWF and factor VIII must be provided to treat bleeding in patients with type 3 vWD.

Desmopressin is available in both IV and intranasal preparations. It can be administered intravenously in a dose of 0.3 μg/kg. A highly concentrated nasal spray (Stimate) is also available and can be self-administered by women with type 1 vWD for management of menorrhagia. This nasal spray can also be effective in controlling bleeding associated with tooth extraction or minor surgery.

Desmopressin therapy is most effective in treating mild bleeding episodes or in preventing bleeding during minor surgery. Patients with baseline vWF and factor VIII levels above 10 to 20 IU/dL do best with this drug, demonstrating a three- to five-fold increase in vWF levels. However, even if the response is suboptimal, bleeding may be partially contained, and total blood loss and the need for transfusion can be reduced. A disadvantage of desmopressin is its relatively short-lived effect, and dosing may need to be repeated at 12 and 24 hours. The response can decrease with repeated doses because of development of tachyphylaxis. Moreover, severe hyponatremia can occur with repeated doses. In situations where control of bleeding is critical (e.g., following major surgery), desmopressin administration by itself may be inadequate, and vWF replacement may be necessary.

All types of vWD can be treated with vWF concentrates, and these are preparations of choice for any major surgery regardless of the type. In addition, any surgeries in patients with type 2N or 3 require administration of vWF concentrates. A recombinant vWF preparation (Vonvendi) does not contain factor VIII. For major surgeries, factor VIII concentrate may need to be coadministered but can be omitted if the recombinant vWF was given 12 hours before allowing for endogenous rise in factor VIII. Three other preparations (Humate-P, Alphanate, and Wilate) are available in the United States, and they all contain vWF/factor VIII replacement therapy prepared from pooled human plasma. They differ in their vWF/factor VIII ratios and the content of large vWF multimers.

Antifibrinolytics can be used as adjunctive therapy during surgical procedures.

Acquired Abnormalities of Platelet Function

Acquired platelet dysfunction is seen in association with hematopoietic disease as part of a systemic illness or as a result of drug therapy.

Myeloproliferative disease. Patients with myeloproliferative disorders such as polycythemia vera, myeloid metaplasia, idiopathic myelofibrosis, essential thrombocythemia, and chronic myelogenous leukemia frequently exhibit abnormal platelet function. Some patients have very high platelet counts and can demonstrate either abnormal bleeding or a tendency for arterial or venous thrombosis. In patients with polycythemia vera, expansion of the total blood volume and an increase in blood viscosity may contribute to the thrombotic risk. The most consistent laboratory abnormalities in patients with myeloproliferative disorders and bleeding are defects in epinephrine-induced platelet aggregation and in dense granule and α-granule function. Bleeding from an acquired form of vWD (due to loss of higher-molecular-weight vWF multimers) may also be observed.

Dysproteinemia. Abnormal platelet function, including defects in adhesion, aggregation, and procoagulant activity, are observed in patients with dysproteinemia. Almost one-third of patients with Waldenström macroglobulinemia or IgA myeloma have a demonstrable defect in platelet function. Multiple myeloma patients are less often affected. The concentration of the monoclonal protein spike appears to correlate with the abnormality in platelet function.

Uremia. Uremic patients consistently show a defect in platelet function that correlates with the severity of the uremia and

anemia. It appears that the uncleared metabolic product guanidinosuccinic acid acts as an inhibitor of platelet function by inducing endothelial cell nitric oxide release. Platelet adhesion, activation, and aggregation are abnormal, and thromboxane A_2 generation is decreased.

The abnormal bleeding in most patients with uremia is corrected by hemodialysis. Interestingly, measures of platelet function improve with either RBC transfusion or erythropoietin therapy. For acute bleeding episodes, desmopressin can transiently improve platelet function.

Liver disease. The most likely cause of hemorrhage in severe liver disease is a discrete anatomic defect such as bleeding varices or a gastric or duodenal ulcer. However, if a cirrhotic patient has widespread bleeding, including ecchymoses and oozing from puncture sites, a coagulopathy should be considered. Such patients can have multiple defects in coagulation. Thrombocytopenia related to hypersplenism is common. Platelet dysfunction resulting from high levels of circulating fibrin degradation products can increase the bleeding tendency. In addition, reduced production of factor VII and/or low-grade chronic DIC with increased fibrinolysis can add to the coagulopathy.

Thrombocytopenic patients due to liver disease should receive platelet transfusions preoperatively to increase the platelet count to greater than 50,000/mL. Two thrombopoietin receptor agonists (avatrombopag and lusutrombopag) are FDA approved for preoperative use in patients with liver disease. They are indicated in an individual with liver disease and severe thrombocytopenia (i.e., platelet count <50,000/mL) undergoing a scheduled invasive procedure with intermediate to high bleeding risk (e.g., spinal surgery, cardiac surgery, large polypectomy, liver biopsy), provided there was sufficient time (10–13 days) to start the drug and to document an increase in the platelet count to 50,000/mL and above.

Drug-induced platelet dysfunction. Several classes of drugs can affect platelet function (Table 23.4). Aspirin and other NSAIDs have a well-recognized impact on platelet function. Aspirin is a powerful inhibitor of platelet thromboxane A_2 synthesis because of its irreversible inhibition of cyclooxygenase function. NSAIDs such as indomethacin, ibuprofen, and sulfinpyrazone also inhibit platelet cyclooxygenase, but their effect is reversible and lasts only as long as the particular drug is in the circulation. Such drugs are weak inhibitors of platelet function and are not usually associated with significant clinical bleeding. However, they can contribute to bleeding when other aggravating factors such as treatment with anticoagulants, a GI disorder, or surgery are present. Certain foods, food additives, vitamins, and herbal products (e.g., vitamins C and E, omega-3 fatty acids, Chinese black tree fungus) can also reversibly inhibit platelet function through the cyclooxygenase pathway.

The impact of antibiotics on platelet function can be a major contributor to hemorrhage in critically ill patients. The penicillins, including carbenicillin, penicillin G, ticarcillin, ampicillin, nafcillin, and mezlocillin, can interfere with both platelet adhesion and platelet activation and aggregation. They bind to the platelet membrane and interfere with vWF binding and the response of platelets to agonists such as ADP and epinephrine. Significant clinical bleeding can occur if these antibiotics are administered in high dosages.

TABLE 23.4 Drugs That Inhibit Platelet Function

Strong Association
- Aspirin (and aspirin-containing medications)
- Clopidogrel, ticlopidine
- Abciximab
- Nonsteroidal antiinflammatory drugs: naproxen, ibuprofen, indomethacin, phenylbutazone, piroxicam, ketorolac

Mild to Moderate Association
- Antibiotics, usually only in high dosages
  - Penicillins, including carbenicillin, penicillin G, ampicillin, ticarcillin, nafcillin, mezlocillin
  - Cephalosporins
  - Nitrofurantoin
- Volume expanders: dextran, hydroxyethyl starch
- Heparin
- Fibrinolytic agents: ε-aminocaproic acid

Weak Association
- Oncologic drugs: daunorubicin, mithramycin
- Cardiovascular drugs: β blockers, calcium channel blockers, nitroglycerin, nitroprusside, quinidine
- Alcohol

Volume expanders such as dextran can interfere with platelet aggregation and procoagulant activity when infused in large amounts. This can be a significant disadvantage in the trauma setting but can be very advantageous in the vascular surgery setting to prevent vascular thrombosis. Hydroxyethyl starch is less likely to interfere with platelet function but can cause a detectable defect if given in amounts in excess of 2 L.

Management of Anesthesia in Patients With Qualitative Platelet Disorders

The therapeutic goal in treating qualitative platelet disorders is less exact than in disorders of thrombocytopenia. Because platelets are dysfunctional, the absolute platelet number does not predict bleeding risk. Treatment with desmopressin may improve a mild to moderate platelet defect, especially if the risk of bleeding is relatively minor. If the bleeding risk is more substantial, platelet transfusion may be required. Platelet function assays or the thromboelastogram may be used to measure the status of coagulation but may not guarantee adequacy of platelet function for the challenge of surgery. As a general rule, sufficient platelet transfusions to increase the percentage of normally functioning platelets to about 10% to 20% of all platelets should be sufficient to provide adequate overall platelet function for surgery.

Platelets become quite dysfunctional in the setting of hypothermia (temperature <35°C) and acidosis (pH <7.3), and platelets transfused into a patient with either or both of these conditions will rapidly become dysfunctional as well.

HYPERCOAGULABLE DISORDERS

Causes of hypercoagulability can be divided into two major classes: (1) congenital hypercoagulability caused by one or more genetic abnormalities, often referred to as thrombophilia, and (2) acquired or environmentally induced hypercoagulability.

Heritable Causes of Hypercoagulability

Hereditary conditions predisposing to venous thromboembolism (VTE) can be divided into conditions that decrease endogenous antithrombotic proteins or increase prothrombotic proteins (Table 23.5).

Thrombophilia Due to Decreased Antithrombotic Proteins

Hereditary antithrombin deficiency. Antithrombin (AT) III is the most important defense against clot formation in healthy blood vessels or at the perimeter of a site of active bleeding. AT III deficiency is inherited as an autosomal dominant trait. Homozygous AT deficiency is not compatible with life. Heterozygous patients have an AT III level between 40% and 70% of normal. Individuals who are heterozygous for AT III deficiency are about 20 times more likely than normal individuals to develop venous thromboembolism at some point in their lives. The thrombotic event usually occurs in association with some trigger that further increases hypercoagulability. In addition, an acquired AT III deficiency can occur in patients with DIC, liver disease, extracorporeal membrane oxygenation, nephrotic syndrome, or asparaginase therapy.

In addition to anticoagulation, anesthetic management for these patients should include maintaining the AT III level above 80% until 5 days after surgery. This is done by administering AT III concentrates. Thrombate III is made from human plasma, and ATryn is a recombinant form of AT III produced by genetically engineered goats that have been modified so they secrete AT III in their milk.

Hereditary protein C and protein S deficiency. Hereditary deficiency of protein C and protein S adversely affects thrombin regulation by restricting the activity of thrombin already formed and interfering with the ability to limit the amount of thrombin generated. The risk of VTE is about the same as with AT III deficiency.

Synthesis of both protein C and protein S is vitamin K dependent, so individuals who are protein C deficient are at particular risk of thrombosis if warfarin therapy is initiated in the absence of protective anticoagulation with heparin. Specifically, during the first days of warfarin treatment, before inhibition of the vitamin K–dependent clotting factors is sufficient to provide the intended anticoagulation, modest suppression of protein C synthesis may compound the already subnormal protein C levels and result in greater hypercoagulability. In addition to therapy to prevent or treat VTE (with warfarin or a DOAC), patients with protein C deficiency can benefit from purified plasma-derived protein C concentrate (Ceprotin).

TABLE 23.5 Major Hereditary Disorders Linked to Hypercoagulability[a]

Disorder	Prevalence in Healthy Controls (%)	Prevalence in Patients With First DVT (%)	Likelihood of DVT by Age 60 (%)
Antithrombin deficiency	0.2	1.1	62
Protein C deficiency	0.8	3	48
Protein S deficiency	0.13	1.1	33
Factor V Leiden	3.5	20	6
Prothrombin 20210A	2.3	18	<5

DVT, Deep vein thrombosis.
[a]All values pertain to the heterozygous state of the given condition.

Thrombophilia Due to Increased Prothrombotic Proteins

Factor V Leiden. Factor V Leiden differs from normal factor V because of a genetic mutation that makes it very resistant to inactivation. Therefore factor V Leiden stays active in the circulation longer than normal and promotes more thrombin generation.

Factor V Leiden carries a low to intermediate procoagulant risk. Patients who are heterozygous for factor V Leiden have a 5- to 7-fold increased risk of VTE, whereas the risk in homozygous individuals is increased up to 80-fold. The prevalence of factor V Leiden varies considerably in different ethnic populations. It is present in 5% of people of Northern European descent but only rarely in those of African or Asian descent. Therefore depending on the ethnic makeup of the community, up to 1 in 20 patients coming for routine surgery could be expected to have some degree of increased risk of VTE attributable to factor V Leiden.

Prothrombin gene mutation. Another thrombophilia that operates via an increase in prothrombotic proteins is known as the prothrombin gene mutation (prothrombin 20210A), which causes levels of prothrombin to be much higher in affected individuals than in the general population. If this mutation is the only thrombophilic risk factor present, the VTE risk is relatively low. The importance of this thrombophilia is similar to that of factor V Leiden and lies in the frequency of the gene rather than its potency. Also, as with factor V Leiden, ethnicity plays a significant role in the prevalence of this gene. It occurs in about 4% of individuals of European descent but rarely in persons of African or Asian descent.

Acquired Causes of Hypercoagulability

Myeloproliferative Disorders

Myeloproliferative disorders, especially polycythemia vera, essential thrombocythemia, and paroxysmal nocturnal hemoglobinuria, are associated with an increased incidence of thrombophlebitis, pulmonary embolism, and arterial occlusion. Patients with these conditions are also at risk of splenic, hepatic, portal vein, and mesenteric blood vessel thrombosis. The pathogenesis of these thromboses is unclear, but increased activation and aggregation of platelets may be important.

Essential thrombocythemia is a myeloproliferative disorder associated with mutations in the *JAK2, CALR,* or *MPL* genes in 90% of cases. It is diagnosed when patients present with a

platelet count above 450,000, bone marrow demonstrating megakaryocyte proliferation, in the presence of a specific gene mutation and the absence of another myeloproliferative disorder. Clinically, patients can be either asymptomatic or present with vasomotor symptoms (lightheadedness, livedo reticularis), thrombotic, or hemorrhagic events. In comparison to PV, pruritus is usually absent. Thrombotic complications are due to an acquired von Willebrand syndrome similar to that described in PV.

Low-risk patients (<60 years of age, no thrombosis) can be managed with low-dose aspirin. High-risk patients are candidates for cytoreductive therapy (hydroxyurea) in addition to low-dose aspirin (no or arterial thrombosis) or long-term anticoagulation (venous thrombosis).

Malignancies

Patients with certain malignancies demonstrate a marked thrombotic tendency. Adenocarcinoma of the pancreas, colon, stomach, and ovaries are the tumors most often associated with thromboembolic events. Indeed, these malignancies often present with an episode of deep vein thrombosis or migratory superficial thrombophlebitis. Of all patients who develop primary thrombophlebitis, 25% to 30% will have a recurrence, and 20% of these will turn out to have cancer. The pathogenesis of the thrombotic tendency appears to relate to the combination of release of one or more procoagulant factors by the tumor that can directly activate factor X, endothelial damage by tumor invasion, and blood stasis. Laboratory testing may show no abnormalities or some combination of thrombocytosis, elevation of the fibrinogen level, and low-grade DIC.

Pregnancy and Oral Contraceptive Use

Pregnancy and oral contraceptive use have been reported to increase the risk of thrombosis. The overall incidence of thrombosis is approximately 1 in 1500 pregnancies but is higher in women who have an inherited hypercoagulable state, a history of deep vein thrombosis or pulmonary embolism, or a family history of thromboembolic disease. The incidence is also higher in women who are obese, kept on bed rest for a prolonged period, or require cesarean section. The risk of pulmonary embolism is highest during the third trimester and immediately postpartum and is a significant cause of maternal death. AT III–deficient women are at greatest risk and should receive anticoagulant therapy throughout pregnancy. Factor V Leiden and the prothrombin mutation are associated with a much lower risk. Women with these inherited traits do not need to receive anticoagulant treatment.

The association of oral contraceptive use with thrombosis and thromboembolism appears to be multifactorial. Women who also smoke, have a history of migraine headaches, or have an inherited hypercoagulable defect are at a 30-fold increased risk of venous thrombosis, pulmonary embolism, and cerebrovascular thrombosis. There appears to be a weaker relationship between estrogen use at the time of menopause and the occurrence of thromboses.

Nephrotic Syndrome

Patients with nephrotic syndrome are at risk of thromboembolic disease, including renal vein thrombosis. The reason is unclear, but lower-than-normal levels of AT III or protein C due to renal loss of coagulation proteins, factor XII deficiency, platelet hyperactivity, abnormal fibrinolytic activity, and higher-than-normal levels of other coagulation factors may be implicated. Hyperlipidemia and hypoalbuminemia have also been proposed as possible contributing factors.

Antiphospholipid Antibodies

The presence of antiphospholipid antibodies does not necessarily correlate with thrombosis. Patients with hepatitis C, mononucleosis, syphilis, Lyme disease, multiple sclerosis, or HIV infection can have circulating antiphospholipid antibodies but do not have a propensity for thrombosis.

The term *antiphospholipid antibody syndrome* is used to describe patients who experience thromboses or pregnancy complications and have laboratory evidence of antiphospholipid antibodies in their blood. Antiphospholipid antibody syndrome can be primary (the sole manifestation of an autoimmune disease) or secondary (i.e., in association with systemic lupus erythematosus). The diagnosis requires the following clinical findings: thrombosis or pregnancy-related morbidity and the presence of one of the antiphospholipid antibodies (anticardiolipin, anti–β_2 glycoprotein I, or the lupus anticoagulant).

The antibodies are clinically defined by the method of their detection. Lupus anticoagulant antibodies are detected by prolongation of the PTT and the dilute Russell viper venom time, whereas anticardiolipin and anti–β_2 glycoprotein I antibodies are measured directly by immunoassay. The risk of thrombosis appears to be greater with lupus anticoagulants and antibodies specifically directed at β_2 glycoprotein I.

If the testing is done in proximity to a thrombotic event and antibodies are present, a repeat assay should be performed 12 weeks later to confirm the persistence of antibodies.

The mechanism of the thrombotic action of these antibodies has yet to be defined. The antibodies might activate endothelial cells to increase the expression of vascular adhesion molecule 1 and E-selectin. This would increase the binding of WBCs and platelets to the endothelial surface and lead to thrombus formation.

Patients with lupus anticoagulants have an increased propensity for thrombosis, with 30% to 60% of patients experiencing one or more thrombotic events during their lifetime. Isolated venous thrombosis or thromboembolism make up two-thirds of these events, and cerebral thrombosis accounts for the other third. Up to 20% of patients who have a VTE not associated with a disease, surgery, or trauma are found to have antiphospholipid antibodies. As with factor V Leiden and the prothrombin gene mutation, the presence of an antiphospholipid antibody must be considered as a likely cause of thromboembolic disease in younger individuals. Patients can also develop catastrophic antiphospholipid syndrome characterized by multiorgan failure resulting from widespread small vessel thrombosis, thrombocytopenia, acute respiratory distress syndrome, DIC, and occasionally an autoimmune hemolytic anemia. This clinical picture is indistinguishable from that of TTP. Bacterial infection is often the triggering event.

Optimal management of patients with antiphospholipid antibodies but no history of thrombotic events is unclear, but low-dose aspirin can be considered. The mainstay of therapy for patients with a history of thrombotic events consists of heparin, LMWH, and warfarin (contraindicated in pregnancy). Catastrophic antiphospholipid syndrome requires antithrombotics in addition to steroids, IVIG, and possibly plasmapheresis.

Management of Anesthesia in Venous Hypercoagulable Disorders

Patients with a history of thrombotic events should be managed based on the anticoagulant they are receiving and the risk of bleeding of the proposed surgery. If the patient is receiving antithrombotic treatment and there is a history of severe thrombophilia, a bridging regimen with parenteral antithrombotics may be considered preoperatively. In cases of mild thrombophilic disease, standard VTE prophylaxis should be sufficient.

Patients with heterozygous or homozygous mutations for inherited thrombophilia but no history of thrombotic events should not receive long-term anticoagulation. However, prophylactic anticoagulation should be used during the perioperative period. VTE prophylaxis can be achieved by using oral or parenteral anticoagulants, compression boots, and early ambulation. Very low-risk patients scheduled for general, abdominopelvic, or reconstructive/plastic procedures with no other risk factors for thrombosis have a very low risk of thrombosis (~0.5%) and can be managed with early ambulation. Minor low-risk procedures (thrombotic risk 1.5%) benefit from intermittent pneumatic compression or elastic stockings. Unless there are contraindications to anticoagulation, all other procedures with a high (>3%) and very high (>6%) thrombotic risk benefit from pharmacologic thromboprophylaxis. Regimens often include LMWH, subcutaneous heparin, or fondaparinux.

Patients undergoing orthopedic surgery merit special attention. In this patient population, for high-risk procedures such as knee/hip replacement, trauma, or hip fractures, thromboprophylaxis can be achieved with LMWH or an oral direct anticoagulant. Aspirin should not be used as a sole agent except for low-risk situations (e.g., surgeries below the knee). In patients undergoing major orthopedic surgeries or complex intraabdominal interventions for cancer, thromboprophylaxis should be continued for 1 month after the surgery.

Patients with cancer also represent a special category. For them, LMWH is the preferred antithrombotic for treatment of VTE in the acute setting, but a DOAC is an acceptable alternative.

Since routine antithrombotic prophylaxis is used daily in the operating room, the advantages of regional anesthesia compared with general anesthesia are less clear in patients at high risk of VTE. Recent meta-analyses have found that regional and general anesthesia for hip surgery produce comparable results in most outcomes. Although there appears to be a slight reduction in VTE incidence with regional anesthesia and a decreased need for transfusion, this does not translate into a significant difference in mortality. Regional anesthetics techniques can be safely performed in patients who are taking or who will be taking anticoagulants for thromboprophylaxis, without an increased risk of spinal/epidural hematoma so long as enough time has passed since the last dose of the anticoagulant for its effect to have dissipated. Similar precautions must be taken prior to catheter removal. Postoperative pharmacologic prophylaxis for VTE is very effective, so it may not be prudent to withhold these drugs just to use epidural analgesia for a longer period of time postoperatively.

Patients with an absolute contraindication to anticoagulant therapy or those with a major bleeding complication who have sustained a thrombotic event may benefit from placement of a vena cava filter to prevent recurrent pulmonary emboli. The filters are effective and reduce the incidence of pulmonary embolism to less than 4%.

Anesthetic Considerations in Patients Receiving Long-Term Anticoagulant Therapy

Perioperative management of patients receiving anticoagulant therapy requires special attention. The risk of perioperative thrombosis must be weighed against the risk of bleeding during and after surgery. Certain operations are at minimal bleeding risk, such as dental, dermatologic, and endoscopic procedures. These can be done without disrupting mucosa and can be accomplished without interruption of chronic anticoagulation therapy.

For most surgeries or procedures, however, long-term oral anticoagulation needs to be temporarily discontinued. Different considerations apply for patients treated with warfarin as compared to those on DOACs.

For patients on warfarin, the oral anticoagulant needs to be discontinued 5 to 7 days prior to the procedure; patients deemed at high thrombotic risk (>10%/year) could receive bridging therapy with unfractionated heparin or LMWH. These are patients with atrial fibrillation and high CHA_2DS_2-VASc of 7 to 9 (Table 23.6) or recent stroke (within 3 months), mechanical mitral valves or older prototype aortic valves, or recent VTE events (within 3 months). The decision to proceed with bridging should be individualized, as most studies detected increased bleeding rates when LMWH was used perioperatively. As such, the majority of patients at intermediate (5–10%/year) and low thrombotic risk (<5%/year) should be managed with stopping warfarin alone and no bridging.

Bridging therapy reduces the risk of VTE by up to 80%. In patients receiving heparin by continuous infusion, the infusion should be stopped 4 to 6 hours before surgery. Patients receiving LMWH should receive the last dose the day before surgery, at half the daily dose.

Different considerations apply for patients on DOACs. DOACs have short half-lives; however, the half-life is affected by patients' renal function as all of them rely on renal excretion to a certain extent. Basic information about DOACs is presented in Table 23.7. Given their short half-life, bridging is not recommended for patients on DOACs. The duration of oral anticoagulant interruption needs to take into account the drug's half-life (as affected by the renal function) and the perioperative bleeding risk. For procedures with low bleeding risk, a two- to three-half-life period of interruption should suffice; however, for high-risk bleeding procedures, a duration of four to five half-lives should be observed (Table 23.8).

TABLE 23.6 Mechanism of Action and Potential Antidotes for Commonly Used Anticoagulants

Generic Name	Brand Name	Mechanism	Route	Reversal
Unfractionated heparin		Antithrombin III–dependent inhibition of factor Xa	SQ or IV	Protamine
Low-molecular-weight heparins	Lovenox, Fragmin	Antithrombin III–dependent inhibition of factor Xa	SQ or IV	Protamine (partial reversal)
Warfarin	Coumadin	Depletion of vitamin K–dependent clotting factors	PO	Vitamin K Fresh frozen plasma Prothrombin complex concentrate (Kcentra)
Fondaparinux	Arixtra	Factor Xa inhibitor	SQ	No reversal drug Factor VIIa, antifibrinolytics
Rivaroxaban	Xarelto	Factor Xa inhibitor	PO	Andexanet alfa (Andexxa) Prothrombin complex concentrate
Apixaban	Eliquis	Factor Xa inhibitor	PO	Andexanet alfa (Andexxa) Prothrombin complex concentrate
Edoxaban	Savaysa	Factor Xa inhibitor	PO	Prothrombin complex concentrate
Dabigatran	Pradaxa	Direct thrombin inhibitor	PO	Idarucizumab (Praxbind) Prothrombin complex concentrate Hemodialysis
Argatroban	Acova	Direct thrombin inhibitor	PO	No reversal drug Factor VIIa
Bivalirudin	Angiomax	Direct thrombin inhibitor	IV	No reversal drug Hemofiltration or hemodialysis, factor VIIa, fibrinogen, antifibrinolytics

ADP, Adenosine diphosphate; *cAMP,* cyclic adenosine monophosphate; *IV,* intravenous; *PDE,* phosphodiesterase; *PO,* oral; *SQ,* subcutaneous.

TABLE 23.7 CHA_2DS_2-VASc Scoring System for Estimating Risk of Stroke in Nonrheumatic Atrial Fibrillation

	Condition	Points
C	Congestive heart failure	1
H	Hypertension	1
A_2	Age ≥75 yr	2
D	Diabetes mellitus	1
S_2	Prior stroke or transient ischemic attack	2
Vascular disease		1
Female sex		1
Age 65–74		1

Resumption of anticoagulation postoperatively requires evaluation of the risk of recurrent thrombosis and consideration of the degree to which surgery itself increases hypercoagulability. These factors must be weighed against the bleeding risk associated with resumption of anticoagulation. Since there is a delay of approximately 24 hours after warfarin administration before the international normalized ratio (INR) begins to increase, warfarin therapy can generally be resumed soon after surgery except in patients at high risk of bleeding. Patients can also be managed with bridging therapy (subcutaneous heparin or LMWH), which can usually be started 24 to 72 hours after surgery if surgical hemostasis has been achieved. Bridging can be

TABLE 23.8 Direct Oral Anticoagulant Interruption Times for Surgical Procedures and Neuraxial Anesthesia

	RIVAROXABAN, APIXABAN, EDOXABAN			DABIGATRAN			
Creatine Clearance (CrCl) mL/min	Low-Risk Bleeding[a]	High-Risk Bleeding[a]	Neuraxial Anesthesia[b]	Low-Risk Bleeding[a]	High-Risk Bleeding[a]	Neuraxial Anesthesia[b]	CrCl mL/min
>90	≥24 h	≥48 h	≥72 h	≥24 h	≥48 h	≥72 h	>80
60–89	≥24 h	≥48 h	≥72 h	≥36 h	≥72 h	≥96 h	60–79
30–59	>24 h	>48 h	• No data	>48 h	>96 h	>120 h	30–59
15–29	>36 h	• No data		≥72 h	• No data	• Avoid neuraxial anesthesia	15–29
<15	• No data • ≥48 h • Consider measuring anti-Xa level	• ≥72 h • Consider measuring anti-Xa level		• No data • ≥96 h • Consider measuring dilute thrombin time			<15

[a]2017 American College of Cardiology Expert Consensus Decision Pathway.
[b]2018 American Society of Regional Anesthesia and Pain Medicine Guidelines for Regional Anesthesia.

TABLE 23.9 Suggested Risk Stratification for Perioperative Thromboembolic Events

Thrombotic Risk	AF	Mechanical Heart Valve	VTE	BRIDGE?
High (>10%/yr)	• CHA_2DS_2-VASc score 7–9 • Recent stroke (<3 months)	• Mechanical MVR • Old mechanical AVR	• VTE <3 months • Severe thrombophilia	**YES**
Moderate (5–10%/yr)	• CHA_2DS_2-VASc 5–6	Bileaflet mechanical AVR with risk factors for stroke[a]	• VTE 3–12 months • Recurrent VTE • Thrombophilia • Active cancer	**NO[b]**
Low (<5%/yr)	• CHA_2DS_2-VASc 0–4	Bileaflet mechanical AVR without risk factors for stroke[a]	VTE >12 months	**NO**

AF, Atrial fibrillation; ***AVR,*** aortic valve replacement; ***CHF,*** congestive heart failure; ***CVA,*** cardiovascular accident; ***DM,*** diabetes mellitus; ***MVR,*** mitral valve replacement; ***TIA,*** transient ischemic attack; ***VTE,*** venous thromboembolism.

[a]**Risk factors for stroke: AF, prior CVA/TIA, hypertension, DM, CHF, ≥75 yo**

[b]**Except in patients with mechanical valves where bridging remains at provider discretion**

Data from Tao J, Oprea AD. Periprocedural anticoagulation management for nonoperating room anesthesia procedures: a clinical guide. *Semin Cardiothorac Vasc Anesth.* 2019;23(4):352-368.

stopped once the INR has been in the therapeutic range for 48 hours.

Patients undergoing device placement (pacemaker or defibrillator) and those undergoing ablative procedures seem to have a higher risk of bleeding with bridging than with continuation of their usual anticoagulation medication. Therefore, in these instances, oral anticoagulation should be continued perioperatively.

When neuraxial anesthesia is desired, the guidelines of the American Society of Regional Anesthesia and Pain Medicine (ARSA) recommend that needle placement for regional anesthesia take place 12 hours after the last dose of LMWH if prophylactic dosing is used and 24 hours after the last dose of LMWH if therapeutic dosing is used. Similarly, epidural catheter removal needs to be carefully coordinated with the heparin dosing. Warfarin is recommended to be stopped 5 days in advance and a normal INR be documented prior to the neuraxial anesthetic. The 2018 updated recommendations from ASRA addressing periprocedural management of DOACs are summarized in Table 23.8.

In summary, hypercoagulability (a state of exaggerated activation of the coagulation system) plays a major role in the pathogenesis of VTE, a process that affects some 2 million Americans annually, with an estimated annual mortality of 150,000 from pulmonary embolism. New heritable causes of hypercoagulability are being identified, and some genetic predispositions to thrombosis can be identified in more than half of patients with deep vein thrombosis. The perioperative period represents a time of high risk for VTE (Table 23.9). Some kinds of surgery are associated with a more than 100-fold increase in the risk of thrombosis. Knowledge of the optimum operative management of these patients is evolving, but understanding the mechanisms of the hypercoagulable states and the mechanism of action of the many anticoagulants now available is a necessary part of the knowledge base for every anesthesiologist.

KEY POINTS

- The erythrocyte and its major protein constituent, Hb, are highly specialized so that oxygen delivery can be rapidly adjusted to meet local tissue needs. Disorders affecting the formation, structure, metabolism, and turnover of RBCs can impair their ability to perform this vital task in patients undergoing surgery.
- Preoperative management of patients with sickle cell disease no longer mandates exchange transfusion to decrease the ratio of sickle Hb to normal Hb. Instead, transfusions are required only as needed to achieve a preoperative Hct (total of all forms of Hb) of 30%.
- Recent advances in cell-based coagulation models have changed our fundamental understanding of in vivo clotting. This improved understanding allows a better appreciation of how specific defects in coagulation components affect the balance of hemostasis and what therapeutic interventions offer the best risk/benefit ratio.
- Sources of hypercoagulability can be divided into two major classes: a congenital predisposition that is usually lifelong and an acquired or environmental hypercoagulability such as may occur during the perioperative period. In patients experiencing a first-time venous thromboembolism, some congenital predisposition to hypercoagulability can be identified in up to 50% of cases. However, almost always, some acquired or environmental hypercoagulable condition seems to be necessary to trigger the thromboembolic event.
- Most disorders producing a state of venous hypercoagulability affect the production and disposition of thrombin, whereas hypercoagulability in the arterial circulation is affected by platelet and endothelial function and regulation in addition to abnormalities in thrombin generation and breakdown.

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24

Skin and Collagen Disorders

Jean Gabriel Charchaflieh

OUTLINE

SKIN DISEASES

Skin disease can have significance for the anesthesiologist due to the skin manifestations itself, the underlying medical condition, or the potential worsening by anesthetic interventions. Examples of skin diseases in which the anesthetic implications are mainly due to the skin lesion itself include Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), either of which can result in significant fluid losses through the skin and mucous membranes as well as in increased risk of systemic infection. Examples of skin diseases in which the anesthetic implications are mainly due to the underlying medical conditions rather than the skin manifestations themselves include acanthosis nigricans and atopic dermatitis. Examples of skin diseases in which the anesthetic implications are due to both the skin lesion and the underlying medical conditions include scleroderma and dermatomyositis. Finally, examples of skin diseases that can be worsened by anesthetic interventions include epidermolysis bullosa, pemphigus, mastocytosis, and various forms of urticaria.

Acanthosis Nigricans

Acanthosis nigricans refers to thickened, darkened, velvety skin that is usually a manifestation of an underlying medical condition. Based on the underlying medical condition, there are five types of acanthosis nigricans: familial, endocrine (diabetes mellitus), metabolic (obesity), chemical (drug related), and neoplastic. Skin manifestations of acanthosis nigricans are thought to be due to activation of insulin-like growth factor (IGF) receptors in the skin leading to proliferation of keratinocytes and fibroblasts, which produce the skin lesions, especially in skinfolds. The clinical significance of acanthosis nigricans

lies mainly in determining its underlying cause and providing appropriate therapy. Some of the most common underlying conditions include insulin resistance and gastrointestinal (GI) cancers (Figs. 24.1 and 24.2). Anesthetic implications of acanthosis nigricans are related to the underlying medical condition and associated therapies.

Atopic Dermatitis

Atopic dermatitis, also known as atopic eczema, is the cutaneous manifestation of an atopic state (i.e., a type 1 hypersensitive allergic reaction), whose manifestations may include eczema, asthma, food allergies, or hay fever. Skin manifestations of atopic dermatitis vary according to age. Diagnostic criteria must include pruritus, typical morphology and distribution of skin lesions, onset in childhood, and chronicity. Atopic dermatitis is thought to be the result of interaction between genetic predisposition and exposure to allergens, including skin colonization with *Staphylococcus aureus*. Treatment is symptomatic with topical steroids and systemic antihistamines, plus lifestyle modifications to remove suspected allergens. Anesthetic implications consist of protecting the eczematous skin from trauma or infection, managing the systemic manifestations of the atopic state (asthma, hay fever, otitis media, sinusitis), and therapeutic adjustments based on the medications used in the treatment of atopic dermatitis (corticosteroids, antihistamines, and immunosuppressants).

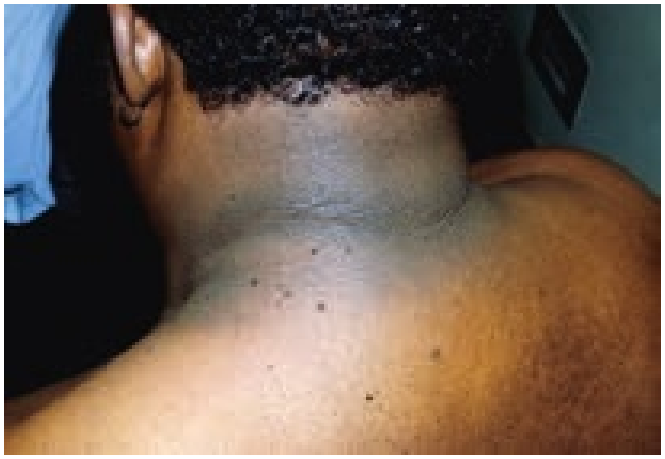

Fig. 24.1 The velvety hyperpigmentation of acanthosis nigricans in a neck crease of a patient with diabetes mellitus. (From Fitzpatrick JE, Morelli JG, eds. *Dermatology Secrets Plus*. ed 5. Philadelphia, PA: Elsevier; 2016.)

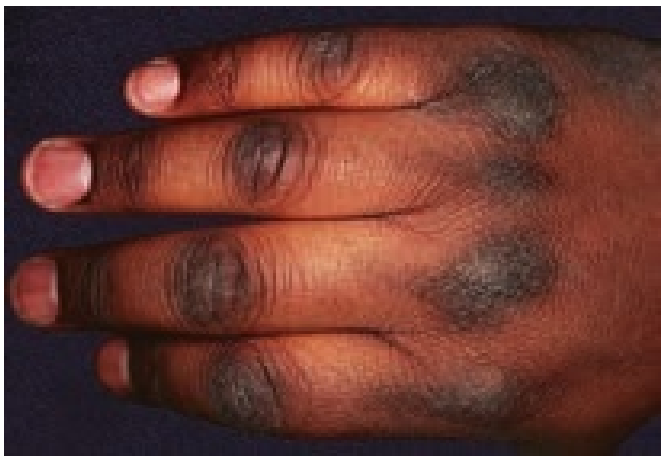

Fig. 24.2 Acanthosis nigricans over the knuckles in a patient with insulin resistance and obesity. (From Bolognia JL, Jorizzo JL, Schaffer JV, eds. *Dermatology*. ed 3. Philadelphia, PA: Elsevier; 2012.)

Epidermolysis Bullosa

Epidermolysis bullosa refers to a group of hereditary disorders, whose manifestations are apparent since birth or early childhood and are characterized by easy blistering of both the skin and mucous membranes, including the oropharynx and esophagus. The painful blisters are produced by minor friction or trauma and can lead to serious complications, including esophageal narrowing, skin cancer, digit amputation, or death. Epidermolysis bullosa has three different types that are divided into nonscarring (simplex and junctional) and scarring (dystrophic).

Epidermolysis bullosa simplex has an age of onset from birth to early childhood. It affects mainly the epidermis, has a relatively benign course, allows normal development of the affected person, but still may result in premature death.

Junctional epidermolysis bullosa has an age of onset at birth. Its lesions extend to the dermal-epidermal junction, producing a more severe form of the disease, and results in premature death in early childhood mostly due to sepsis but also due to metastatic squamous cell cancer. Features of junctional epidermolysis bullosa include early blistering since birth, absence of scar formation, and mucosal involvement of the GI, genitourinary, and respiratory tracts.

Dystrophic epidermolysis bullosa may appear at birth through recessive inheritance or during infancy through dominant inheritance. Its manifestations are varied in scope and severity and include dystrophic changes in the skin and mucous membranes, scarring and fusion of the digits, constriction of the oral aperture, esophageal stricture, dysplastic teeth, malnutrition, anemia, electrolyte derangements, hypoalbuminemia, chronic infection, general debilitation, renal dysfunction, and premature death in the second decade of life. Subtypes of dystrophic epidermolysis bullosa include epidermolysis bullosa pruriginosa and albopapuloid epidermolysis bullosa.

Other types of epidermolysis bullosa include epidermolysis bullosa acquisita and acral peeling. Systemic diseases that can be associated with epidermolysis bullosa include porphyria cutanea tarda, amyloidosis, multiple myeloma, diabetes mellitus, and hypercoagulable states. Treatment of epidermolysis bullosa includes symptomatic relief, skin protection, treatment of secondary infection, support of organ function, corticosteroids, intravenous granulocyte colony-stimulating factor (G-CSF), and transplanting skin derived from genetically modified stem cells.

Anesthetic implications of epidermolysis bullosa are related to the primary disease process affecting the skin and mucous membranes, the associated systemic complications, and ongoing therapies.

Throughout the perioperative period, protection of the skin and mucous membranes from even minor trauma is crucial. Blood pressure cuffs should be padded with a loose cotton dressing. Electrocardiogram (ECG) electrodes should have the adhesive portion removed and be held in place using petroleum jelly gauze. A nonadhesive pulse oximetry sensor should be used. Intravenous and intraarterial catheters should be either sutured or held in place with gauze wraps rather than tape. A soft foam, sheepskin, or gel pad should be placed under the patient. Linen creases should be removed. Anesthetic face mask should be gently applied against the face. Lubrication of the face and mask with cortisol ointment or another lubricant can be helpful.

Upper airway instrumentation should be minimized because the squamous epithelium lining the oropharynx and esophagus is very susceptible to trauma, bullae formation, and extensive hemorrhage. Hemorrhage from ruptured oral bullae can be treated by topical application of epinephrine-soaked gauze. In epidermolysis bullosa dystrophica, endotracheal intubation has not been associated with laryngeal or tracheal complications due to greater resistance of laryngotracheal columnar epithelium in comparison with oropharyngeal squamous epithelium. Still, generous lubrication of the laryngoscope blade with cortisol ointment or petroleum jelly and selection of a smaller-than-usual endotracheal tube are recommended. Video laryngoscopy intubation is recommended in cases of small mouth opening due to chronic scarring.

After intubation, the tube must be positioned so that it does not exert pressure at the corners of the mouth and should be immobilized with soft cloth bandages and not taped to the skin. Oropharyngeal suctioning should be avoided as it can lead to life-threatening bulla formation. Aspiration precautions should be implemented in the presence of esophageal stricture.

Epidermolysis bullosa is associated with increased occurrence of porphyria cutanea tarda, which is the type of porphyria that does not precipitate attacks of acute porphyria. Therefore commonly used anesthetic agents, including volatile anesthetics, can be safely used. Skeletal muscle dystrophy of epidermolysis bullosa dystrophica is not associated with excessive hyperkalemic response to succinylcholine. Regional anesthesia (spinal, epidural, brachial plexus block) is an acceptable technique in these patients. Epidermolysis bullosa patients who are on long-term therapy with corticosteroids should receive supplemental corticosteroids therapy to compensate for the needs of the perioperative surgical stress.

Pemphigus

Pemphigus refers to autoimmune vesiculobullous lesions that involve the skin and mucous membranes. Pemphigus is caused by autoantibodies to adherence molecules in the skin called desmogleins, which results in frictional bulla formation in the skin and mucous membranes, leading to fluid and protein loss through the skin and increased risk of infection. The protein loss through the skin is compounded by decreased food intake by mouth due to painful oropharyngeal lesions, which are present in 50% of cases (Fig. 24.3). There are a dozen subtypes of pemphigus, including a drug-induced form. Pemphigus vulgaris is the most common and most significant form of pemphigus because of its high incidence of oropharyngeal lesions. Paraneoplastic pemphigus is a complication of many forms of cancer, including non-Hodgkin lymphoma, chronic lymphocytic leukemia (CLL), thymoma, spindle cell tumors, and Waldenström macroglobulinemia.

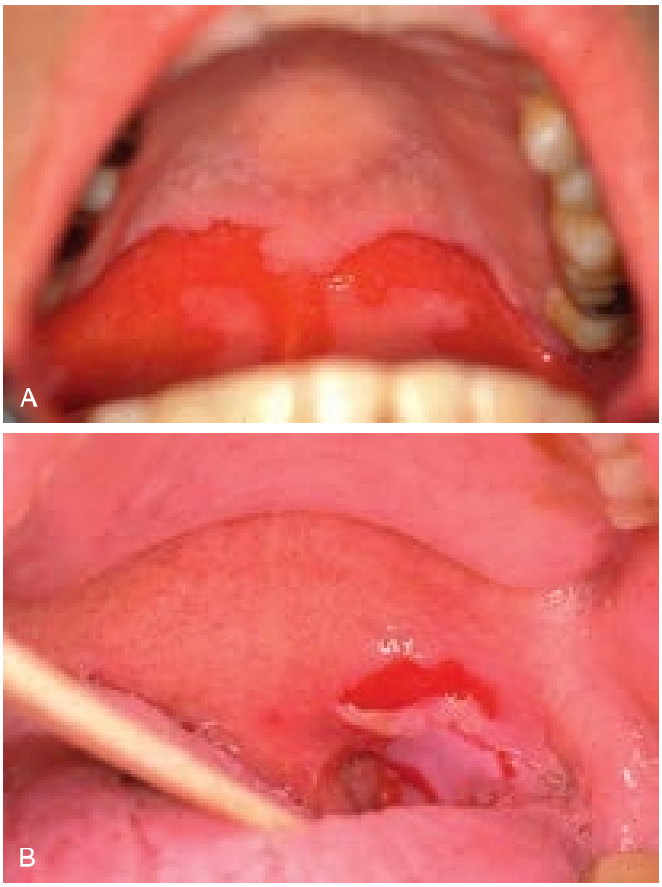

Fig. 24.3 Two images of pemphigus with lesions of the palate. Essentially all patients with pemphigus develop painful oral mucosal erosions, with the most common sites being the buccal and palatine mucosa. These lesions are flaccid, thin-walled, easily ruptured blisters. (From Bolognia JL, Jorizzo JL, Schaffer JV, eds. *Dermatology*. ed 3. Philadelphia, PA: Elsevier; 2012.)

Untreated pemphigus can be fatal due to secondary infection and hypoproteinemia. Immunosuppression therapy is the mainstay of treatment, in conjunction with symptomatic and supportive therapy. High-dose corticosteroid therapy is the first line of treatment and has decreased the associated mortality rates from 70% to 5%. Other immunosuppressive therapy includes mycophenolate mofetil, azathioprine, methotrexate, and cyclophosphamide. Resistant disease may respond well to rituximab, intravenous immunoglobulin (IVIG), or plasmapheresis.

Anesthetic considerations are similar to those of epidermolysis bullosa. Preoperative evaluation must include assessment for dehydration, electrolyte derangements, and current immunosuppression therapy. Supplemental stress-dose corticosteroids are often required. Airway management may be difficult and can result in bulla formation, airway obstruction, and bleeding. Regional anesthesia is an acceptable alternative with

meticulous sterile and antiseptic conditions, and avoidance of skin infiltration with a local anesthetic solution.

Mastocytosis

Mastocytosis refers to the accumulation of defective mast cells (mastocytes) and mast cell precursors in body tissues, resulting in cutaneous and systemic manifestations. Cutaneous manifestations of mastocytosis include urticaria pigmentosa, which commonly starts at childhood and improves with aging. Urticaria pigmentosa manifests as pruritic rash with dermatographia on the trunk and extremities.

Systemic mastocytosis spares the central nervous system (CNS) and ranges in severity from indolent to aggressive. It may progress to myelodysplastic disorders, myeloproliferative disorders, or mast cell leukemia, with mast cell proliferation in parenchymal organs, especially bone marrow, which is usually biopsied to categorize the type of systemic mastocytosis. Many of the symptoms of systemic mastocytosis are the result of mast cell degranulation, which can be triggered spontaneously or by nonimmune factors, including temperature changes, exercise, psychological stimuli, alcohol, spicy foods, and histamine-releasing drugs.

Mast cell degranulation results in the release of many cell products, including histamine, leukotrienes, prostaglandins, proteases (tryptases, hydrolases), and proteoglycans (heparin and chondroitin sulfate). Clinical symptoms of mast cell degranulation include pruritus, urticaria, flushing, nausea and vomiting, abdominal cramping, diarrhea, bronchospasm, tachycardia, and hypotension, which may be life threatening.

Medications used for the prevention and treatment of systemic mastocytosis include histamine (H_1 and H_2) receptor blockers, mast cell stabilizers, leukotriene receptor–binding inhibitors, proton pump inhibitors (PPIs), adrenergic β agonists, and corticosteroids. In most severe cases, cytoreductive therapy as well as allogenic stem cell transplantation have been used.

Anesthetic implications of mastocytosis include preoperative plan formulation through discussions with the patient, surgeon, and allergist; possible preoperative skin testing to determine the potential of commonly used anesthetic drugs to trigger mast cell degranulation; possible preoperative administration of H1- and H2-receptor antagonists and oral cromolyn sodium; and perioperative avoidance of triggers of mast cell degranulation, including temperature changes, histamine-releasing drugs, emotional distress, and unblocked surgical stress response.

Means for dealing with life-threatening anaphylactoid reactions should be made readily available. Measuring serum tryptase concentration, up to 3 hours after a suspected anaphylactoid reaction, may be useful for detecting mast cell degranulation, but it cannot differentiate between nonimmunologic mast cell degranulation or classic anaphylaxis. Similar precautions should be taken before procedures involving administration of radiocontrast, including pretreatment with H1- and H2-receptor antagonists and corticosteroids.

Urticaria

Urticaria refers to itchy, red, raised skin rash that is also known as hives. Urticaria is commonly categorized into acute, chronic, or physical. Acute urticaria can be encountered in 10% to 20% of the US population at one time or another. Most cases of acute urticaria have undefined cause and resolve within hours, either spontaneously or after administration of antihistamines.

Chronic urticaria is characterized by hives, localized edema, and intense pruritus that last less than 24 hours, whereas urticaria lasting longer than 24 hours raises the possibility of urticarial vasculitis. Chronic urticaria affects approximately twice as many women as men. It follows a remitting and relapsing course, with symptoms typically increasing at night. Its pathophysiology involves stimulation of mast cells and basophils either by nonimmunologic or by immunologic factors, which results in release of histamine and other vasoactive substances such as bradykinin, leading to localized vasodilation, edema, and pruritus. The trigger of chronic urticaria is often unidentified (idiopathic). Treatment aims at dealing with the underlying cause, when identified, and alleviation of symptoms through physical and chemical means, such as tepid showers, antihistamines (H1-receptor antagonists), terfenadine, systemic corticosteroids (~21-day course), and omalizumab (Xolair), which is an antiimmunoglobulin E (anti-IgE) antibody that binds to IgE and lowers free IgE levels. Acute treatment of oropharyngeal edema includes topical spray with 2% ephedrine and, in severe cases, subcutaneous injection of epinephrine. Chronic urticaria patients should be advised to avoid angiotensin-converting enzyme (ACE) inhibitors, aspirin, and nonsteroidal antiinflammatory drugs (NSAIDs).

Physical urticaria is characterized by hives, itching, and possible angioedema in response to physical stimulation of the skin, such as by cold temperatures. Cold urticaria accounts for 3% to 5% of all physical urticarias and may be either familial or acquired in origin (Table 24.1). It is characterized by development of urticaria and angioedema following exposure to cold air, rain, aquatic activities, snow, consumption of cold foods and beverages, and contact with cold objects. Severe cold urticaria may be life threatening due to laryngeal edema, bronchospasm, and hypotension. The diagnosis is based on skin stimulation at a temperature of 0°C to 4°C for a period of 1 to 5 minutes (cold stimulation test). In cold urticaria, cutaneous mast cells rather than intravascular basophils seem to be the target cells for degranulation, and serum IgE concentrations may be increased. Treatment consists of avoidance of known triggers and administration of systemic antihistamines and topical doxepin.

Urticarial vasculitis may be a presenting symptom of immunologic disorders such as systemic lupus erythematosus (SLE) and Sjögren syndrome.

Management of anesthesia in patients with urticaria focuses on avoiding any known triggers, including histamine-releasing drugs, cold intravenous fluids and drugs, cold ambient temperature, as well as the preoperative prophylactic administration of H1- and H2-receptor antagonists and corticosteroids.

Patients with cold urticaria undergoing cardiac surgery have been managed in three ways: off-pump coronary artery bypass grafting (in patients with suitable coronary anatomy), use of cardiopulmonary bypass under normothermic conditions with isothermic cardioplegia, and cardiopulmonary bypass with systemic hypothermia and cold cardioplegia. If the patient is exposed to cold, clinical manifestations of cold urticaria typically become apparent during rewarming rather than during cooling.

TABLE 24.1 Features of Common Types of Chronic Urticaria

Type of Urticaria	Age Range (yr)	Clinical Features	Angioedema	Diagnostic Test
Chronic idiopathic urticaria	20–50	Pink or pale edematous papules or wheals, wheals often annular; pruritus	Yes	
Symptomatic dermatographism	20–50	Linear wheals with a surrounding bright red flare at sites of stimulation; pruritus	No	Light stroking of skin causes wheal
Physical Urticarias				
Cold	10–40	Pale or red swelling at sites of contact with cold surfaces or fluids; pruritus	Yes	Application of ice pack causes wheal within 5 minutes of removing ice (cold stimulation test)
Pressure	20–50	Swelling at sites of pressure (soles, palms, waist) lasting 2–24 hr; pain, pruritus	No	Application of pressure perpendicular to skin produces persistent red swelling after a latent period of 1–4 hr
Solar	20–50	Pale or red swelling at site of exposure to ultraviolet or visible light; pruritus	Yes	Radiation by solar simulator for 30–120 seconds causes wheals in 30 min
Cholinergic	10–50	Monomorphic pale or pink wheals on trunk, neck, and limbs; pruritus	Yes	Exercise or hot shower elicits wheals

Adapted from Greaves MW. Chronic urticaria. *N Engl J Med.* 1995;332:1767–1772.

Erythema Multiforme

Erythema multiforme is a recurrent disease of the skin and mucous membranes characterized by lesions ranging from edematous macules and papules to vesicles (⌝0.5 cm) and bullae (⌜0.5 cm), which may ulcerate. Erythema multiforme attacks can be triggered by infection (especially herpes simplex, hemolytic streptococci), cancer, collagen vascular disease, and drug-induced hypersensitivity.

Stevens-Johnson syndrome and toxic epidermal necrolysis are severe manifestations of erythema multiforme that are associated with multisystem dysfunction, including fever, tachycardia, tachypnea, and skin sloughing (Figs. 24.4 and 24.5). Skin surface area involved in SJS is typically less than 10% of total body surface area, in SJS/TEN overlap syndrome about 10% to 30%, and in TEN more than 30%. Mortality correlates with the surface area of skin involved and is less than 5% for SJS and up to 50% for TEN. Drug triggers of SJS and TEN include antibiotics, analgesics,

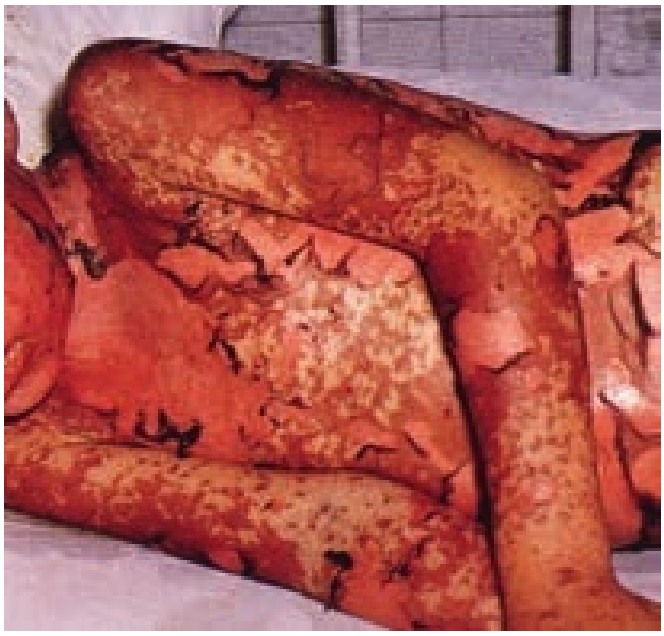

Fig. 24.4 Large areas of desquamation in Stevens-Johnson syndrome. (From Baren JM, Rothrock SG, Brennan J, et al. *Pediatric Emergency Medicine*. Philadelphia, PA: Saunders; 2008.)

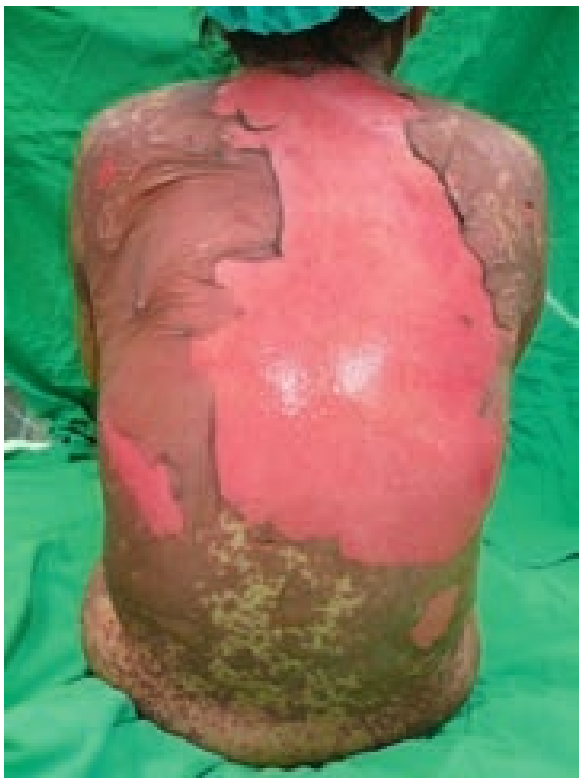

Fig. 24.5 Back lesion in a woman presenting with toxic epidermal necrolysis involving 48% of total body surface area. (From Huang SH, Yang PS, Wu SH, et al. Aquacel Ag with Vaseline gauze in the treatment of toxic epidermal necrolysis [TEN]. *Burns*. 2010;36:121-126. Copyright Elsevier and ISBI with permission.)

and certain over-the-counter medications. Corticosteroids are used in the management of severe cases.

Anesthetic risks and precautions in patients with SJS or TEN are similar to those in patients with epidermolysis bullosa or pemphigus, including those related to airway management and tracheal intubation. Patients with moderate to severe SJS and TEN are best treated as a burn patient in a closed burn unit.

Scleroderma

Scleroderma (also known as systemic sclerosis) is an autoimmune disorder that involves the skin in addition to other body tissues and organs. It is characterized by three interrelated processes: (1) inflammation and autoimmunity, (2) vascular injury with eventual vascular obliteration, and (3) fibrosis and accumulation of excess matrix in many organs and tissues. The etiology is unclear, but triggers may include exposure to toxins, drugs, and microbial pathogens. Pathophysiology consists of irreversible vascular endothelial cell injury that produces capillary loss, vascular obliteration, leakage of serum proteins into the interstitial space, tissue edema, lymphatic obstruction, and ultimately tissue fibrosis and organ sclerosis. In some patients the disease evolves into CREST syndrome (calcinosis, Raynaud phenomenon, esophageal hypomotility, sclerodactyly, telangiectasia).

The prognosis is poor and is related to the extent of visceral involvement. No drugs or treatments have proved safe and effective in altering the underlying disease process. The typical age at onset is 20 to 40 years, and women are most often affected. Pregnancy accelerates the progression of scleroderma in about half of patients. The incidence of spontaneous abortion, premature labor, and perinatal mortality is high. Manifestations of scleroderma occur in the skin, musculoskeletal system, nervous system, cardiovascular system, lungs, kidneys, and GI tract.

Skin manifestations include thickening, edema, and decreased elasticity to the point of producing flexion contractures, especially in the fingers. Muscular manifestations include myopathy, proximal weakness, and increased plasma creatine kinase concentration. Skeletal manifestations include mild inflammatory arthritis and avascular necrosis of the femoral head. Neuronal manifestations include autonomic, peripheral, and cranial neuropathy, including trigeminal neuralgia. Ocular manifestations include keratoconjunctivitis sicca and corneal abrasions. Cardiovascular manifestations include sclerosis in the small coronary arteries and the conduction system, fibrosis in the cardiac muscle, systemic and pulmonary hypertension, cardiac dysrhythmias, cardiac conduction abnormalities, congestive heart failure, cor pulmonale, pericarditis, pericardial effusion, cardiac tamponade, intermittent vasospasm in the small arteries of the digits, Raynaud phenomenon, and oral or nasal telangiectasias.

Pulmonary manifestations are a major cause of morbidity and mortality and include diffuse interstitial pulmonary fibrosis, with resulting arterial hypoxemia and decreased pulmonary compliance. Renal manifestations include renal artery stenosis, decreased renal blood flow and systemic hypertension, and irreversible renal failure, which used to be the most common cause of death in patients with scleroderma until the introduction of ACE inhibitors, which helped control the hypertension and improve the associated impaired renal function and effectively treat the 10% to 15% of patients who develop a scleroderma renal crisis. It should be noted that corticosteroids can precipitate a renal crisis in patients with scleroderma.

GI manifestations include dryness of the oral mucosa (xerostomia), dysphagia, hypomotility of the lower esophagus, decreased lower esophageal sphincter (which increases the risk of reflux of gastric fluid into the esophagus), and hypomotility of small intestine, which can lead to pseudoobstruction as well as bacterial-induced malabsorption syndrome, including malabsorption of vitamin K, which might lead to coagulation disorders. Broad-spectrum antibiotics are effective in treating bacterial-induced malabsorption syndrome. Somatostatin analogues such as octreotide are effective in improving small intestine hypomotility, whereas prokinetic drugs such as metoclopramide are not.

The only treatment that has been shown to alter the course of scleroderma is the use of ACE inhibitors to treat scleroderma renal crisis. Other aspects of therapy are aimed at monitoring disease activity, alleviating symptoms, and managing complications such as pulmonary hypertension.

Management of Anesthesia

Preoperative evaluation of patients with scleroderma is aimed at documenting the myriad systemic manifestations of the disease, any associated functional limitation, and ongoing therapy. Manifestations of scleroderma that could be detected during preoperative evaluation include decreased mandibular mobility, decreased oral aperture, oral or nasal telangiectasias, dermal thickening, Raynaud phenomenon, pulmonary hypertension, systemic hypertension, intravascular volume depletion, renal dysfunction, esophageal hypomotility and hypotonia of the lower esophagus, gastroesophageal reflux disease (GERD), and various forms of neuropathy. Ongoing therapy with H2-receptor antagonists or PPIs should be continued preoperatively or started de novo.

Pulmonary considerations are the main intraoperative anesthetic implications of scleroderma. These include providing prolonged periods of preoxygenation to compensate for the decreased pulmonary oxygen reserve and diffusion capacity, the possible need for higher driving pressures during mechanical ventilation to compensate for decreased pulmonary compliance, avoidance of hypercarbia and hypoxemia that both aggravate pulmonary hypertension, awareness of the increased sensitivity to the respiratory depressant effects of opioids, and preparations for possible need for postoperative ventilatory support in patients with significant pulmonary dysfunction. Drug selection and dosing should take into consideration the degree of renal dysfunction. Hypothermia-induced vasoconstriction should be minimized by active warming of the patient and intravenous fluids. Precautions should be undertaken to prevent corneal abrasions. Regional anesthesia is an attractive choice as it provides peripheral vasodilation and postoperative analgesia, but it might be

technically difficult because of the skin and joint changes that accompany scleroderma.

DISORDERS OF ELASTIN AND COLLAGEN

Pseudoxanthoma Elasticum

Pseudoxanthoma elasticum is a rare hereditary disorder that causes mineralization of elastic fibers in the skin, eyes, and blood vessels, with the latter leading to premature arteriosclerosis. Cutaneous manifestations are among the earliest clinical features and include the appearance of leathery cobblestone-like skin in skinfolds such as the axilla, neck creases, and groin. Ocular manifestations, which are often the basis of diagnosis, include retinal angioid streaks and vitreous hemorrhage, resulting in loss of visual acuity. Vascular manifestations include hypertension, ischemic heart disease, occlusive peripheral arterial disease of radial and ulnar arteries, which leads to loss of pulses, and degenerative changes of gastrointestinal arteries, which leads to gastrointestinal hemorrhage in about 10% of patients. Cardiac manifestations include endocardial calcification, including the valves, conduction abnormalities, dysrhythmias, and sudden death. Interestingly, some tissues rich in elastic fibers (e.g., lungs, aorta, palms, soles) are not affected by this disease process.

Management of Anesthesia

Preoperative assessment and intraoperative management should focus on the increased risk of cardiovascular complications. ECG monitoring is particularly important in view of the potential for cardiac dysrhythmias and conduction abnormalities. There are no specific recommendations regarding the choice of anesthetic drugs or techniques in these patients, provided that adequate control of blood pressure is maintained. Instrumentation of the mouth and GI tract should take into consideration the increased risk of vascular injury of the GI tract.

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome refers to a group of inherited disorders that affect an estimated 1 in 5000 people and result in abnormal production of procollagen and collagen, which affects all body tissues, including the skin, musculoskeletal, vasculature, and smooth muscles. The most common symptoms are skin fragility and hyperelasticity, easy bruising and scarring, musculoskeletal discomfort, joint hypermobility, and susceptibility to osteoarthritis. There are about a dozen forms of Ehlers-Danlos syndrome, of which the vascular form is most markedly associated with increased risk of death due to increased risk of rupture of blood vessels, intestines, or uterus—structures that are rich with type III collagen. Arterial ruptures are notoriously difficult to repair due to marked fragility of the affected arterial wall. Pregnant Ehlers-Danlos syndrome patients are more prone to premature labor, rupture of uterus or large arteries, and excessive bleeding during delivery. Additional complications encountered in various forms of Ehlers-Danlos syndrome include tracheal dilation, spontaneous pneumothorax, mitral regurgitation, cardiac conduction abnormalities, and easy bruisability.

Management of Anesthesia

The most important perioperative consideration in patients with Ehlers-Danlos syndrome is the propensity for hemorrhage and tissue rupture. The benefit of any anesthetic intervention is to be weighed against the increased risks of bleeding and tissue rupture. Interventions that are best avoided include instrumentation of the nose or esophagus, intramuscular injections, arterial or central venous cannulation, and regional anesthesia. The least traumatic means of airway instrumentation should be selected. Intermittent inspection of intravenous cannulation sites should be maintained to detect any extravasation of intravenous fluids. During positive pressure ventilation, particular attention should be paid to maintain low peak and plateau airway pressures to minimize the risk of pneumothorax. Surgical complications to be particularly watched for include hemorrhage and wound dehiscence.

Marfan Syndrome

Marfan syndrome is an autosomal dominant genetic disorder that is caused by a mutation in the fibrillin-1 *(FBN1)* gene, which leads to production of defective large glycoprotein fibrillin-1 proteins, which leads to defective connective tissues. It affects about 1 of 20,000 live births. Clinical manifestations include increased length of tubular bones, high-arched palate, pectus excavatum or carinatum, kyphoscoliosis, joint hyperextensibility, emphysema, and increased risk of spontaneous pneumothorax. Ocular manifestations occur in 50% of patients and include myopia, lens dislocation, and retinal detachment. Cardiovascular abnormalities are responsible for nearly all premature deaths in patients with Marfan syndrome. They include dilation, dissection or rupture of the thoracic aorta, mitral valve prolapse or regurgitation, bacterial endocarditis, and conduction abnormalities. For patients with dilated thoracic aorta, prophylactic ∃ blocker therapy is recommended throughout life as it slows the rate of aortic dilation and decreases the risk of aortic dissection. Surgical replacement of the aortic valve and ascending aorta is indicated in Marfan syndrome when the diameter of the ascending aorta exceeds 4.5 cm and substantial aortic regurgitation is present. Pregnancy increases the risk of aortic dissection and rupture.

Management of Anesthesia

Preoperative evaluation aims at detecting the variety of manifestations of Marfan syndrome, particularly the cardiovascular abnormalities. Airway management may be complicated by the presence of high-arched palate and propensity for temporomandibular joint dislocation. Video laryngoscopy may facilitate these challenges. The risk of aortic dissection should be minimized by avoiding increases in systemic blood pressure such as during direct laryngoscopy or painful instrumentation. Invasive hemodynamic monitoring, including transesophageal echocardiography (TEE), may be a consideration in selected patients to monitor aortic arch as well as cardiac structure and function. During positive pressure ventilation, the aim is to maintain low airway pressure and keep a high index of suspicion for development of pneumothorax.

DISORDERS OF MUSCLES AND NEUROMUSCULAR JUNCTION

Inflammatory Myopathies

Polymyositis and Dermatomyositis

Polymyositis and dermatomyositis are idiopathic inflammatory myopathies with multisystem manifestations. Dermatomyositis has characteristic skin changes in addition to muscle weakness that are the results of abnormal immune responses. Dermatomyositis can be considered a paraneoplastic syndrome as it is associated in up to 30% of cases with latent or occult cancer, including that of the breast, colon, or lung. Polymyositis may be associated with other connective tissue diseases, including SLE, scleroderma, rheumatoid arthritis, and mixed connective tissue disorder (MCTD).

Cutaneous manifestations include blue-purple periorbital heliotrope discoloration of the upper eyelids, periorbital edema, scaly erythematous malar rash, and symmetric erythematous raised papules overlying the metacarpal and interphalangeal joints (Gottron papules). The presence or absence of the characteristic skin rash differentiates between dermatomyositis and polymyositis, respectively.

Skeletal muscle manifestations include proximal muscle weakness, especially the flexors of the neck, shoulders, and hips, leading to difficulty in climbing stairs. Pharyngeal muscle weakness leads to dysphagia and increased risk of pulmonary aspiration and pneumonia. Diaphragmatic and intercostal muscle weakness may lead to ventilatory insufficiency. Cardiac manifestations include left ventricular dysfunction, myocarditis, myocardial fibrosis (which may lead to conduction abnormality), and heart block.

Laboratory findings include increase in serum creatine kinase concentrations, which parallel the extent and rapidity of skeletal muscle destruction. Electromyography (EMG) findings consist of a triad of spontaneous fibrillation potentials, decreased amplitude of voluntary contraction potentials, and repetitive potentials on needle insertion. Microscopic findings of muscle biopsy include muscle cell degeneration, regeneration, necrosis phagocytosis, and infiltration by mononuclear white blood cells.

Corticosteroids are the usual treatment for dermatomyositis and polymyositis. When the response to corticosteroids is inadequate, immunosuppressive therapy with methotrexate, azathioprine, cyclophosphamide, mycophenolate, or cyclosporine may be effective. Cyclophosphamide and tacrolimus may be particularly helpful if there is coexisting interstitial lung disease. IVIG may be useful in refractory cases. Biologic agents that have been approved to treat other immune diseases may be considered as experimental treatments if there has been an inadequate response to steroids, traditional immunosuppressive therapy, or immunoglobulins.

Management of anesthesia. Anesthetic implications are related to muscle weakness in the skeletal, cardiac, respiratory, and GI tract muscles. These muscle weaknesses increase the risk of cardiopulmonary complications, including aspiration pneumonia. The pharmacologic responses to depolarizing and nondepolarizing muscle relaxants are normal. However, disease-induced muscle weakness can compound any residual pharmacologic muscle weakness upon emergence from anesthesia leading to difficulty in weaning from mechanical ventilation. In addition, there is an increased risk for aspiration pneumonia upon emergence from anesthesia due to inability to produce effective cough and clear pharyngeal secretions.

Muscular Dystrophy

Muscular dystrophy refers to a hereditary muscular disorder characterized by degeneration of muscle fibers due to breakdown of the dystrophin-glycoprotein protein complex, which binds myofibrils to the matrix and stabilizes the sarcolemma during contraction and relaxation (Box 24.1). Loss of this protein complex leads to myonecrosis, fibrosis, and increased skeletal muscle membrane permeability. The main clinical manifestation is progressive symmetric skeletal muscle weakness and wasting, with no abnormalities in motor or sensory innervation or deep tendon reflexes. In order of decreasing frequency, muscular dystrophy types include pseudohypertrophic muscular dystrophy (Duchenne muscular dystrophy), limb-girdle, facioscapulohumeral muscular dystrophy (Landouzy-Dejerine dystrophy), and oculopharyngeal muscular dystrophy.

Pseudohypertrophic Muscular Dystrophy (Duchenne Muscular Dystrophy)

Duchenne muscular dystrophy is the most common and most severe form of childhood progressive muscular dystrophies. It is caused by a mutation in the dystrophin gene located on the X chromosome and therefore it manifests clinically in boys only. Symptoms typically appear by age 2 to 5 years. Initial symptoms include waddling gait, frequent falls, and difficulty climbing stairs. Affected muscles increase in size due to fatty infiltration but remain weak, therefore this increase in muscle size is labeled pseudohypertrophy. Muscle weakness progresses in severity so that by age 8 to 10 years affected persons are wheelchair bound. Death is common by age 20 to 25 years due to cardiopulmonary complications, including congestive heart failure and pneumonia.

Additional manifestations include kyphoscoliosis, long bone fragility, intellectual disability, myocardial degeneration, mitral regurgitation, sinus tachycardia, ECG changes (tall R waves in V_1, deep Q waves in the limb leads, a short PR interval), respiratory muscle weakness, recurrent pneumonia, sleep apnea, and pulmonary hypertension. Laboratory findings include increased creatine kinase concentrations by 20- to 100-fold due to increased skeletal muscle membrane permeability and skeletal muscle necrosis. Elevated serum creatine kinase concentrations are encountered in 70% of female carriers.

BOX 24.1 Muscular Dystrophies

- Duchenne muscular dystrophy
- Becker muscular dystrophy
- Limb-girdle muscular dystrophy
- Facioscapulohumeral muscular dystrophy
- Emery-Dreifuss muscular dystrophy
- Myotonic muscular dystrophy

Skeletal muscle biopsies demonstrate necrosis and phagocytosis of muscle fibers.

Management of anesthesia. Use of succinylcholine is contraindicated in Duchenne muscular dystrophy because of the risk of rhabdomyolysis, hyperkalemia, ventricular fibrillation, cardiac arrest, and death. The occurrence of ventricular fibrillation in children receiving succinylcholine and who were later discovered to have Duchenne muscular dystrophy is the basis of including a black box warning against the use of succinylcholine in children below the age of 8 years due to the possibility of the presence of latent Duchenne muscular dystrophy or other forms of muscular dystrophy. Malignant hyperthermia has been observed in Duchenne muscular dystrophy patients even after brief exposure to halothane, although most malignant hyperthermia cases in Duchenne muscular dystrophy have been triggered by succinylcholine or prolonged inhalation of halothane. Therefore a nontriggering technique should be used in patients with Duchenne muscular dystrophy despite the lack of definite genetic association between malignant hyperthermia and Duchenne muscular dystrophy. In addition to using a nontrigger technique, a malignant hyperthermia cart containing dantrolene should be available in anesthetic locations because malignant hyperthermia can be triggered by stressors other than anesthetic agents. Besides the concern about triggering malignant hyperthermia, volatile anesthetics, even in the absence of succinylcholine, have been observed to trigger rhabdomyolysis in patients with Duchenne muscular dystrophy. Other anesthetic considerations in Duchenne muscular dystrophy are related to skeletal muscle weakness, decreased cardiopulmonary reserve, and increased risk of aspiration pneumonia. The pharmacologic response to nondepolarizing muscle relaxants is normal in Duchenne muscular dystrophy. However, disease-induced muscle weakness may obviate the need for their use and may compound any pharmacologic residual muscle weakness during emergence from anesthesia. Pharyngeal and respiratory muscle weakness as well as GI hypomotility decrease the ability to clear airway secretions and increase the risk of pulmonary aspiration of gastric contents during both induction and emergence from general anesthesia. Delayed pulmonary insufficiency may occur up to 36 hours postoperatively even when skeletal muscle strength has apparently returned to its preoperative level. Myocardial depression, cardiac arrhythmias, and conduction abnormalities can be triggered by anesthetic agents or perioperative stress. Regional anesthesia is an attractive choice in Duchenne muscular dystrophy, as it avoids the many risks of general anesthesia, provides postoperative analgesia, and facilitates chest physiotherapy. Monitoring should take into consideration the unique risks of malignant hyperthermia and cardiopulmonary complications.

Becker Muscular Dystrophy

Becker muscular dystrophy is a milder form of Duchenne muscular dystrophy. Like Duchenne muscular dystrophy, it is an X-linked recessive inherited dystrophinopathy caused by mutation in the dystrophin gene, which encodes the protein dystrophin. The age of onset is later than that of Duchenne muscular dystrophy, with a range of 5 years up to adulthood. The severity of muscle weakness and pseudohypertrophy is less than that of Duchenne muscular dystrophy. The milder severity allows some patients to have a normal life span, but others die prematurely due to cardiopulmonary complications. Anesthetic implications are similar to those of Duchenne muscular dystrophy.

Limb-Girdle Muscular Dystrophy

Limb-girdle muscular dystrophy (LGMD) refers to a group of muscular dystrophies rather than a single disease. It has an autosomal pattern of inheritance, so it can affect both males and females. It has a later onset (second to fifth decade), slower progression, and more benign course than Duchenne muscular dystrophy or Becker muscular dystrophy. It affects mostly the shoulder and hip girdle muscles. Anesthetic considerations are similar to those of Becker muscular dystrophy and Duchenne muscular dystrophy.

Facioscapulohumeral Muscular Dystrophy

Facioscapulohumeral muscular dystrophy is the third most common muscular dystrophy after Duchenne muscular dystrophy and myotonic muscular dystrophy, with an incidence of about 1:15,000. It is characterized by a slowly progressive wasting of facial, scapular, and humeral muscles during adolescence but eventually extends into lower limbs also. Symptoms include difficulty raising the arms above the head and difficulty smiling or whistling, with no involvement of cardiac muscle and no increase in serum levels of creatine kinase. Most patients have a normal life span. Anesthetic considerations are similar to other muscular dystrophies.

Oculopharyngeal Dystrophy

Oculopharyngeal dystrophy is a rare autosomal inherited muscular dystrophy with late onset of symptoms during the fourth to sixth decade of life. The main symptoms consist of ptosis and dysphagia, with increased risk of aspiration during the perioperative period. There is also increased sensitivity to muscle relaxants. Anesthetic considerations are similar to other muscular dystrophies.

Emery-Dreifuss Muscular Dystrophy

Emery-Dreifuss muscular dystrophy is an X-linked recessive disorder characterized by development of skeletal muscle contractures that precede the onset of skeletal muscle weakness. These contractures are typically in a scapuloperoneal distribution. Respiratory function is usually maintained. Cardiac involvement may be life threatening and present as congestive heart failure, thromboembolism, or a cardiac conduction disorder such as bradycardia. Female carriers of this disorder may experience weakness and cardiac disease. Anesthetic considerations are similar to other muscular dystrophies, with the additional risk of cardiopulmonary complications.

Myotonic Dystrophy

Myotonic dystrophy refers to a group of autosomal dominant hereditary disorders whose clinical muscular manifestations consist of the triad of muscle weakness, muscle wasting, and the occurrence of myotonic contractures after muscle contraction

or electrical stimulation. These disorders are the second most common inherited muscle diseases. Clinical manifestations of myotonia include inability to relax the fingers after a firm handshake or grip, inability to relax a muscle after it is tapped with a reflex hammer, and inability to open the eyelids after forcible closure. EMG findings are diagnostic and consist of prolonged discharges of repetitive muscle action potentials.

This inability of skeletal muscle to relax after voluntary contraction or stimulation results from the inability of intracellular adenosine triphosphatase (ATPase) to return calcium to the sarcoplasmic reticulum after contraction. Because the pathophysiology does not involve neural conduction or neuromuscular junction, general anesthesia, regional anesthesia, or neuromuscular blockade is not able to prevent or relieve the skeletal muscle contractions of myotonia, whereas direct infiltration of contracted skeletal muscles with local anesthetic or intravenous administration of quinine (300–600 mg) may induce relaxation.

Cold temperatures and shivering can precipitate myotonia, whereas warm ambient temperature can decrease the incidence of shivering and the severity of myotonia. Most patients with myotonic dystrophy survive to adulthood with little impairment and no apparent symptoms, so they may come for surgery without the underlying myotonia being recognized.

Myotonia dystrophica. is the most common and most serious form of myotonic dystrophy affecting adults. It is inherited as an autosomal dominant trait, with the onset of symptoms during the second or third decade of life. Unlike other myotonic syndromes, myotonia dystrophica is a multisystem disease, although skeletal muscles are affected the most. Death from pneumonia or heart failure often occurs by the sixth decade of life. This reflects progressive involvement of skeletal, cardiac, and smooth muscles. Cardiac conduction system defects are common and could lead to sudden death. Perioperative morbidity and mortality rates are high and are principally due to cardiopulmonary complications.

Treatment is symptomatic and may include use of mexiletine to improve muscle relaxation. Quinine and procainamide also have antimyotonic properties but can worsen cardiac conduction abnormalities. These three drugs depress sodium influx into skeletal muscle cells and delay the return of membrane excitability.

Muscular manifestations of myotonia dystrophica typically consist of facial weakness (expressionless facies), wasting and weakness of sternocleidomastoid muscles, ptosis, dysarthria, dysphagia, and inability to relax the hand grip (myotonia). Other typical features include the triad of intellectual disability, frontal baldness, and cataracts. Endocrine gland involvement may be indicated by gonadal atrophy, diabetes mellitus, hypothyroidism, and adrenal insufficiency. Delayed gastric emptying and intestinal pseudoobstruction may be present. Central sleep apnea may occur and contribute to hypersomnolence. There is an increased incidence of cholelithiasis, especially in men. Exacerbation of symptoms during pregnancy is common, and uterine atony and retained placenta often complicate vaginal delivery. Cardiac dysrhythmias and conduction abnormalities presumably reflect myocardial involvement by the myotonic process. First-degree atrioventricular heart block is common and is often present before the clinical onset of the disease. Up to 20% of patients have asymptomatic mitral valve prolapse. Reports of sudden death may reflect development of complete heart block. Pharyngeal and thoracic muscle weaknesses make these patients vulnerable to pulmonary aspiration.

Management of anesthesia. Preoperative evaluation and management of anesthesia in patients with myotonia dystrophica must consider the likelihood of cardiomyopathy, respiratory muscle weakness, and the potential for abnormal responses to anesthetic drugs. Succinylcholine should be avoided because it can trigger prolonged myotonia that cannot be reversed with either general anesthesia or nondepolarizing neuromuscular blocking agents. Other pharmacologic triggers of myotonia include methohexital, etomidate, and neostigmine. Physical triggers of myotonia include hypothermia, mechanical stimulation, or electrical stimulation. The pharmacologic response to neuromuscular blocking agents is normal; however, the underlying muscle weakness may obviate the need for their use, which would also obviate the need for the use of neostigmine, which is a myotonia trigger. There is no reported association between myotonic dystrophy and malignant hyperthermia; however, in a group of 44 patients who had in vitro contracture testing (IVCT) for malignant hyperthermia, 4 patients tested positive, 10 patients tested equivocal, and 30 patients tested negative. In addition, volatile anesthetic drugs can aggravate both cardiomyopathy and cardiac conduction problems by direct myocardial depression and by increasing vagal tone. Therefore total intravenous anesthetic (TIVA) technique may be preferable over an inhalation anesthetic technique, while keeping in mind the increased sensitivity of these patients to the respiratory depressant effects of opioids, benzodiazepines, and propofol. This is most likely due to drug-induced central respiratory depression acting in tandem with weak respiratory muscles. In addition, hypersomnolence and central sleep apnea compound increased sensitivity to respiratory depressant drugs. Myotonic contracture during surgical manipulation or use of electrocautery may interfere with surgical access. Drugs such as phenytoin, quinine, and procainamide, which stabilize skeletal muscle membranes, may alleviate this problem. High concentrations of volatile anesthetics can also abolish myotonic contractions but at the expense of myocardial depression. Maintenance of normothermia and avoidance of shivering are very important, since both cold and shivering may induce myotonia. Epidural anesthesia is considered safe in patients with myotonic dystrophy.

Inherited Myopathies

Congenital myopathies are primarily muscle disorders that are characterized by structural abnormalities of muscle fibers and accumulation of abnormal proteins in the sarcoplasm (Box 24.2). In contrast to congenital muscular dystrophies, these disorders do not show muscle necrosis or fibrosis on muscle biopsy. Some of these muscle disorders involve abnormal chloride, sodium, and calcium channel genes.

Nemaline Rod Myopathy

Nemaline rod myopathy refers to a congenital myopathy in which muscle biopsy shows threadlike (*nema* is Latin for

BOX 24.2 Inherited Myopathies

- Nemaline rod myopathy
- Myotonic congenita
- Paramyotonia congenita
- Periodic paralysis
- Central core disease
- Multicore myopathy
- Centronuclear myopathy

thread) rods between normal myofibrils. It is an autosomal dominant myopathy affecting skeletal and smooth muscle of the face, neck, chest, and arms, with clinical manifestations, including muscle weakness, hypoventilation, swallowing dysfunction, and impaired speech. Some forms of nemaline rod myopathy are associated with an abnormal ryanodine receptor 1 *(RYR1)* gene, which is the main site of genetic mutation resulting in malignant hyperthermia susceptibility. Nemaline rod myopathy is usually a progressive myopathy manifesting as delayed motor development, generalized skeletal muscle weakness, decreased muscle mass and tone, abnormal gait, and loss of deep tendon reflexes. Affected infants may present with hypotonia, dysphagia, respiratory distress, and cyanosis. Additional findings include micrognathia, dental malocclusion, kyphoscoliosis, pectus excavatum, restrictive lung disease, cardiomyopathy, and cardiac failure.

Management of anesthesia. Preoperative evaluation should aim to detect and document pertinent systemic manifestations, including airway abnormalities, cardiac dysfunction, pulmonary disease, muscle weakness, speech and swallow dysfunction, and skeletal deformities. Intraoperatively, preparations should be in place for difficult tracheal intubation due to anatomic abnormalities such as micrognathia and a high-arched palate. Awake fiberoptic intubation may be prudent. Drug selection and dosage should take into account the likelihood of exaggerated respiratory depressant effects due to respiratory muscle weakness, chest wall abnormalities, ventilation/perfusion mismatching, and blunted ventilatory response to carbon dioxide. Aspiration precautions should be in place due to likelihood of bulbar palsy.

Succinylcholine is best avoided because it has unpredictable response in addition to the possibility of excessive potassium release. The response to nondepolarizing neuromuscular blockers is also unpredictable, ranging from resistance to increased sensitivity. The existing myopathy may obviate the need for the use of muscle relaxants in most cases. Volatile anesthetics may exacerbate existing myocardial depression. Plans for regional anesthesia must consider the possible respiratory compromise that could accompany a high motor block. In addition, the exaggerated lumbar lordosis or kyphoscoliosis may make neuraxial anesthesia technically difficult.

Myotonia Congenita

Myotonia congenita is a congenital autosomal myopathy that manifests at birth or early childhood, with widespread skeletal muscle involvement but sparing other organ systems. Myopathy consists of muscle hypertrophy and myotonia leading to childhood symptoms of difficulty swallowing, gagging, stiff movements, frequent falling, and difficulties opening eyelids after strenuous contraction or crying (von Graefe sign). Complications include aspiration pneumonia, frequent choking or gagging in infants, abdominal muscle weakness, chronic joint problems, and injury due to falls. Episodes of increased muscle tone may respond to phenytoin, mexiletine, or quinine therapy. Succinylcholine should be avoided due to abnormal response, including triggering myotonia with muscle rigidity and inability to intubate or ventilate, excessive hyperkalemia, prolonged weakness, and increased risk for malignant hyperthermia. Nonpharmacologic triggers of myotonia should be avoided, including hypothermia and shivering. Drugs effective in the treatment of myotonia include class Ib antiarrhythmic drugs such as lidocaine and phenytoin and in severe cases dantrolene, which inhibits the release of calcium from the sarcoplasmic reticulum.

Paramyotonia Congenita

Paramyotonia congenita is a rare autosomal dominant sodium channel dysfunction that manifests during early childhood with both generalized myotonia (triggered by exercise or cold) and flaccid paralysis (triggered by rewarming or spontaneously). The ability of hyperkalemia to trigger paralysis in some patients indicates that this condition could be a form of hyperkalemic periodic paralysis. The electromyogram may be normal at room temperature, but typical myotonic discharges become evident as muscles are cooled. Anesthetic management should focus on avoiding triggers of myotonia or paralysis, avoidance of hyperkalemia, and maintenance of normothermia.

Periodic Paralysis

Periodic paralysis is a spectrum of diseases characterized by intermittent acute attacks of skeletal muscle weakness or paralysis (sparing the muscles of respiration) in association either with hyperkalemia or, more commonly, with hypokalemia (Table 24.2). Attacks generally last for a few hours but may persist for days. Muscle strength is normal between attacks. Familial periodic paralysis is due to inherited genetic mutations

TABLE 24.2 Clinical Features of Familial Periodic Paralysis

Type	Serum Potassium Concentration During Symptoms (mEq/L)	Precipitating Factors	Other Features
Hypokalemic	⊔3.0	High-carbohydrate meal, strenuous exercise, glucose infusion, stress, menstruation, pregnancy, anesthesia, hypothermia	Cardiac dysrhythmias, electrocardiographic signs of hypokalemia
Hyperkalemic	⊓5.0	Exercise, potassium infusion, metabolic acidosis, hypothermia	Skeletal muscle weakness may be localized to tongue and eyelids

in one or more voltage-dependent sodium channels or in some inward rectifier potassium channels, which affects muscle membrane excitability. Diagnosis of hypokalemic familial periodic paralysis is supported by observing muscle weakness induced by hypokalemia, which is induced by intravenous infusion of a solution containing glucose and insulin, whereas the diagnosis of hyperkalemic familial periodic is supported by observing muscle weakness induced by hyperkalemia, which is induced by oral ingestion of potassium-containing solution. Through different mechanisms, acetazolamide is effective in the treatment of both forms of familial periodic paralysis. By producing a nonanion gap metabolic acidosis, acetazolamide protects against hypokalemia; and by promoting renal excretion of potassium, acetazolamide protects against hyperkalemia.

Management of anesthesia. In both forms of periodic paralysis, hypothermia must be avoided, which may require the use of normothermic cardiopulmonary bypass during cardiac surgery. Anesthetic and electrolyte management differ in the two forms of periodic paralysis.

Hypokalemic periodic paralysis. Preoperative considerations include maintenance of carbohydrate balance, without a carbohydrate load, correction of any electrolyte abnormalities, and avoidance of sympathetic system stimulation through avoidance of psychological stress or cold temperatures. Intraoperatively, glucose-containing solutions and drugs known to cause intracellular shifts of potassium (e.g., ¯-adrenergic agonists) must also be avoided. If diuresis is needed, mannitol can be administered in lieu of a potassium-wasting drug, such as thiazide diuretics. Frequent perioperative monitoring of serum potassium concentration is useful, and aggressive intervention to increase the serum potassium concentration (infusion of potassium chloride at a rate of up to 40 mEq/h) may occasionally be needed. Since hypokalemia may precede the onset of muscle weakness by several hours, prompt correction of hypokalemia may help avoid muscle weakness. Type 1 hypokalemic familial periodic paralysis is associated with mutation in *CACNA1S* gene, which is one of the genetic mutations that are also associated with malignant hyperthermia susceptibility. Therefore these patients could be at increased risk of malignant hyperthermia, and the use of nontrigger technique would be preferable. The response to nondepolarizing neuromuscular blockers could be prolonged; therefore their use is best avoided, or a short-acting nondepolarizing neuromuscular blocker should be used if skeletal muscle relaxation is required for the surgery. Regional anesthesia has been safely used and would allow avoiding many of the challenges associated with general anesthesia. Postoperative monitoring of respiratory function should be maintained until patient demonstrates complete recovery from anesthetic effects, and the means for mechanical support of ventilation should be made available.

Hyperkalemic periodic paralysis. Preoperative considerations include potassium depletion with potassium-wasting diuretics such as thiazides, prevention of carbohydrate depletion by administration of glucose-containing solutions, and avoidance of potassium-containing solutions and potassium-releasing drugs such as succinylcholine. Frequent monitoring of serum potassium concentration is indicated. Means of decreasing serum potassium levels include hyperventilation, adrenergic ⊥₂ agonists, and intravenous administration of glucose and insulin. Intravenous calcium administration is used for rapid antagonism of myocardial depressant effects of hyperkalemia. General anesthesia using inhalation or intravenous anesthetics is considered safe in these patients, as is epidural anesthesia. Postoperative monitoring of respiratory function should be maintained until patient demonstrates complete recovery from anesthetic effects and the means for mechanical support of ventilation should be made available.

Central Core Disease

Central core disease is an autosomal dominant muscular disorder that is named based on the histologic appearance of a central core of damaged area within muscle cell (fiber), which represents an area of disorganized myofibrils with missing mitochondria. Most cases have demonstrable de novo mutation in the ryanodine receptor type 1 *(RYR1)* gene, which is the most common site of genetic mutations associated with malignant hyperthermia susceptibility. Therefore all patients with central core disease are treated as malignant hyperthermia susceptible unless they had documented negative in vitro contractility testing, which is almost never done due to the high degree of association between the two conditions. The *RYR1* mutation leads to the production of defective sodium channels, which affects the influx of sodium and efflux of potassium and cell membrane depolarization. Clinical manifestations appear since birth and include hypotonia, mild developmental delay, facial muscle weakness, respiratory insufficiency, and subsequent skeletal malformations such as scoliosis and hip dislocation. Because central core disease has one of the highest associations with malignant hyperthermia, a nontrigger technique must be used in all patients in addition to having immediate availability of means of treatment of any malignant hyperthermia event.

Multicore Myopathy

Multicore (or multiminicore) myopathy is a histologic diagnosis that refers to multifocal areas of reduced oxidative staining, low myofibrillar ATPase, and paucity of mitochondria on muscle biopsy. These minicores do not extend the entire length of the muscle fiber as they do in central core disease. There may be mutations in the selenoprotein N gene *(SEPN1)* and the *RYR1* gene. The *SEPN1* mutation is not associated with increased susceptibility to malignant hyperthermia, but the *RYR1* mutation is. This myopathy represents a heterogeneous group of diseases characterized by severe axial skeletal muscle weakness (respiratory, bulbar, and extraocular), a decrease in muscle mass, kyphoscoliosis, high-arched palate, respiratory impairment, recurrent pulmonary infection, and cardiomyopathy. Unlike in other myopathies, serum creatine kinase concentration is usually normal, and intelligence is normal.

Management of anesthesia. Preoperative assessment of respiratory function is necessary in all patients, especially those with kyphoscoliosis and recurrent lung infection. Difficulty swallowing and an inability to clear secretions may reflect pharyngeal and laryngeal muscle involvement. Postoperative aspiration may be associated with impaired upper airway reflexes

and the lingering effects of drugs administered during anesthesia. Patients with multicore myopathy are treated as malignant hyperthermia susceptible with no need for further testing. A malignant hyperthermia nontrigger anesthetic technique must be implemented. Means of treatment of a malignant hyperthermia event, including the ryanodine receptor antagonist dantrolene, must be immediately available.

Centronuclear Myopathy

Centronuclear myopathy refers to a group of congenital myopathies in which the nucleus of the muscle cell is located in the center of the muscle cell instead of its normal location at the periphery of the muscle cell (hence the name). The disease is also known as myotubular myopathy when it is confirmed to be due to mutation in the myotubularin *(MTM1)* gene, which encodes for the myotubularin protein, which is involved in muscle cell growth, cell differentiation, cellular transport, molecule trafficking, and electrical signaling. There are severe neonatal forms of this disease, as well as slowly progressive forms that can begin any time from birth to adulthood. Clinically there is progressive muscle weakness in the muscles of the eye, face, neck, and limbs; scoliosis; restrictive lung disease; and ventilatory impairment, which may necessitate mechanical support of ventilation. Serum creatine kinase concentration is usually normal. Surgical repair of ptosis and strabismus is a frequent cause of surgical intervention in these patients.

Management of anesthesia. Management of anesthesia is influenced by the degree of skeletal muscle weakness, the presence of restrictive lung disease, ventilatory impairment, and gastroesophageal reflux. Muscle relaxants are to be avoided and a nontriggering general anesthetic technique is to be used.

Mitochondrial Myopathies

Mitochondrial myopathies are a heterogeneous group of disorders that affect skeletal muscle energy metabolism. Mitochondria produce the energy required by skeletal muscle cells through the oxidation-reduction reactions of the electron transfer chain and oxidative phosphorylation, thereby generating ATP. Oxidative phosphorylation reactions involve more than 80 proteins, 13 of which are encoded by mitochondrial DNA, while the others are encoded by nuclear DNA. Mitochondrial DNA differ from nuclear DNA in being maternally inherited, having higher number of genetic copies, having higher rate of spontaneous mutations, and in not containing intron (noncoding DNA). Mitochondrial myopathies are caused either by point mutations or sporadic large-scale mutations in mitochondrial DNA. Clinically there are five forms of mitochondrial myopathy caused by point mutations and three forms caused by sporadic large-scale mutations. Because energy metabolism affects all body functions there is usually involvement of all organ systems, particularly those with high energy demands (brain, heart, liver, kidney). Clinical muscular manifestations include easy fatigability, skeletal muscle pain, and progressive weakness. Histologically there are large subsarcolemmal accumulations of abnormal mitochondria that appear as red-staining granules (ragged-red fibers). Kearns-Sayre syndrome is one of the three mitochondrial myopathies that are caused by sporadic large-scale mutations. In addition to muscular manifestations, its clinical manifestations include progressive external ophthalmoplegia, retinitis pigmentosa, hearing loss, short stature, peripheral neuropathy, impaired ventilatory drive, heart block, cardiomyopathy, and congestive heart failure.

Management of Anesthesia

Preoperative evaluation requires thorough functional evaluation of all organ functions, particularly those with high energy demands, including the brain, heart, lungs, liver, endocrine glands, and musculoskeletal system. This is accomplished through comprehensive history and physical examination, and comprehensive ancillary testing, including ECG, echocardiography, and comprehensive metabolic and endocrine laboratory testing. Preoperative sedation outside the operating room should be avoided to avoid its respiratory depressant effects. Intraoperatively, capacity for artificial pacing should be readily available to deal with heart blocks or any arrhythmias. Succinylcholine should be avoided to avoid any additional increase in creatine kinase, lactic acidosis, or hyperkalemia. Drug selection should take into consideration the increased risk of drug-induced myocardial depression, development of cardiac conduction defects, and hypoventilation during the early postoperative period. Postoperatively, shivering, hypoxia, and hypotension should be avoided as they may lead to increased accumulation of lactic acid. These patients are at increased risk of infectious complications due to decreased mitochondrial activity, liver function, phagocytosis, and activity of the reticuloendothelial system.

Other Myopathies

Alcoholic Myopathy

Acute and chronic forms of proximal skeletal muscle weakness occur frequently in alcoholic patients. Differentiation of alcoholic myopathy from alcoholic neuropathy is based on the presence of proximal rather than distal skeletal muscle involvement, an increased serum creatine kinase concentration, myoglobinuria in acute cases, and rapid recovery after cessation of alcohol consumption.

Floppy Infant Syndrome

Floppy infant syndrome describes weak, hypotonic skeletal muscles in infants. A diminished cough reflex and difficulty swallowing predispose to aspiration, and recurrent pneumonia is common. Progressive weakness and atrophy of skeletal muscles leads to contractures and kyphoscoliosis.

Management of anesthesia. Anesthesia may be associated with increased sensitivity to nondepolarizing muscle relaxants and hyperkalemia with cardiac arrest after administration of succinylcholine. These infants are also susceptible to malignant hyperthermia. Ketamine can be useful for anesthesia because it does not cause significant respiratory depression.

Diseases of the Neuromuscular Junction

Myasthenia Gravis

Myasthenia gravis is the most common disease affecting the neuromuscular junction. It is a chronic autoimmune disorder

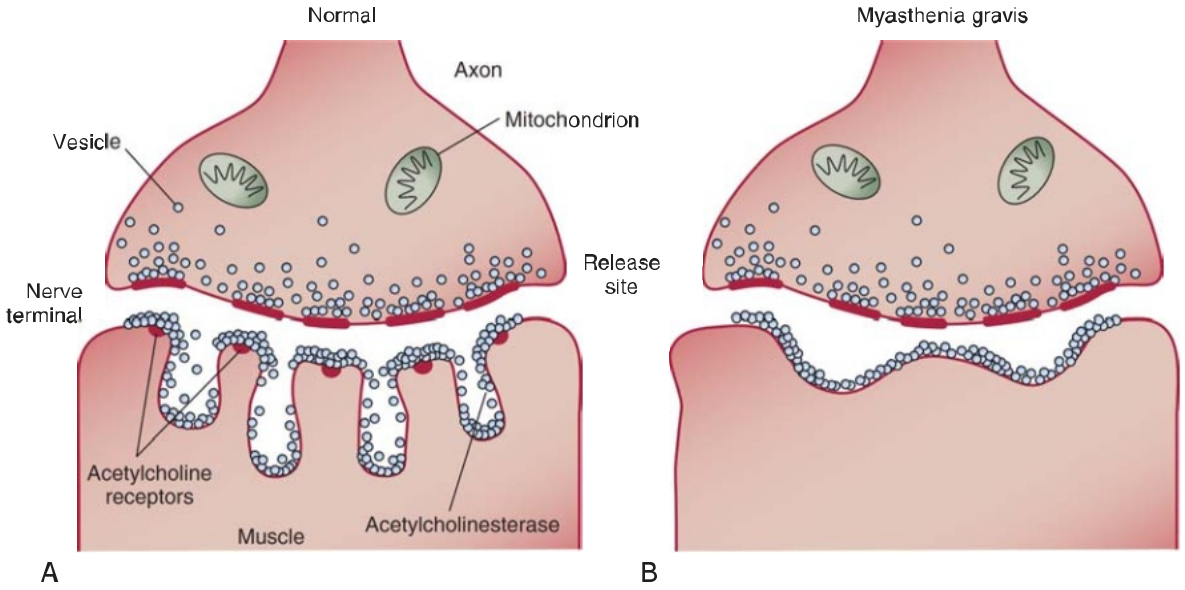

Fig. 24.6 Normal (A) and myasthenic (B) neuromuscular junctions. Compared with normal neuromuscular junctions, myasthenic neuromuscular junctions have fewer acetylcholine receptors, simplified synaptic folds, and widened synaptic spaces. (From Drachman DB. Myasthenia gravis. *N Engl J Med.* 1994;330:1797-1810. Copyright 1994 Massachusetts Medical Society. All rights reserved.)

caused by a decrease in functional acetylcholine receptors at the neuromuscular junction due to their destruction or inactivation by circulating autoantibodies (Fig. 24.6). The circulating autoantibodies are directed against the postsynaptic subunit of muscle-type acetylcholine receptors, leading to destruction of the receptor, while they spare the _ subunits of the neural-type acetylcholine receptors. This pathophysiology results in muscle weakness without peripheral, central, or autonomic nervous system dysfunction. In affected persons, as many as 80% of muscle-type postsynaptic acetylcholine receptors can be lost. Autoantibodies against muscle-type acetylcholine receptors are present in more than 85% of patients with myasthenia gravis. The origin of these antibodies is unknown, but a relationship to the thymus gland is suggested by the finding of thymic hyperplasia in 70% of patients and thymoma in 10% to 15% of patients. About 10% of patients with myasthenia gravis do not have autoantibodies against muscle-type acetylcholine receptor, but they do have antibodies against muscle-specific kinase (MuSK), which is a tyrosine kinase specifically present at the neuromuscular junction and is crucial in the formation and maintenance of the postsynaptic membrane. MuSK antibodies cause loss of acetylcholine receptors and a change in the structure of postsynaptic folds. Patients with MuSK antibodies do not have associated thymic disease. Some cases of myasthenia gravis are part of paraneoplastic syndrome.

Myasthenia gravis is not a rare disease. It has a prevalence of 1 in 7500. Women aged 20 to 30 years are most often affected; men with myasthenia gravis are often older than 60 years when the disease presents. After the age of 60 years, the incidence in men and women becomes almost the same. Skeletal muscles innervated by cranial nerves (ocular, pharyngeal, and laryngeal muscles) are especially vulnerable, as indicated by the early appearance of ptosis, diplopia, and dysphagia, which are often the initial symptoms of the disease. Other conditions that cause weakness of the cranial and somatic musculature must be considered in the differential diagnosis of myasthenia gravis (Table 24.3).

Myasthenia gravis is classified based on the skeletal muscles involved and the severity of symptoms. Type I is limited to involvement of the extraocular muscles. Approximately 10% of patients show signs and symptoms confined to the extraocular muscles and are considered to have ocular myasthenia gravis. Patients in whom the disease has been confined to the ocular muscles for longer than 2 years are unlikely to experience any progression in their disease. Type IIa is a slowly progressive, mild form of skeletal muscle weakness that spares the muscles of respiration. The response to anticholinesterase drugs and corticosteroids is good in these patients. Type IIb is a more rapidly progressive and more severe form of skeletal muscle weakness. The response to drug therapy is not as good, and the muscles of respiration may be involved. Type III is characterized by acute onset and rapid deterioration of skeletal muscle strength within 6 months. It is associated with a high mortality rate. Type IV is a severe form of skeletal muscle weakness that results from progression of type I or type II myasthenia.

Signs and symptoms. The clinical course of myasthenia gravis is marked by periods of exacerbation and remission. Muscle strength may be normal in well-rested patients, but weakness occurs promptly with exercise. Ptosis and diplopia resulting from extraocular muscle weakness are the most common initial complaints. Weakness of pharyngeal and laryngeal muscles can result in dysphagia, dysarthria, and difficulty handling saliva. Patients with myasthenia gravis are at high risk of pulmonary aspiration. Arm, leg, or trunk weakness can occur in any combination and is usually asymmetric. Muscle atrophy does not occur. Myocarditis can result in atrial fibrillation, heart block,

TABLE 24-3 Differential Diagnosis of Myasthenia Gravis

Condition	Symptoms and Characteristics	Comments
Congenital myasthenic syndromes	Rare, early onset, not autoimmune	Electrophysiologic and immunocytochemical tests required for diagnosis
Drug-induced myasthenia gravis		
Penicillamine	Triggers autoimmune myasthenia gravis	Recovery within weeks of discontinuing drug
Nondepolarizing muscle relaxants, aminoglycosides, procainamide	Weakness in normal persons; exacerbation of myasthenia	Recovery after drug discontinuation
Eaton-Lambert syndrome	Small cell lung cancer, fatigue	Incremental response on repetitive nerve stimulation, antibodies to calcium channels
Hyperthyroidism	Exacerbation of myasthenia gravis	Thyroid function abnormal
Graves disease	Diplopia, exophthalmos	Thyroid-stimulating immunoglobulin present
Botulism	Generalized weakness, ophthalmoplegia	Incremental response on repetitive nerve stimulation, mydriasis
Progressive external ophthalmoplegia	Ptosis, diplopia, generalized weakness in some cases	Mitochondrial abnormalities
Intracranial mass compressing cranial nerves	Ophthalmoplegia, cranial nerve weakness	Abnormalities on computed tomography or magnetic resonance imaging

Adapted from Drachman DB. Myasthenia gravis. *N Engl J Med.* 1994;330:1797-1810. Copyright 1994 Massachusetts Medical Society. All rights reserved.

or cardiomyopathy. Other autoimmune diseases may occur in association with myasthenia gravis. For example, hyperthyroidism is present in approximately 10% of patients with myasthenia gravis. Rheumatoid arthritis, SLE, and pernicious anemia occur more commonly in patients with myasthenia than in those without myasthenia. Approximately 15% of neonates born to mothers with myasthenia gravis demonstrate transient (2–4 weeks) skeletal muscle weakness. Infection, electrolyte abnormalities, pregnancy, emotional stress, and surgery may precipitate or exacerbate muscle weakness. Antibiotics, especially aminoglycosides, can aggravate muscle weakness. Isolated respiratory failure may occasionally be the presenting manifestation of myasthenia gravis. Testing for myasthenia gravis include Tensilon test and EMG. Tensilon test consists of intravenous injection of the short-acting anticholinesterase drug edrophonium (Tensilon), which decreases the activity of the enzyme cholinesterase and therefore increases the availability of the neurotransmitter acetylcholine at the neuromuscular junction and results in increased muscle strength. The Tensilon test is considered positive if it results in increased muscle strength within 5 minutes and its effect lasts 10 minutes. EMG usually demonstrates decreased compound muscle action potential after repetitive nerve stimulation.

Treatment. Treatment modalities for myasthenia gravis include anticholinesterase drugs to enhance neuromuscular transmission, thymectomy, immunosuppression, and short-term immunotherapy, including plasmapheresis and administration of IVIG.

Anticholinesterase drugs are the first line of treatment for myasthenia gravis. These drugs are effective because they inhibit the enzyme responsible for hydrolysis of acetylcholine and thus increase the amount of neurotransmitter available at the neuromuscular junction. Pyridostigmine is the most widely used anticholinesterase drug for this purpose. Its onset of effect occurs in 30 minutes, and peak effect is achieved in approximately 2 hours. Oral pyridostigmine lasts longer (3–6 hours) and produces fewer side effects than neostigmine. Pyridostigmine dosing is tailored to response, but the maximal dosage of pyridostigmine rarely exceeds 120 mg every 3 hours. Higher dosages may actually induce more muscle weakness (cholinergic crisis). The diagnosis of a cholinergic crisis is confirmed by the presence of significant muscarinic side effects (salivation, miosis, bradycardia) and accentuated muscle weakness after intravenous administration of edrophonium (1–2 mg). Although anticholinesterase drugs benefit most patients, the improvements may be incomplete and wane after weeks or months of treatment.

Thymectomy is intended to induce remission or at least allow the doses of immunosuppressive medications to be reduced. Patients with generalized myasthenia gravis are candidates for thymectomy. Preoperative preparation should include optimizing strength and respiratory function. Immunosuppressive drugs should be avoided if possible because they can increase the risk of perioperative infection. If the vital capacity is less than 2 L, plasmapheresis can be performed before surgery to improve the likelihood of adequate spontaneous respiration during the perioperative period. A surgical approach via median sternotomy optimizes visualization and removal of all thymic tissue. Mediastinoscopy through a cervical incision has been advocated as an alternative because it is associated with a smaller incision and less postoperative pain. The use of neuraxial analgesia minimizes postoperative pain and thus improves postoperative ventilation. The need for anticholinesterase medication may be decreased for a few days postoperatively, but the full benefit of thymectomy is often delayed for months. The mechanism by which thymectomy produces improvement is uncertain, although acetylcholine receptor antibody levels usually decrease after thymectomy.

Immunosuppressive therapy (corticosteroids, azathioprine, cyclosporine, mycophenolate) is indicated when skeletal muscle weakness is not adequately controlled by anticholinesterase drugs. Corticosteroids are most commonly used and are the most consistently effective immunosuppressive drugs for the treatment of myasthenia gravis.

Plasmapheresis removes antibodies from the circulation and produces short-term clinical improvement in patients with myasthenia gravis who are experiencing myasthenic crises or are being prepared for thymectomy. The beneficial effects of plasmapheresis are transient, and repeated treatment introduces the risk of infection, hypotension, and pulmonary embolism. The indications for administration of IVIG are the same as for plasmapheresis. The effect is temporary, and this treatment has no effect on circulating concentrations of acetylcholine receptor antibodies.

Management of anesthesia. Patients with myasthenia gravis often require ventilatory support after surgery. Therefore it is important to advise these patients during the preoperative interview that they may remain intubated and mechanically ventilated in the immediate postoperative period. Factors that may correlate with the need for mechanical ventilation during the postoperative period following transsternal thymectomy include (1) disease duration longer than 6 years, (2) a daily dose of pyridostigmine of more than 750 mg, (3) vital capacity less than 2.9 L, and (4) presence of chronic obstructive pulmonary disease (COPD) unrelated to myasthenia gravis. These factors are less predictive of the need for ventilatory support following transcervical thymectomy, which indicates that this less invasive surgical approach produces less respiratory impairment.

The acetylcholine receptor–binding antibodies of myasthenia gravis decrease the number of functional acetylcholine receptors, and this results in an increased sensitivity to nondepolarizing muscle relaxants. The balance between active and nonfunctional acetylcholine receptors modulates the sensitivity to nondepolarizing muscle relaxants. The initial muscle relaxant dose should be titrated according to response at the neuromuscular junction as monitored using a peripheral nerve stimulator. Monitoring these responses at the orbicularis oculi muscle may overestimate the degree of neuromuscular blockade but may help to avoid unrecognized persistent neuromuscular blockade in these patients.

It is possible that drugs used to treat myasthenia gravis can influence the response to muscle relaxants independent of the disease process. For example, anticholinesterase drugs not only inhibit true cholinesterase but also impair plasma pseudocholinesterase activity, which introduces the possibility of a prolonged response to succinylcholine. They could also antagonize the effects of nondepolarizing muscle relaxants. However, neither of these effects is seen clinically. Corticosteroid therapy does not alter the dose requirement for succinylcholine but has been reported to produce resistance to the neuromuscular blocking effects of steroidal muscle relaxants such as vecuronium.

Measurement of neuromuscular function in patients with myasthenia gravis treated with pyridostigmine demonstrates resistance to the effects of succinylcholine. The ED_{95} dose is approximately 2.6 times higher than normal. Because the dose of succinylcholine often administered to patients without myasthenia gravis (1–1.5 mg/kg) represents three to five times the ED_{95}, it is likely that adequate intubating conditions can be achieved in patients with myasthenia gravis using these typical doses of succinylcholine. The mechanism for the resistance to succinylcholine is unknown, but the decreased number of acetylcholine receptors at the postsynaptic junction may play a role.

However, in contrast to the resistance to succinylcholine, patients with myasthenia gravis exhibit marked sensitivity to nondepolarizing muscle relaxants. Even small doses of nondepolarizing muscle relaxant, such as those intended to block succinylcholine-induced fasciculations, can produce profound skeletal muscle weakness in some patients. In patients with mild to moderate myasthenia gravis, the potency of atracurium and vecuronium is increased at least twofold compared with the response in patients without the disease. Despite the increase in potency, the duration of action of intermediate-acting muscle relaxants is short enough that adequate skeletal muscle paralysis can be achieved intraoperatively and yet be predictably reversed at the conclusion of surgery.

Induction of anesthesia with a short-acting IV anesthetic is acceptable for patients with myasthenia gravis. However, the respiratory depressant effects of these drugs may be accentuated. Tracheal intubation can often be accomplished without neuromuscular blockers because of intrinsic muscle weakness and the relaxant effect of volatile anesthetics on skeletal muscle.

Maintenance of anesthesia is often provided with a volatile anesthetic with or without nitrous oxide. Use of volatile anesthetics can decrease the required dose of muscle relaxant or even eliminate the need for them altogether. Should administration of a nondepolarizing neuromuscular blocker be necessary, the initial dose should be decreased by one-half to two-thirds and the response monitored using a peripheral nerve stimulator. The relatively short duration of action of intermediate-acting muscle relaxants is a desirable characteristic in this patient group. The respiratory effects of opioids, which can linger into the postoperative period, detract from their use for maintenance of anesthesia. When the steroidal nondepolarizing neuromuscular blocker rocuronium is used, reversal of its action through the use of the chelating agent sugammadex may produce more reliable reversal of the neuromuscular blockade than through the use of a combination of neostigmine and glycopyrrolate.

At the conclusion of surgery, it is important to postpone extubation until clear evidence of good respiratory function is present. Skeletal muscle strength often seems adequate during the early postoperative period but may deteriorate a few hours later. The need for mechanical ventilation during the postoperative period should be anticipated in those patients meeting the criteria known to correlate with inadequate ventilation after surgery.

Myasthenic Syndrome

Myasthenic syndrome (Eaton-Lambert syndrome) is a disorder of neuromuscular transmission that differs from myasthenia gravis in its pathophysiology, clinical findings, and treatment (Table 24.4). Myasthenic syndrome was originally described as a paraneoplastic syndrome in patients with small cell carcinoma of the lung but was later found to occur in patients without cancer. Myasthenic syndrome is an acquired immune-mediated channelopathy in which IgG autoantibodies are

TABLE 24.4 Comparison of Myasthenic Syndrome and Myasthenia Gravis

Characteristic	Myasthenic Syndrome	Myasthenia Gravis
Muscular involvement	Proximal limb (legs L arms)	Extraocular, bulbar, and facial
Muscle pain	Common	Uncommon
Deep tendon reflexes	Absent or decreased	Normal
Gender likelihood	Males I I females	Females males
Likely coexisting neoplasm	Small cell lung cancer	Thymoma
Response to exercise	Improves	Worsens
Response to succinylcholine	Sensitive	Resistant
Response to nondepolarizing muscle relaxants	Sensitive	Sensitive
Response to anticholinesterases	Poor	Good

directed against presynaptic voltage-sensitive calcium channels and other presynaptic elements leading to decreases in both calcium entry and acetylcholine release from the presynaptic membrane upon depolarization.

Unlike myasthenia gravis, muscular weakness and fatigability are more likely to involve proximal muscles of the lower extremities than extraocular or bulbar muscles. Unlike myasthenia gravis, the symptoms are worse in the morning and improve throughout the day due to the accumulation of presynaptic calcium and subsequent release of acetylcholine. Unlike myasthenia gravis, autonomic dysfunction may exist. Unlike myasthenia gravis, EMG shows increase in motor action potential with nerve stimulation at 30 to 50 Hz. Unlike myasthenia gravis, Tensilon test is negative as the injection of this anticholinesterase drug produces little effect in symptom improvement. Unlike myasthenia gravis, treatment with anticholinesterase drugs is not effective in myasthenic syndrome. Rather, the drug 3,4-diaminopyridine (3,4-DAP), which increases acetylcholine release at the neuromuscular junction, improves muscle strength in myasthenic syndrome. In addition, IVIG, plasmapheresis, immunosuppressive therapy, and treatment of the underlying cancer can all cause improvement in this condition.

Management of anesthesia. Patients with myasthenic syndrome are sensitive to the effects of both depolarizing and nondepolarizing muscle relaxants. Antagonism of neuromuscular blockade with anticholinesterase drugs may be inadequate. The potential presence of myasthenic syndrome and the need to decrease doses of muscle relaxants should be considered in patients undergoing bronchoscopy, mediastinoscopy, or thoracoscopy for suspected lung cancer.

Malignant Hyperthermia Susceptibility

Malignant hyperthermia susceptibility is an inherited myopathy that remains largely symptomless until it is triggered by one of its three known triggers: halogenated vapor general anesthetics, the depolarizing muscle relaxant succinylcholine, and stress to skeletal muscles such as by strenuous exercise in hot environment. When triggered, malignant hyperthermia susceptibility turns into a malignant hyperthermia crisis, which consists of a hypermetabolic state of skeletal muscles with its wide range of physiologic and biochemical sequelae, including skeletal muscle rigidity, hypercarbia, tachypnea, tachycardia, tachyarrhythmias, hyperthermia in excess of 44°C (104°F), hypertension followed by hypotension, acidemia due to combined respiratory and metabolic acidosis, arterial and venous hypoxemia, rhabdomyolysis, myoglobinemia, myoglobinuria, acute kidney injury, hyperkalemia, hyperphosphatemia, hypermagnesemia, disseminated intravascular coagulopathy (DIC), and ultimately death.

The history of the recognition of malignant hyperthermia in humans and the subsequent discovery of its pathophysiology and treatment paralleled, and rather followed, its counterpart in pigs.

In 1960, Dr. Michael Denborough in Australia encountered a 21-year-old man who presented for surgical repair of leg fracture and who was more anxious about anesthesia than surgery because 10 of his relatives had died during or after receiving general anesthesia. Nevertheless, the patient was brought to the operating room and anesthetized with halothane, which resulted in a malignant hyperthermia crisis, which was promptly treated by halting the administration of halothane and aborting the surgery. The treatment of the malignant hyperthermia crisis was successful, and on a subsequent date the patient underwent surgery under spinal anesthesia and the operation was uneventful.

During the same period of the 1960s, a condition labeled porcine stress syndrome (PSS) was being recognized in pig farming. PSS was encountered in pigs that were being inbred for increased growth rate and muscle mass. While these breeds produced increased amount of meat, they were also susceptible to PSS, which, when occurred, rendered the produced meat unmarketable because it was pale, soft, and exudative (indicating rhabdomyolysis). In pigs susceptible for PSS, the stress consisted of events such as separation, shipping, weaning, fighting, coitus, and slaughter.

The manifestation of PSS consisted of increased muscle metabolism, including rigidity, pyrexia, sweating, panting, tachycardia, arrhythmia, and ultimately death. Pig farmers learned that pigs susceptible to PSS were also susceptible to dying from rigid pyrexia upon exposure to halothane. Pig farmers used the halothane challenge as a method of weeding off piglets susceptible to PSS by exposing piglets to halothane through halothane cones in pig yards and thus allowing those piglets who died from rigid pyrexia due to the exposure to halothane to be weeded off both from being raised to produce unmarketable meat and from breeding into a stock that is susceptible to PSS.

In 1966, a single genetic basis for both PSS and porcine malignant hyperthermia was experimentally demonstrated by producing a malignant hyperthermia crisis through the administration of halothane and succinylcholine in a pig susceptible to PSS that had a single missense mutation (Arg615Cys) in the gene *RYR1*, which encodes the ryanodine receptor (RyR1) of the sarcoplasmic reticulum calcium release unit (CRU). Subsequently, similar, although more complex, genetic basis for malignant hyperthermia was noted in humans.

In 1975, Dr. Harrison in South Africa demonstrated that a hydantoin derivative named dantrolene was effective in preventing and treating malignant hyperthermia in susceptible pigs. Subsequently, in 1982, similar efficacy of dantrolene was demonstrated in humans.

Thus the underlying genetic basis, pathophysiology, and treatment were demonstrated to be biologically similar in pigs and humans. Also, the developed musculature feature as a phenotypical feature of genetic susceptibility for malignant hyperthermia was noted in different species. Among animals, malignant hyperthermia susceptibility is encountered in pigs, horses, and dogs. In horses, malignant hyperthermia susceptibility is encountered in a breed known as the American Quarter Horse, which is known for its well-developed muscularity, especially hindquarters, which allows these horses to excel in short distance (quarter-mile) sprinting with speeds of 55 mph. In humans, anecdotal observations also indicate well-developed muscularity, especially calf muscles, in children susceptible to malignant hyperthermia, which lends further support to the notion of a unified biologic basis for malignant hyperthermia susceptibility across species.

Unlike pigs, in whom malignant hyperthermia susceptibility is linked to a single missense mutation (Arg615Cys) in a single gene *(RYR1)*, in humans malignant hyperthermia susceptibility has been linked to more than one genetic mutation in more than one gene, including genes on chromosomes 1, 3, 5, 7, 12, 17, and 19.

Specific genes in which mutations have been linked to malignant hyperthermia susceptibility include *CACNA1S* on chromosome 1, *STAC3* on chromosome 12, *CACNL1A3* on chromosome 17, and *RYR1* on the long arm of chromosome 19 (19q13.2).

In the *RYR1* gene, which codes for the calcium release channel of the skeletal muscle ryanodine receptor RYR1, more than 210 genetic mutations have been identified in 50% to 80% of families of malignant hyperthermia susceptibility, with more than 202 mutations being missense mutations and 8 being deletion mutations. The *RYR1* gene is the mutation site for almost 100% of families with central core disease (CCD) and King-Denborough syndrome (KDS), in the form of 29 missense mutations, which accounts for the high likelihood of malignant hyperthermia susceptibility in these two conditions, CCD and KDS, and why patients with these conditions are treated as malignant hyperthermia susceptible unless proven otherwise through an in vitro contraction test, which is a rare occurrence. About 40% of missense *RYR1* mutations occur at CpG nucleotide, which is labeled malignant hyperthermia susceptibility chromosomal locus 1 (MHS locus 1). There are five other malignant hyperthermia susceptibility chromosomal loci, labeled MHS loci 2-6, which are 17q21-24, 1q32, 3q13, 7q21-24, and 5p.

The *CACNL1A3* gene, which codes for the voltage-activated β_1 subunits of the calcium channel $Ca_V1.1$ of the dihydropyridine receptor (DHPR), is the site of four mutations linked to about 1% of cases of malignant hyperthermia susceptibility.

Other inherited myopathies that are highly associated with malignant hyperthermia susceptibility include Duchene and Becker muscular dystrophies. Patients with osteogenesis imperfecta may develop hyperkalemic response to succinylcholine and halogenated vapors without other manifestations of malignant hyperthermia.

The ryanodine receptor (RyR) is the largest protein channel in mammals, weighing more than 2 megadaltons. It is named after the poisonous herbal alkaloid ryanodine, which has high affinity to the animal receptor. In humans, the ryanodine receptor has three isoforms that are encoded by three different genes. The skeletal muscle isoform (RyR1) is encoded by a gene on chromosome 19q13.1. The cardiac muscle isoform (RyR2) is encoded by a gene on chromosome 1q42.1-q43. The brain isoform (RyR3) is encoded by a gene on chromosome 15q14-q15.

The skeletal muscle ryanodine receptor (RyR1) is the central component of the CRU of the sarcoplasmic reticulum, which regulates the release of calcium from the sarcoplasmic reticulum and interacts with four voltage-activated β_1 subunits of a calcium channel ($Ca_V1.1$) of a DHPR in the transverse tubules (T tubules) of the muscle cell membrane (sarcolemma). These muscle cell structures are responsible for muscle contraction and relaxation.

Muscle contraction begins with a nerve impulse arriving at the nerve terminal, which activates a voltage-gated calcium channel in the nerve, which leads to increased cytoplasmic calcium in the nerve, which leads to the release of acetylcholine from the presynaptic membrane of the neuromuscular junction to the postsynaptic nicotinic acetylcholine receptors, which leads to depolarization of the muscle membrane (sarcolemma), which activates the voltage-gated sodium channels in the muscle, which generates muscle action potential impulses, which propagate into the muscle T-tubule system, which activates the L-type voltage-gated calcium channels, which activates both the β_1 subunits ($Ca_V1.1$) of the DHPR and RyR1, which leads to calcium release from the sarcoplasmic reticulum, which leads to 100-fold increase in the cytoplasmic calcium concentration (from 10^{-7} μM to 10^{-5} μM), which results in calcium binding to contractile proteins, which leads to shortening of the muscle fibers and the occurrence of muscle contraction.

Muscle relaxation occurs mainly by returning the cytoplasmic calcium concentration to its baseline, which occurs as a result of sarcoplasmic/endoplasmic reticulum calcium-ATPase (SERCA) pumps that rapidly sequester calcium back into the sarcoplasmic reticulum lumen at the end of muscle contraction, which leads to 100-fold decrease in cytoplasmic calcium concentration from 10^{-5} M to 10^{-7} M, which leads to muscle relaxation that begins at cytoplasmic calcium concentration of 10^{-6} μM and is completed at cytoplasmic calcium concentration of 10^{-7} μM.

Mutations in the RyR1, the $Ca_V1.1$, or other receptors can alter protein-protein interactions in the calcium release unit and disrupt the normal excitation-contraction coupling of muscle contraction and muscle relaxation.

Succinylcholine enhances the steps in muscle contraction from the point of the release of acetylcholine from the presynaptic membrane to the point of activation of the L-type voltage-gated calcium channels in the muscle.

Halogenated vapors enhance the steps in muscle contraction from the point of activation of the α_1 subunit ($Ca_V1.1$) of the

DHPR and RyR1 to the point of calcium binding to the contractile proteins and the production of muscle contraction.

In malignant hyperthermia–susceptible individuals, exposure to the chemical or physical stressor produces a runaway unabated muscle contraction process that leads to the muscular hypermetabolic and hypercatabolic state that is known as a malignant hyperthermia crisis.

Because malignant hyperthermia crisis can be triggered by exposure to certain drugs, malignant hyperthermia susceptibility is called a pharmacogenetic disorder. However, abnormalities in muscle physiology can be demonstrated outside of the period of malignant hyperthermia crisis.

Animal models of malignant hyperthermia susceptibility have demonstrated that muscles expressing malignant hyperthermia mutations in the *RYR1* gene have elevated resting intracellular concentrations of both calcium and sodium. These biochemical changes reflect the channelopathy in the muscles and might explain the susceptibility of these muscles to undergo an uncontrolled contraction once exposed to certain triggers.

Human studies have demonstrated that persons with malignant hyperthermia susceptibility demonstrate manifestations of muscular hypermetabolism even during moderate exercise testing. This might explain the ability of extreme exercise in hot environment to produce malignant hyperthermia crisis in persons with genetic susceptibility to malignant hyperthermia. Case reports of exercise-induced malignant hyperthermia crises often include a history of previous milder episodes that were controlled with resting and cooling. Persons who are malignant hyperthermia susceptible are more likely to have exercise-induced rhabdomyolysis and are at increased risk of exercise-induced malignant hyperthermia crisis. One study that examined 12 patients with exercise-induced rhabdomyolysis found that 3 patients had *RYR1* mutation, 10 had abnormal in vitro contracture tests, and 1 patient had equivocal in vitro contracture test. Another indication of muscle hypermetabolism and catabolism is elevated levels of serum creatine kinase, which indicates muscle fiber breakdown. In relatives of persons who are malignant hyperthermia susceptible, elevated resting serum kinase concentration is used as an indication of having similar susceptibility. Indeed, the finding of elevated resting serum kinase levels in relatives of malignant hyperthermia–susceptible persons is sufficient to treat these relatives as malignant hyperthermia susceptible, with no need for genetic testing or in vitro contractile testing on a muscle biopsy.

The mechanism of action of dantrolene sodium as a specific antidote for malignant hyperthermia is consistent with the pathophysiology of malignant hyperthermia. Dantrolene is a hydantoin derivative. It acts by binding and blocking the RYR1 receptor, which blocks the release of calcium of the sarcoplasmic reticulum and the subsequent entry of calcium from the extracellular fluid. Thus it blocks specifically the physiologic process that initiates and maintains the malignant hyperthermia crisis. Dantrolene was a game changer in altering the treatment and prognosis of malignant hyperthermia. Before the introduction of dantrolene, mortality rates for malignant hyperthermia crises approached 80%. After the introduction of dantrolene, mortality rates were in the range of 1% to 30%, with rates currently probably closer to 1%, in view of the better understanding of the pathophysiology and the availability of preventative and therapeutic measures. One study in New Zealand reported zero mortality in a series of more than 120 malignant hyperthermia crises.

As the name indicates, hyperthermia is a main feature of malignant hyperthermia crises. Data from the malignant hyperthermia registry indicate that hyperthermia is the first sign of malignant hyperthermia event in one-third of the cases and it is one of the three initial signs in two-thirds of the cases. As the appellation malignant indicates, the hyperthermia rises rapidly at a rate of 1°C/5 minutes and reaches lethal levels of 42°C within minutes.

Although hyperthermia is not the sole manifestation of malignant hyperthermia, lack of temperature monitoring during general anesthesia can delay recognition of a malignant hyperthermia crisis, and temperature monitoring is important both during the administration and the recovery from general anesthesia.

During preoperative anesthetic evaluation, inquiry about personal or familial anesthetic complications is an essential component. Any account of personal or familial history of malignant hyperthermia should be investigated in detail, including complete details of the event, the circumstances of the event, and the outcome. Any subsequent or associated testing in the patient or family should be inquired about and documented. Genetic testing has a sensitivity of less than 50% of detecting malignant hyperthermia susceptibility; therefore it is not sufficient by itself to rule out the presence of malignant hyperthermia susceptibility. It should be also noted that previous uneventful exposure to triggering agents does not rule out malignant hyperthermia susceptibility. About 50% of patients of malignant hyperthermia crises had previous exposure to triggers with no reaction. Data from the North American Malignant Hyperthermia Registry (NAMHR) indicate that the median number of uneventful anesthesia experiences prior to a malignant hyperthermia crisis is 2 and the maximum is 30.

In vitro contracture testing of a muscle biopsy has been and remains the gold standard for the diagnosis of malignant hyperthermia susceptibility. However, in clinical settings, due to the safe feasibility of providing a nontrigger anesthetic technique, it is prudent to provide a nontrigger anesthetic technique whenever there is any doubt about the possibility of the presence of malignant hyperthermia susceptibility. The decision about proceeding with in vitro contracture testing of a muscle biopsy is governed by many factors, including the pretest probability based on clinical history and finding, the desire of the patient and family to increase the certainty of the diagnosis, the inconvenience of undergoing the test, and the desire to increase general knowledge about the condition. Studies of genetic inheritance patterns in humans indicate that in about 50% of families, malignant hyperthermia susceptibility has an autosomal dominant pattern with variable penetrance. An autosomal dominant inheritance pattern means that susceptibility to malignant hyperthermia would be found in 50% of

siblings, 50% of offspring, 25% of aunts and uncles, and 12.5% of cousins. Therefore, if a malignant hyperthermia episode occurs in a person, all the degrees of relatives mentioned should be alerted about their own possibility of having the condition. In KDS, an autosomal recessive pattern of inheritance of malignant hyperthermia susceptibility has been found. As indicated, in close relatives of a malignant hyperthermia–susceptible person, the finding of elevated resting serum creatine kinase level is sufficient to consider the relative susceptible to malignant hyperthermia without undergoing in vitro contracture testing. If resting serum creatine kinase levels are normal on several occasions, then an in vitro contracture testing is indicated.

If the decision is made to perform in vitro contracture testing, it is prudent to perform the muscle biopsy at the same institution that is going to perform the in vitro contracture testing to ensure muscle viability. There is a limited number of medical centers that perform in vitro contracture testing with about a dozen centers in the United States and about 30 centers worldwide. Myopathies not related to malignant hyperthermia susceptibility contribute to false positive results. In general, a positive in vitro contracture test is followed by genetic testing to detect any associated DNA mutations. Relatives who are carrying the same genetic mutations of a known malignant hyperthermia–susceptible person are considered malignant hyperthermia susceptible even without in vitro contracture testing.

There are two protocols for the in vitro contractile test: European and North American.

The European test is the in vitro caffeine halothane contracture test (IVCT) according to the European Malignant Hyperthermia Group (EMHG). It consists of the following.

The muscle biopsy source should be the quadriceps: either vastus medialis or vastus lateralis. Testing on the muscle requires three tests:

1. Static caffeine test. It aims to establish the caffeine threshold, which is the lowest caffeine concentration (0.5, 1, 1.5, 2, 3, 4, 32 mmol/L) that leads to sustained increase in baseline tension of more than 0.2 g.
2. Static halothane test. It aims to establish the halothane threshold, which is the lowest halothane concentration (0.5%, 1%, 2%, 3%) that leads to sustained increase in baseline tension of more than 0.2 g.
3. Dynamic halothane test. It aims to establish a dynamic halothane threshold, which is the lowest concentration (0.5%, 1%, 2%, 3%) that leads to sustained increase in posthalothane tension of _ 0.2 g, compared with a prehalothane control, achieved by stretching the muscle (4 mm/min to achieve a force of 3 g) and holding it for 1 minute before a 3-minute halothane exposure.

Based on this testing the results can be one of three possibilities:

1. Malignant hyperthermia susceptible: if caffeine threshold ¬2 mmol and halothane threshold ⌐ 2%
2. Malignant hyperthermia negative: if caffeine threshold ¬3 mmol without halothane threshold ¯ 2%
3. Malignant hyperthermia equivocal: if any other than possibilities 1 and 2 is obtained

The European test has high sensitivity and specificity. The sensitivity is 99.0% if the malignant hyperthermia equivocal result is considered malignant hyperthermia susceptible. The specificity is 94% (i.e., there is 6% false positive).

The American test is the in vitro caffeine halothane contracture test (CHCT) according to the North American Malignant Hyperthermia Group (NAMHG). It consists of the following:

The muscle source could be from the vastus group, the rectus abdominus, or other. Testing on the muscle consists of required tests and optional tests.

1. The required tests consist of exposure to 3% halothane alone, and to caffeine (0.5, 1, 2, 4, 8.0, 32 mmol) alone.
2. The optional tests consist of exposure to both 1% halothane and caffeine (0.5, 1, 2, 4, 8.0, 32 mmol), and to 2% halothane alone.

Based on this testing the results can be either one of two possibilities:

1. Malignant hyperthermia susceptible: if either halothane or caffeine test is positive
2. Malignant hyperthermia negative: if both halothane and caffeine tests are negative

The North American protocol has lower sensitivity and specificity than the European protocol. The sensitivity is 97%. The specificity is 80% (i.e., 20% false positive).

The effects of other substances and conditions on the in vitro contracture test highlight some physiologic aspects of the condition of malignant hyperthermia susceptibility. Both ryanodine, the herbal alkaloid after which the animal receptor is named, and the ryanodine receptor–agonist 4-chloro-m-cresol have been suggested for in vitro contractile testing and have been used in some centers.

Statins, which inhibit ATPase production in mitochondria and can lead to elevated serum creatine kinase and rhabdomyolysis in some persons, have been shown to result in contractures in muscles taken from malignant hyperthermia–susceptible persons but not in muscle taken from malignant hyperthermia–negative persons.

Professional athletes who have highly developed musculature are more likely to have statin-related muscle problems than persons with less developed musculature.

Like statins, fluoroquinolones have been found to produce contractures in muscles taken from malignant hyperthermia–susceptible persons but not in muscle taken from malignant hyperthermia–negative persons.

Both ondansetron and 3,4-methylenedioxymethamphetamine (MDMA) have been shown to produce contracture and increase sensitivity to calcium both in malignant hyperthermia–susceptible persons and malignant hyperthermia–negative persons.

With current understanding of the pathophysiology of malignant hyperthermia and availability of anesthetic techniques that avoid pharmacologic triggers of malignant hyperthermia, it is possible to provide safe anesthesia to patients who are susceptible to malignant hyperthermia. Besides avoiding the use of pharmacologic triggers of malignant hyperthermia, preparations for safe anesthetic for a malignant hyperthermia patient should include the following:

Having an anesthetic plan that consists of any combination of monitored anesthesia care (MAC) with intravenous sedation, total intravenous anesthesia (TIVA), or regional anesthesia.

Having malignant hyperthermia cart, containing dantrolene, immediately available.

Performing anesthesia machine preparation for a nontrigger technique, including the following:

Removing the vaporizers from the anesthesia machine, to avoid accidental use.

Changing the carbon dioxide absorbent, to avoid delivery of any residual halogenated vapor.

Changing the breathing circuit, which is done routinely anyway, to avoid delivery of any residual halogenated vapor.

Placing activated charcoal filters both on the inhalation and exhalation limbs of the breathing circuit. This maneuver can be also implemented in case a malignant hyperthermia crisis occurs unexpectedly. These filters are effective in absorbing halogenated vapors within 1 minute of implementation and their efficacy lasts for 12 hours.

Flushing the anesthesia machine from any residual halogenated vapors by using fresh gas flow rates of 10 to 15 L/min for a period of 10 to 15 minutes. This should reduce the concentration of residual halogenated vapor to less than 5 parts per million. Some authors suggest that modern anesthetic machines may have to be flushed for a period of 60 minutes due to the presence of more rubber and plastic components in these machines than older ones. However, with the use of all these measures, including the charcoal filters, the shorter duration of 10 to 15 minutes would probably be sufficient.

Checking the gas analyzer on the anesthesia machine to confirm a reading of zero halogenated vapor both in the inhalation and the exhalation limbs of the breathing circuit.

The incidence of malignant hyperthermia crisis varies depending on the geographic location and the studied population. Overall reported incidence ranges from 1:8000 to 1:100,000. The prevalence of genetic susceptibility to malignant hyperthermia similarly varies according to the studied population and performance of testing, but in general it has an overall prevalence of 1:2000. In the United States there are about 10 to 12 cases per year of malignant hyperthermia crises. Current mortality rate is probably in the range of 1%, but mortality due to both anesthesia-related and nonanesthesia-related malignant hyperthermia crises still occurs. It is possible that the ratio of nonanesthesia-related cases to anesthesia-related cases would increase due to less awareness and readiness in the nonanesthesia environment than in the anesthesia environment.

The anesthetic triggers of malignant hyperthermia consist of halogenated vapors and depolarizing muscle relaxant. The halogenated vapors include methoxyflurane ($CHCl_2CF_2OCH_3$), enflurane ($C_3H_2ClF_5O$), halothane ($CF_3CHBrCl$), isoflurane (CHF_2-O-$CHCl$-CF_3), desflurane (CHF_2-O-CHF-CF_3), and sevoflurane (CH_2F-O-$CH(CF_3)_2$). The depolarizing muscle relaxant is succinylcholine, which is also named suxamethonium.

Onset of a malignant hyperthermia crisis is more explosive if both succinylcholine and halogenated vapor are used. About 80% of malignant hyperthermia crises include the use of both halogenated vapor and succinylcholine.

Halogens are salt-producing chemical elements so named because they produce salts upon reacting with metals (*halo* is Greek for salt). A halogenated vapor is a vapor into which a halogen was introduced. The three halogens that are introduced into anesthetic vapors are fluorine, chlorine, and bromine. Fluorine is the most reactive element in the periodic table. It is a yellow poisonous gas that burns the skin upon contact. It is present in all halogenated vapors. Chlorine is a green poisonous gas that was used during World War I and is currently used as a water disinfectant in pools. It is present in the older halogenated vapors (methoxyflurane, enflurane, halothane, and isoflurane) but not in the newer ones (desflurane and sevoflurane). Bromine is a red, fuming toxic liquid with chocking smell (hence the name: *bromos* is Greek for stench). It is present in halothane only.

The effect of halogenated vapors on the excitation-contraction coupling of muscle contraction is that they stimulate RyR1 in the skeletal muscles and the subsequent step of calcium release from the sarcoplasmic reticulum, which can explain the role of halogenated vapors in triggering the unabated muscle contraction in patients with mutations in the *RyR1* gene.

The effect of succinylcholine on the excitation-contraction coupling of muscle contraction is that it stimulates the early stages of excitation-contraction coupling, including the release of acetylcholine from the presynaptic membrane of neuromuscular junction and the subsequent activation of the voltage-gated sodium channels and the L-type voltage-gated calcium channels. This activation of the early stages can extend into the final stages of the excitation-contraction coupling that involves RyR1. This can explain the role of succinylcholine in triggering malignant hyperthermia crisis in some with genetic mutations affecting either the *RyR1* gene or genes affecting the sodium or calcium channels.

Succinylcholine-induced masseter muscle rigidity, which is also called masseter spasm or trismus, has been linked to malignant hyperthermia susceptibility. Masseter muscle rigidity refers to contraction of slow tonic fibers in masseter and lateral pterygoid muscles. It is usually not preventable by defasciculating dose of a nondepolarizing muscle relaxant. It could be a sign of myotonia or malignant hyperthermia susceptibility. It can be associated with positive in vitro contraction test in up to 50% of patients. It is associated with rigidity of other muscles and could be a sign of malignant hyperthermia in up to 20% of patients. It is encountered in 15% to 30% of cases of malignant hyperthermia crisis. It is encountered in up to 1% of children who receive succinylcholine. There are two management options after masseter muscle spasm rigidity:

a. Consider it a case of malignant hyperthermia crisis, postpone the scheduled elective surgery, monitor the patient for any signs of malignant hyperthermia, and treat accordingly.
b. Proceed with the scheduled case using nontrigger anesthesia technique.

Either way, it is recommended to observe the patient postoperatively for a period of 12 to 24 hours for any signs of malignant hyperthermia by monitoring end-tidal carbon dioxide concentration, urine analysis, serum creatine kinase, potassium level,

and ABGs. The Malignant Hyperthermia Association of the United States (MHAUS) recommends measuring creatine kinase and urine myoglobin every 6 hours for a period of 36 hours.

Besides potentially triggering malignant hyperthermia crises and master muscle rigidity, succinylcholine can induce excessive hyperkalemia and myotonic contractures in a host of other conditions.

Succinylcholine-induced excessive hyperkalemia is encountered in anatomic or functional muscle denervation disorders in which proliferation of extrajunctional acetylcholine receptors leads to excessive hyperkalemia upon exposure to succinylcholine, or in conditions of acidemia. Medical disorders that have been associated with succinylcholine-induced excessive hyperkalemia are listed in Box 24.3.

Medical disorders in which succinylcholine can induce myotonic contractures include amyotrophic lateral sclerosis (ALS), hyperkalemic familial periodic paralysis, muscular denervation due to peripheral nerve injury, and various types of myotonia (dystrophica, congenita, and paramyotonia).

Certain neurologic and neuromuscular disorders are associated with increased sensitivity to succinylcholine. These include cerebral palsy, dermatomyositis, polymyositis, systemic lupus erythematosus, and Eton-Lambert myasthenic syndrome. In contrast, myasthenia gravis can be associated with resistance to succinylcholine and proneness to phase II block.

Reports of increased likelihood of malignant hyperthermia crisis during certain types of surgical procedures are probably related to the presence of certain underlying medical conditions that predispose these patients to malignant hyperthermia. Types of surgical procedures that have been reported to be associated with increased risk of malignant hyperthermia crises include joint dislocation repair, idiopathic scoliosis repair, clubfoot repair, ptosis repair, strabismus repair, tonsillectomy and adenoidectomy, dental procedures, and cleft palate repair.

BOX 24.3 Disorders Associated With Succinylcholine-Induced Excessive Hyperkalemia

- Acidosis
- Burn injury
- Cerebral aneurysm, ruptured
- Duchenne muscular dystrophy (in addition to malignant hyperthermia susceptibility)
- Encephalitis
- Hyperkalemic familial periodic paralysis
- Guillain-Barré syndrome (GBS)
- Immobilization, prolonged
- Infection, severe
- Parkinson disease, severe
- Polyneuropathy, peripheral nerve injury, muscular denervation
- Spinal cord injury
- Shock
- Stroke, hemiplegia
- Tetanus
- Trauma
- Traumatic brain injury (TBI)

Hyperthermia is not one of the earliest signs of malignant hyperthermia crisis. Earlier signs of malignant hyperthermia crisis include increases in end-tidal carbon dioxide concentration ($EtCO_2$), heart rate and respiratory rate (if the patient is able to breath spontaneously), masseter muscle rigidity (if succinylcholine was used), generalized muscle rigidity, mixed metabolic and respiratory acidosis, profuse sweating, mottling of skin, cardiac arrhythmias, and lability in blood pressure. Later signs of malignant hyperthermia crisis include rapidly rising core body temperature (at a rate of 1°C/5 min to levels ⩾ 44°C [104°F]), hyperkalemia, elevated serum creatine kinase levels, myoglobinemia, myoglobinuria, cardiac arrest, and DIC.

Differential diagnoses of intraoperative hyperthermia are listed in Box 24.4.

If a malignant hyperthermia crisis is encountered intraoperatively, a malignant hyperthermia crisis code should be activated. A member of the malignant hyperthermia crisis code team should call the malignant hyperthermia hotline for assistance. The toll-free number is 1-800-MH-Hyper (1-800-644-9737), the direct number is 1-315-464-7079, and the toll-free fax number is 1-800-440-9990. Steps taken by the malignant hyperthermia crisis code team should include:

- Stop the malignant hyperthermia crisis trigger, which consists of:
  - Discontinuing any halogenated vapor
  - Increasing the fresh gas flow to 10 to 15 L/min
  - Changing the breathing circuit
  - Changing the CO_2 absorber
  - Applying charcoal filters to both the inhalation and the exhalation limbs of the breathing circuit
- Treat the life-threatening hypermetabolic state, which consists of:
  - Increasing the minute ventilation to more than twofold from baseline
  - Applying 100% Fio_2
  - Increasing the rates of IV fluids
- Apply cooling measures, which consists of:
  - Cooling the skin by using cooling blankets or ice bags

BOX 24.4 Differential Diagnosis of Intraoperative Hyperthermia

- Malignant hyperthermic (MH)
- Neuroleptic malignant syndrome (NMS), also known as antidopaminergic syndrome
- Thyroid storm
- Pheochromocytoma
- Iatrogenic hyperthermia
- Brainstem-hypothalamic injury
- Sepsis
- Transfusion reaction
- Drug-induced hyperthermia:
  - Serotonin syndrome (SSRI)
  - Tyramine crisis (monoamine oxidase inhibitors [MAOIs], meperidine)
  - Anticholinergic crisis (tricyclic antidepressant [TCA])
  - Sympathomimetic crisis (cocaine, amphetamine, MDMA [ecstasy], phencyclidine [PCP], LSD)

  - Cooling body cavities with irrigation fluids such as gastric or rectal irrigation
  - Using cold IV fluids
  - Performing hemodialysis or cardiopulmonary bypass
  - Stopping cooling when core body temperature is down to 38°C
- Administer the specific antidote dantrolene at an initial dose of 2.5 mg/kg IV bolus, which can be repeated every 5 minutes until resolution of the crisis, or a dose of 10 mg/kg has been given.
- Administer medications to treat hyperkalemia, including sodium bicarbonate ($NaHCO_3$) at a dose of 1 to 4 mEq/kg IV, a combination of insulin and dextrose, and calcium chloride.
- Administer medications to treat arrythmias, including amiodarone.
- Administer medications to promote diuresis, including Lasix and mannitol, which is usually contained in the dantrolene preparation at a rate of 3 mg mannitol/20 mg dantrolene.
- Obtain laboratory tests and correct accordingly, including arterial blood gases, urine analysis, complete blood count, comprehensive metabolic panel, serum creatine kinase, disseminated intravascular coagulation panel (including platelet count, prothrombin time, partial thromboplastin time, and international normalized ratio), fibrinogen, and fibrinogen degradation products.
- Insert additional catheter as needed, including peripheral intravenous catheters, arterial catheters, Foley bladder catheter, nasogastric tube, and central venous catheter.

Dantrolene is a hydantoin derivative that binds to the RYR1 receptor and blocks the release of calcium from the sarcoplasmic reticulum and the subsequent entry of calcium from the extracellular fluid. It is available in three forms: oral capsules for prophylaxis of muscle spasm in spastic conditions, a powder form for dissolution into an injectable solution for IV injection, and a suspension form for reconstitution into an injectable solution for IV injection. The initial dose in the treatment of a malignant hyperthermia crisis is 2.5 mg/kg IV, which can be repeated every 5 minutes until resolution of the malignant hyperthermia crisis or until a 10-mg/kg dose has been given. After resolution of the crisis, it is given in a dose of 1 mg/kg every 6 hours for a duration of 48 hours. The frequency is based on a half-life of 6 hours.

Dantrolene sodium is also effective in the treatment of thyroid storm and neuroleptic malignant syndrome, two conditions that can mimic malignant hyperthermia. The dose for chronic prophylaxis in spastic conditions is 5 to 10 mg/kg orally. The powder form has low water solubility requiring 60 mL of sterile water to dissolve each 20 mg of powder over a period of 20 seconds. This task can be time consuming considering that a dose of 2.5 mg/kg for the average adult consists of about 10 vials containing 20 mg powder each. The suspension form is much more convenient to use, as it contains 250 mg to be reconstituted with 5 mL sterile water, which provides the initial dose for an average adult requiring 2.5 mg/kg. MHAUS recommends stocking dantrolene sodium in the malignant hyperthermia cart in a total dose of 720 mg, which is sufficient to provide a dose of 10 mg/kg for a 72-kg person. When stocking dantrolene in the powder form, a dose of 720 mg would require 36 vials of the 20-mg vials, while the same dose would require stocking only 3 vials of the suspension form containing 250 mg per vial. Complications of dantrolene sodium include muscle weakness (21.7%), including pharyngeal and respiratory muscles; phlebitis (9%), therefore it should be injected through the largest available intravenous catheter; gastrointestinal upset (4.1%); respiratory failure (3.8%); hyperkalemia (3.3%); excessive salivary secretions (8.2%); and liver dysfunction.

At the conclusion of acute treatment for a malignant hyperthermia crisis, the patient should be admitted to an intensive care unit (ICU) for continued treatment and monitoring for the first 24 hours or as needed afterwards. In the ICU, all therapeutic and resuscitative measures should be continued as needed. Due to a 50% likelihood of recurrence in the postoperative period, dantrolene therapy should be continued in the form of either intermittent dose of 1 mg/kg every 6 hours or as a continuous infusion of 0.25 mg/kg/h for a duration of 1 to 2 days. Continuous temperature monitoring should continue in the ICU. Laboratory testing should continue, including ABGs, creatine kinase, coagulation profile, complete blood count, comprehensive panel, and urine analysis. Particularly hyperkalemia should be continually evaluated and treated until resolved and remains stable. Calcium channel blockers should be avoided for two reasons: (1) They can increase intracellular calcium in skeletal muscles, which can aggravate any malignant hyperthermia pathophysiology. This effect is more prominent in nifedipine than verapamil, and more so than diltiazem. (2) The combination of calcium channel blocker and dantrolene can lead to worsening of hyperkalemia, including the possibility of leading to cardiac arrest. All cases of malignant hyperthermia crisis should be reported to MHAUS (www.mhaus.org). An Adverse Metabolic Reaction to Anesthesia (AMRA) form should be completed, and the patient should be entered into the North American Malignant Hyperthermia Registry (NAMHR, www.mhreg.org).

SKELETAL DISEASES

Osteoarthritis

Osteoarthritis is by far the most common joint disease, which is one of the leading chronic diseases of the elderly and a major cause of disability. Osteoarthritis is a degenerative process that affects articular cartilage. This process is different from rheumatoid arthritis because there is minimal inflammatory reaction in the joints. The pathogenesis is likely related to joint trauma from biomechanical stresses, joint injury, or abnormal joint loading resulting from neuropathy, ligamentous injury, muscle atrophy, or obesity. Pain is usually present on motion and is relieved by rest. Stiffness tends to disappear rapidly with joint motion, in contrast to the morning stiffness associated with rheumatoid arthritis, which can last for several hours.

One or several joints can be affected by osteoarthritis. The knees and hips are common sites of involvement. Bony enlargements referred to as Heberden nodes are seen at the distal

interphalangeal joints of the fingers. There may be degenerative disease of the vertebral bodies and intervertebral disks, which can be complicated by protrusion of the nucleus pulposus and compression of nerve roots. Degenerative changes are most significant in the middle to lower cervical spine and the lumbar area. Radiographic findings include narrowing of the intervertebral disk spaces and osteophyte formation.

Although often overlooked, physical therapy and exercise programs can provide benefits for patients with osteoarthritis. Maintaining muscle function is important for both cartilage integrity and pain reduction. Pain can also be relieved by application of heat, use of simple analgesics such as acetaminophen, and treatment with antiinflammatory drugs. Symptomatic improvement with application of heat may be due to an increase in pain threshold in warm tissues compared with that in cold tissues. Transcutaneous nerve stimulation and acupuncture can be effective in some patients. Systemic corticosteroids have no place in the treatment of osteoarthritis. Joint replacement surgery may be recommended when pain caused by osteoarthritis is persistent and disabling or significant limitation of joint function is present.

Anesthetic Considerations

Preoperative evaluation should document the extent of limitation in range of motion of involved joints, particularly those of the cervical spine; any associated radiculopathy; baseline severity of pain; and all pain management interventions, including NSAIDS and opioids, and any possible side effects of these medications. Intraoperatively, limitation in range of motion can affect patient position, even though many of these limitations can attenuate with skeletal muscle relaxants. Limitations in range of motion of cervical spine or other joints can affect airway management and may necessitate using video laryngoscopy or fiberoptic bronchoscopy for endotracheal intubation. Postoperative analgesic requirements may be increased in patients who are opioid users.

Kyphoscoliosis

Kyphoscoliosis is a spinal deformity characterized by anterior flexion (kyphosis) and lateral curvature (scoliosis) of the vertebral column. Idiopathic kyphoscoliosis, which accounts for 80% of cases, commonly begins during late childhood and may progress in severity during periods of rapid skeletal growth. The incidence of idiopathic kyphoscoliosis is approximately 4 per 1000 population. There may be a familial predisposition to this disease, and females are affected four times more often than males. Diseases of the neuromuscular system (e.g., poliomyelitis, cerebral palsy, muscular dystrophy) may also be associated with kyphoscoliosis.

Spinal curvature of more than 40 degrees is considered severe and is likely to be associated with physiologic derangements in cardiac and pulmonary function. Restrictive lung disease and pulmonary hypertension progressing to cor pulmonale are the principal causes of death in patients with kyphoscoliosis. As the scoliosis curvature worsens, more lung tissue is compressed, which results in a decrease in vital capacity and dyspnea on exertion. The work of breathing is increased because of the abnormal mechanical properties of the distorted thorax and the increased airway resistance that results from small lung volumes. The alveolar-arterial oxygen difference is increased. Pulmonary hypertension is the result of increased pulmonary vascular resistance due to compression of lung vasculature and the response to arterial hypoxemia. The Paco2 is usually maintained at normal levels, but an insult such as bacterial or viral upper respiratory tract infection can result in hypercapnia and acute respiratory failure. A poor cough contributes to frequent pulmonary infection.

Management of Anesthesia

Preoperatively it is important to assess the severity of the physiologic derangements produced by this skeletal deformity. Pulmonary function test results reflect the magnitude of restrictive lung disease. Arterial blood gas (ABG) values are helpful for detecting unrecognized hypoxemia or acidosis that could be contributing to pulmonary hypertension. These patients may have preoperative pulmonary infection resulting from chronic aspiration. Certainly, any reversible component of pulmonary dysfunction such as infection or bronchospasm should be corrected before elective surgery.

Although no specific drug or drug combination can be recommended as optimal for patients with kyphoscoliosis, it should be remembered that nitrous oxide may increase pulmonary vascular resistance. This could be particularly problematic in patients with pulmonary hypertension. Monitoring central venous pressure (CVP) may provide data suggesting an increase in pulmonary vascular resistance, although the benefits of CVP measurements must be weighed against the risks of central venous catheter insertion, particularly in patients with the anatomic abnormalities of kyphoscoliosis.

When a patient is undergoing surgery to correct the spinal curvature, special anesthetic considerations include the potential for blood loss, surgically induced spinal cord damage, and ischemic optic neuropathy. Controlled hypotension as a way of decreasing blood loss should be used with caution because of the risk of ischemic optic neuropathy and spinal cord ischemia. Prolonged surgery and a high transfusion threshold could increase the risk of ischemia. At the time the spinal curvature is straightened or distracted, excessive traction on the spinal cord can result in spinal cord ischemia, which can produce paralysis. Intraoperative neurophysiologic monitoring is commonly used to monitor the functional integrity of the spinal cord during surgery. Somatosensory and/or motor evoked potentials are most commonly used. The addition of processed electroencephalogram (EEG) monitoring as a monitor for depth of anesthesia can help in the differential diagnosis of abnormalities of evoked potentials whether they are induced by ischemic or mechanical injury to the spinal cord or by pharmacologic suppression of neural function. The addition of an intraoperative wake-up test can further help in the detection and differential diagnosis of spinal cord injury. Neurophysiologic monitoring techniques and the wake-up test can be used separately or in combination during spine surgery. The wake-up test consists of brief waking up of the patient, after surgical correction has been performed and while the patient is still in the operative surgical position and conditions, and asking

the patient to move limbs to ensure spinal cord functional integrity, after which general anesthesia is reinduced and the surgery is completed. The wake-up test requires that adequate reversal of any neuromuscular blockade has taken place and that the state of general anesthesia has been sufficiently resolved to allow the patient to perceive and respond to verbal commands of moving the limbs. Neurophysiologic monitoring in the form of evoked potentials requires adjusting anesthetic drug selection and dosage to provide the least pharmacologic interference with the physiologic monitoring. Neuromuscular blockers cannot be used if motor evoked potentials are being monitored. Volatile anesthetics and nitrous oxide interfere with evoked potentials to a greater degree than intravenous anesthetics, therefore total IV anesthesia alone or in combination with low-dose volatile anesthetic is usually chosen to provide general anesthesia. Upon emergence from anesthesia the two main concerns are patency of the upper airway and restoration of adequate ventilation. If either is not sufficiently restored, continued intubation and mechanical ventilation are maintained until there is resolution of upper airway edema and restoration of adequacy to perform the work of breathing in the presence of adequate analgesia.

Back Pain

Low back pain is the most common musculoskeletal complaint requiring medical attention. Risk factors for low back pain include male gender, frequent lifting of heavy objects, and smoking. In many patients the cause of the back pain cannot be determined with certainty, and it is usually attributed to muscular or ligamentous strain, facet joint arthritis, or disk pressure on the annulus fibrosus, vertebral end plate, or nerve roots. According to duration, low back pain may be classified into acute if lasting less than 6 weeks, subchronic if lasting 6 to 12 weeks, and chronic if lasting more than 12 weeks.

Acute Low Back Pain

Acute low back pain refers to pain lasting less than 6 weeks. It usually improves within 30 days in 90% of patients. Continuing ordinary activities within the limits permitted by the pain can lead to more rapid recovery than bed rest or back-mobilizing exercises. NSAIDs are often effective for analgesia for acute back pain. Pain arising from inflammation initiated by mechanical or chemical insult to a nerve root may be responsive to epidural administration of corticosteroids, but few patients experience symptomatic relief from epidural corticosteroids if the radicular pain has been present for longer than 6 months or if laminectomy has been performed. A herniated disk should be considered in any patient with a radiculopathy. Pain will be described as radiating down a leg and can be reproduced by a straight leg–raising test. Most lumbar disk herniations producing sciatica occur at the L4-L5 and L5-S1 levels. Magnetic resonance imaging (MRI) can confirm a herniated disk, but findings should be interpreted with caution because many asymptomatic people also have disk abnormalities. Surgical intervention is indicated in patients with persistent radiculopathy or neurologic deficits. Patients who have persistent back pain after 30 days of conservative treatment with NSAIDs should be evaluated for systemic illness. Preoperative evaluation should include any cervical spine or airway involvement as well as documentation of any existing neurologic deficit. Intraoperative management may require adjustment of anesthetic technique according to implemented neurophysiologic monitoring. Postoperative management should take into account the increased analgesic requirements of these patients with possible tolerance to opioid medications through extensive preoperative use.

Lumbar Spinal Stenosis

Lumbar spinal stenosis is a narrowing of the spinal canal or neural foramen leading to pressure on the spinal cord or nerve roots. It typically results from degenerative changes in spinal structures, including herniation of the nucleus pulposus or osteophyte formation. It occurs most often in elderly patients. Symptoms include pain, numbness, and weakness in the buttocks that can extend down one or both legs. Symptoms often worsen with standing or walking and improve in the flexed or supine position. The diagnosis of lumbar spinal stenosis is confirmed by MRI or myelography. Conservative measures may be helpful in some patients, but surgical decompression and fusion are needed for those with progressive functional deterioration. Anesthetic implications are related to any associated changes in cervical spine and airway involvement. Preoperative evaluation should include documentation of existing neurologic deficit. Intraoperative management may require adjustment of anesthetic technique accordingly if neurophysiologic monitoring is implemented. Spinal surgery in the prone position is a risk factor for perioperative visual loss (POVL) due to y retinal vascular occlusion and ischaemic optic neuropathy. Postoperative management should take into account the increased analgesic requirements of these patients with possible tolerance to opioid medications through extensive preoperative use.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a long-term autoimmune disorder that primarily affects joints. It is the most common chronic inflammatory arthritis, affecting approximately 1% of adults. The incidence is two to three times higher in women than in men. The etiology of RA is unknown, but it is suspected to be a complex interaction between genetic and environmental factors and the immune system. The disease is characterized by symmetric polyarthropathy and significant systemic involvement (Table 24.5). Involvement of the proximal interphalangeal and metacarpophalangeal joints of the hands and feet helps distinguish RA from osteoarthritis, which typically affects weight-bearing joints and distal interphalangeal joints. The disease course is characterized by exacerbations and remissions. Rheumatoid nodules are typically present at pressure points, particularly under the elbows. Rheumatoid factor (RF) is an immunoglobulin antibody that is present in the serum of roughly 90% of patients with RA but not present in osteoarthritis. However, the presence of rheumatoid factor is not specific to RA. It is also present in patients with viral hepatitis, SLE, bacterial endocarditis, sarcoidosis, and Sjögren syndrome.

The onset of RA in adults may be acute, involving single or multiple joints, or insidious with symptoms such as fatigue,

TABLE 24.5 Comparison of Rheumatoid Arthritis and Ankylosing Spondylitis

Characteristic	Rheumatoid Arthritis	Ankylosing Spondylitis
Family history	Rare	Common
Gender/age likelihood	Female (30–50 yr)	Male (20–30 yr)
Joint involvement	Symmetric polyarthropathy	Asymmetric oligoarthropathy
Sacroiliac involvement	No	Yes
Vertebral involvement	Only cervical	Total (ascending from lumbosacral region)
Cardiac involvement	Pericardial effusion, aortic regurgitation, cardiac conduction abnormalities, cardiac valve fibrosis, coronary artery arteritis	Cardiomegaly, aortic regurgitation, cardiac conduction abnormalities
Pulmonary involvement	Pulmonary fibrosis, pleural effusion	Pulmonary fibrosis
Eye involvement	Keratoconjunctivitis sicca	Conjunctivitis, uveitis
Rheumatoid factor	Positive	Negative
HLA-B27 antigen	Negative	Positive

anorexia, and weakness preceding overt arthritis. In some patients the onset of RA coincides with trauma, a surgical procedure, childbirth, or exposure to extremes of temperature. Morning stiffness is a hallmark of RA. Several joints—often the hands, wrists, knees, and feet—are affected in a symmetric distribution. Fusiform swelling is typical when there is involvement of the proximal interphalangeal joints. These joints are swollen and painful and remain stiff for several hours after the start of daily activity. Synovitis of the temporomandibular joint can produce marked limitation of mandibular motion. When the disease is progressive and unremitting, nearly every joint is affected except for the thoracic and lumbosacral spine.

Cervical spine involvement is frequent and can result in pain and neurologic complications. The most significant abnormality of the cervical spine is atlantoaxial subluxation and consequent separation of the atlantoodontoid articulation (Fig. 24.7). Normally, with the neck flexed, the separation of the anterior margin of the odontoid process from the posterior margin of the anterior arch of the atlas is less than 3 mm. When this separation is severe, the odontoid process can protrude into the foramen magnum and exert pressure on the spinal cord or impair blood flow through the vertebral arteries. Since the odontoid process is often eroded, effects on the spinal cord may be minimized. Subluxation of other cervical vertebrae can also occur. MRI has confirmed the frequency of cervical spine involvement in RA.

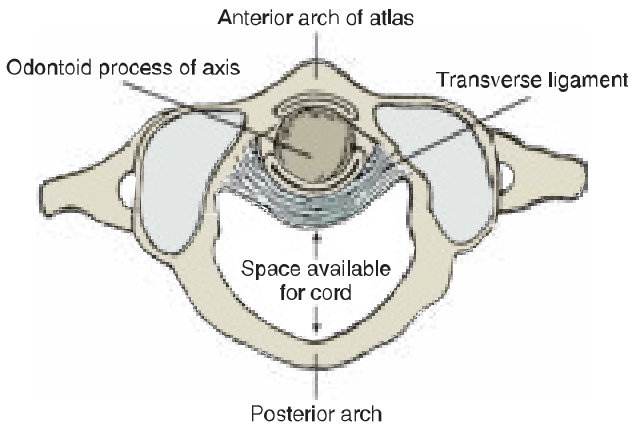

Fig. 24.7 The atlantoaxial articulation seen from above. With atlantoaxial subluxation the odontoid process is no longer positioned close to the anterior arch of the atlas and can move posteriorly to compress the spinal cord. It can also move vertically through the foramen magnum. (From Atlee JL, ed. *Complications in Anesthesia*. ed 2. Philadelphia, PA: Saunders; 2007.)

Cricoarytenoid arthritis is common in patients with generalized RA. With acute cricoarytenoid arthritis, hoarseness, pain on swallowing, dyspnea, and stridor may accompany tenderness over the larynx. Redness and swelling of the arytenoids can be seen on direct laryngoscopy. With chronic cricoarytenoid arthritis, patients may be asymptomatic or manifest variable degrees of hoarseness, dyspnea, and upper airway obstruction. Cricoarytenoid arthritis may make endotracheal intubation difficult. Osteoporosis is ubiquitous in patients with RA.

Many of the systemic manifestations of RA are a result of small and midsize artery vasculitis due to deposition of immune complexes. Systemic involvement is usually most obvious in patients with severe arthritis.

In the cardiovascular system, RA may manifest as pericarditis, myocarditis, coronary artery arteritis, accelerated coronary atherosclerosis, cardiac valve fibrosis, and formation of rheumatoid nodules in the cardiac conduction system. Aortitis with dilatation of the aortic root may result in aortic regurgitation. Pericardial thickening or effusion is present in about one-third of patients. Vasculitis in small synovial blood vessels is an early finding in patients with RA, but more widespread vascular inflammation may occur, especially in older men. Patients may demonstrate a neuropathy (mononeuritis multiplex), skin ulcerations, and purpura. The neuropathy is presumably due to deposition of immune complexes in the vasa nervorum. Manifestations of visceral ischemia, including bowel perforation, myocardial infarction, and cerebral infarction, are possible.

The most common pulmonary manifestation is pleural effusion. Many of these effusions are small and asymptomatic. Rheumatoid nodules can develop in the pulmonary parenchyma and on pleural surfaces and may mimic tuberculosis or cancer on chest radiographs. Progressive pulmonary fibrosis associated with cough, dyspnea, and diffuse honeycomb changes on chest radiographs is rare. Costochondral involvement may affect chest wall motion and produce restrictive lung changes, with a decrease in vital capacity and lung volumes. This may result in ventilation/perfusion mismatching and decreased arterial oxygenation. Neuromuscular involvement can be seen, with loss of strength in skeletal muscles adjacent to joints with active synovitis. Peripheral neuropathies resulting from nerve compression, carpal tunnel syndrome, and tarsal tunnel syndrome are common.

The most common hematologic abnormality in patients with RA is anemia of chronic disease, the severity of which usually parallels the severity of the RA. Felty syndrome consists of

RA with splenomegaly and leukopenia. Juvenile rheumatoid arthritis refers to disease onset before the age of 16 years and a duration of at least 6 weeks. It has seven subtypes: oligoarticular, polyarticular RF negative, polyarticular RF positive, systemic onset, psoriatic, enthesitis-related arthritis, and undifferentiated. The systemic onset subtype is most associated with extraarticular manifestations, including fever, rash, lymphadenopathy, enlarged liver and spleen, and serositis. Other subtypes can be also associated with systemic manifestation, including uveitis, which can lead to scarring, cataract, glaucoma, and even blindness. Juvenile rheumatoid arthritis can be severe enough to cause severe contractures and skeletal deformities that present a great challenge to airway management and patient position. Keratoconjunctivitis sicca (dry eyes) occurs in approximately 10% of patients with RA. The cause is lack of tear formation due to impaired lacrimal gland function. A similar pathologic process may involve the salivary glands resulting in xerostomia (dry mouth). These are both manifestations of Sjögren syndrome. Mild abnormalities of liver function are common in patients with RA. Renal dysfunction may be due to amyloidosis, vasculitis, or drug therapy.

Treatment of RA includes measures to relieve pain, preserve joint function and strength, prevent deformities, and attenuate systemic complications. These objectives may be met by a combination of drugs, physical therapy, occupational therapy, and orthopedic surgery. Drug therapy is used to provide analgesia, control inflammation, and produce immunosuppression.

NSAIDs are important for symptomatic relief of RA but have little role in changing the underlying disease process. They should not be used without the concomitant use of disease-modifying antirheumatic drugs (DMARDs). NSAIDs decrease swelling in affected joints and relieve stiffness, but associated GI irritation and inhibition of platelet cyclooxygenase 1 (COX-1) may necessitate discontinuation of these drugs. Selective COX-2 inhibitors are as effective as COX-1 inhibitors in producing analgesia and reducing inflammation, and they may evoke fewer GI side effects and do not interfere with platelet function. It appears, however, that some COX-2 inhibitors increase the risk of coronary artery disease and stroke. Both COX-1 and COX-2 drugs can adversely affect renal blood flow and glomerular filtration rate.

Corticosteroids are potent antiinflammatory drugs that decrease joint swelling, pain, and morning stiffness in patients with RA. However, the dosages of systemic corticosteroids necessary to maintain desirable effects are often associated with significant long-term side effects, including osteoporosis, osteonecrosis, increased susceptibility to infection, myopathy, hyperglycemia, and poor wound healing. Intraarticular corticosteroids produce beneficial effects lasting about 3 months, but repeated injections may result in cartilage destruction and osteonecrosis. Corticosteroids are indicated as bridge therapy (i.e., therapy to decrease inflammation rapidly) while DMARDs are starting to work in controlling the disease process. Prednisone dosages greater than 10 mg/day are rarely indicated for joint disease, but higher dosages may be needed to treat other manifestations of RA, especially vasculitis.

DMARDs are a group of drugs that have the potential to modify or change the course of RA. They can slow or halt progression of the disease. Included in this group are methotrexate, sulfasalazine, leflunomide, antimalarials, D-penicillamine, azathioprine, and minocycline. These drugs generally take 2 to 6 months to achieve their effects. Patients who show no response to one drug may respond to another. Methotrexate is the preferred DMARD in the treatment of RA. It is given in a once-a-week dosing regimen. Methotrexate is primarily antiinflammatory. Monitoring of hematologic parameters and liver function test results is necessary in individuals being treated with methotrexate because of the risk of bone marrow suppression and cirrhosis. Daily folic acid therapy can decrease methotrexate toxicity.

It appears that cytokines, especially tumor necrosis factor (TNF_) and interleukin-1 (IL1), play a central role in the pathogenesis of RA. Interference with the function of TNF_ either by drug-induced receptor blockade or by monoclonal antibodies is effective in treating RA. Drugs such as infliximab and etanercept, TNF_ inhibitors, are quite effective in treating RA and act more rapidly than other DMARDs. Long-term toxicities such as infection (tuberculosis) and demyelinating syndromes are a concern. Anakinra, an IL1 receptor antagonist, is effective against the signs and symptoms of RA, but its onset of action is slower and its overall effect is less than that of the TNF_ inhibitors. Gold, the traditional DMARD, is extremely effective therapy for some patients with RA, but it is not commonly used because of its toxicities.

Indications for surgery in patients with RA include intractable pain, impairment of joint function, and the need for joint stabilization. Eroded cartilage, ruptured ligaments, and progressive bone destruction can lead to impairments that are only amenable to surgical treatment. Arthroscopic surgery can be used to remove cartilaginous fragments and to perform partial synovectomy. When joints are destroyed by the disease process, total replacement of large and small joints can be considered.

Management of Anesthesia

Anesthetic implications are related to the multiorgan involvement in rheumatoid arthritis as well as the side effects and drug interactions of associated therapies. Preoperatively, patients should be evaluated for airway involvement by the disease process. Compromise of the airway may occur at the cervical spine, temporomandibular joint, and cricoarytenoid joint. Flexion deformity of the cervical spine may make it difficult if not impossible to straighten the neck. Atlantoaxial subluxation may be present. Radiographic evidence (during neck extension) that the distance from the anterior arch of the atlas to the odontoid process exceeds 3 mm confirms the presence of atlantoaxial subluxation. This abnormality is important because the displaced odontoid process can compress the cervical spinal cord or medulla or occlude the vertebral arteries. When atlantoaxial subluxation is present, care must be taken to minimize movement of the head and neck during direct laryngoscopy to avoid further displacement of the odontoid process and damage to the brainstem or spinal cord. It is helpful to evaluate preoperatively whether there is interference with vertebral artery blood flow during flexion, extension, or rotation of the head and

cervical spine. This can be accomplished by having the awake patient demonstrate head movement or positioning that can be tolerated without discomfort or symptoms.

Limitation of temporomandibular joint movement must be recognized before induction of anesthesia. The combination of limited mobility of these joints plus cervical spine stiffness may make visualizing the glottic opening by direct laryngoscopy difficult or impossible. Endotracheal intubation by fiberoptic laryngoscopy or by use of a video laryngoscope may be indicated if preoperative evaluation suggests that direct visualization of the glottic opening will be difficult. Involvement of the cricoarytenoid joints by arthritic changes is suggested by the preoperative presence of hoarseness or stridor or by the observation of erythema or edema of the vocal cords during direct laryngoscopy. Diminished movement of these joints can result in narrowing of the glottic opening and interference with passage of the endotracheal tube or an increased risk of cricoarytenoid joint dislocation. Severe fixed neck flexion in some patients may make surgical rescue of the airway not an option, therefore conservative management of the airway in these patients becomes an absolute necessity.

Preoperative pulmonary function studies and assessment of ABG values may be indicated if severe rheumatoid lung disease is suspected. Postoperative ventilatory support might be needed in the subset of patients with such disease. The effect of aspirin or NSAIDs on platelet function must be considered. Corticosteroid supplementation may be indicated in patients being treated long term with these drugs. Postextubation laryngeal obstruction may occur in patients with cricoarytenoid arthritis.

Systemic Lupus Erythematosus

SLE is an autoimmune multisystem chronic inflammatory disease characterized by antinuclear antibody production, even though these antinuclear antibodies may not be directly involved in the pathogenesis of the disease. SLE typically occurs in young women with an incidence rate of up to 1 in 1000 women. It is exacerbated by stress such as infection, pregnancy, or surgery. It can be drug induced, particularly in slow acetylators with the most common drugs being procainamide, hydralazine, isoniazid, D-penicillamine, and ¯-methyldopa. Drug-induced SLE has usually slower progression and milder symptoms with the most common symptoms being arthralgias, maculopapular rash, fever, anemia, and leukopenia. SLE has a highly variable natural history. Nephritis and hypertension are associated with worse prognosis, including during pregnancy, leading to disease exacerbation and worsening of fetal outcome.

Antinuclear antibody is a sensitive screening test and is encountered in more than 95% of cases. It is one of the typical diagnostic features of SLE. The diagnosis of SLE is likely in the presence of three of five typical manifestations: antinuclear antibodies, characteristic rash, thrombocytopenia, serositis, and nephritis. Additional common features include arthralgias, vague CNS symptoms, rash, Raynaud phenomenon, and/or a weakly positive antinuclear antibody test. Many of the clinical manifestations of SLE are the result of tissue damage from a vasculopathy mediated by immune complexes. Others, such as thrombocytopenia and antiphospholipid syndrome, are a direct result of antibodies to cell surface molecules or serum components.

Clinical manifestations of SLE are categorized into articular or systemic, with polyarthritis and dermatitis being the most common.

Lupus arthritis occurs in 90% of patients. It spares the spine but commonly affects the hands, wrists, elbows, knees, and ankles. The arthritis is symmetric, episodic, migratory, and painful in excess to existing synovitis. Avascular necrosis of the head or condyle of the femur can occur.

Systemic manifestations of SLE involve the CNS, heart, lungs, kidneys, liver, neuromuscular system, and skin.

Neurologic complications can affect any part of the CNS. Cognitive dysfunction occurs in approximately one-third of individuals. Psychological changes ranging from depression and anxiety to psychosomatic complaints to signs of organic psychosis with deterioration in intellectual capacity are seen in more than half of patients. Most serious CNS manifestations appear to be the result of vasculitis. Fluid and electrolyte disturbances, fever, hypertension, uremia, infection, and drug-induced effects may contribute to CNS dysfunction. Atypical migraine headaches are common and may be accompanied by cortical visual disturbances.

Pericarditis resulting in chest pain, a friction rub, ECG changes, and pericardial effusion is the most common cardiac manifestation of SLE. Myocarditis may result in abnormalities of cardiac conduction. Congestive heart failure can develop with extensive cardiac involvement. Valvular abnormalities can be identified by echocardiography. These include verrucous endocarditis (Libman-Sacks endocarditis) that can involve the aortic and/or mitral valves.

Pulmonary involvement can manifest as lupus pneumonia characterized by diffuse pulmonary infiltrates, pleural effusion, dry cough, dyspnea, and arterial hypoxemia. Pulmonary function testing typically shows restrictive lung disease. Recurrent atelectasis can result in shrinking or vanishing lung syndrome. This may be a result of diaphragmatic weakness or elevation caused by phrenic neuropathy. Pulmonary angiitis with lung hemorrhage may complicate severe SLE. Pulmonary hypertension is present in some patients.

The most common renal abnormality is glomerulonephritis with proteinuria, which can result in hypoalbuminemia. Hematuria is a frequent finding. The glomerular filtration rate can decrease dramatically and result in oliguric renal failure.

Liver function test findings are abnormal in approximately 30% of patients. Severe liver disease is most likely due to infection or to undiagnosed autoimmune hepatitis or primary biliary cirrhosis.

Neuromuscular manifestations include myopathy with proximal skeletal muscle weakness and increased serum creatine kinase concentration. Tendinitis is common and can result in tendon rupture.

Hematologic abnormalities may be present. Thromboembolism associated with antiphospholipid antibodies can be an important cause of CNS dysfunction. Leukopenia, granulocyte dysfunction, decreased complement levels, and functional asplenia have been implicated in an increased risk of infection. Thrombocytopenia and hemolytic anemia are seen in some patients. The presence of circulating anticoagulants is reflected

in a prolonged activated partial thromboplastin time (aPTT). Patients with circulating anticoagulants often manifest a false-positive test result for syphilis.

Some patients with lupus have cutaneous manifestations. The classic butterfly-shaped malar rash occurs in approximately half of patients. This rash can be transient and is often exacerbated by sunlight. Discoid lesions on the face, scalp, and upper trunk develop in approximately 25% of patients with SLE but may occur in the absence of any other features of SLE. Alopecia is common.

Treatment is determined by individual disease manifestations. Arthritis and serositis can often be controlled with aspirin or NSAIDs. Antimalarial drugs such as hydroxychloroquine and quinacrine are also effective in treating the dermatologic and arthritic manifestations of SLE. Patients should use sunscreens and avoid intense sun exposure. Thrombocytopenia and hemolytic anemia usually respond to corticosteroid therapy. Danazol, vincristine, cyclophosphamide, or splenectomy can be used if thrombocytopenia does not respond to glucocorticoid administration. In view of the increased susceptibility to infection, the risk/benefit ratio of splenectomy must be carefully considered.

Corticosteroids are the principal treatment for severe manifestations of SLE. Corticosteroids effectively suppress glomerulonephritis and cardiovascular abnormalities. However, corticosteroid therapy can be a major cause of morbidity in patients with SLE. Death during the course of SLE may be due to coronary atherosclerosis. The development and progression of coronary atherosclerosis is accelerated by treatment with corticosteroids. Immunosuppressive treatment with alternative drugs such as methotrexate, cyclophosphamide, azathioprine, or mycophenolate mofetil may be preferable to prolonged treatment with high-dose corticosteroids.

Management of Anesthesia

Management of anesthesia is influenced by the magnitude of organ system dysfunction and the drugs used to treat SLE. Airway management can be complicated by laryngeal involvement, including mucosal ulceration, cricoarytenoid arthritis, and recurrent laryngeal nerve palsy, which may be present in up to one-third of patients.

Spondyloarthropathies

Spondyloarthropathies refer to nonrheumatic arthropathies that involve the vertebral column. They include ankylosing spondylitis, reactive arthritis (Reiter syndrome), juvenile chronic polyarthropathy, psoriatic arthritis, and enteropathic arthritis. Characteristic features include involvement of sacroiliac joints, asymmetric peripheral arthritis and synovitis, absence of rheumatoid nodules or detectable circulating rheumatoid factor, inflammatory bone formation and joint ankylosis, ocular inflammation, and strong association with human leukocyte antigen B27 (HLA-B27) (see Table 24.5).

Ankylosing Spondylitis

Ankylosing spondylitis is the most common inflammatory disease of the axial skeleton. The disease occurs predominantly in men and often begins in young adulthood. Spinal disease begins in the sacroiliac joints and spreads cranially to result, in severe cases, with complete ankylosis of the spine. Hip involvement occurs in approximately one-third of patients. Spinal symptoms include back pain and morning stiffness that improves with activity and exercise. Physical examination may reveal skeletal muscle spasm, loss of lordosis, and decreased mobility of the vertebral column. Radiographic examination reveals sacroiliitis. Laboratory findings demonstrate HLA-B27–positive status in 90% of patients compared to 6% in the general population. Systemic manifestations include weight loss, fatigue, and low-grade fever. Conjunctivitis and uveitis occur in about 40% of patients and manifest as visual impairment, photophobia, and eye pain. Thoracic spine and costovertebral arthritis may lead to decreased chest wall compliance and vital capacity.

Pulmonary abnormalities include apical cavitary lesions and pleural thickening that mimic tuberculosis. Cardiovascular manifestations are encountered in 40% of patients and include aortic regurgitation and bundle branch block.

Treatment of ankylosing spondylitis consists of exercises designed to maintain joint mobility and posture plus antiinflammatory drugs. NSAIDs are commonly used. Infliximab and etanercept may cause profound improvement in this disease, but patients often experience relapse when treatment is discontinued. For uveitis, topical corticosteroid eye drops are an integral part of management.

Management of anesthesia. Management of anesthesia is influenced by the severity of spinal and systemic manifestations. The spinal column can be stiff and deformed and prevent appropriate cervical spine motion for endotracheal intubation. Fiberoptic or video laryngoscope assistance may be needed for endotracheal intubation. Restrictive lung disease from costochondral rigidity and flexion deformity of the thoracic spine must be appreciated. Sudden or excessive increases in systemic vascular resistance are poorly tolerated if significant aortic regurgitation is present. Management of aortic regurgitation includes keeping the heart rate at 90 beats per minute or higher and the systemic vascular resistance lower than normal. Neurologic monitoring is a consideration for patients undergoing corrective spinal surgery. Epidural or spinal anesthesia is an acceptable alternative to general anesthesia for perineal or lower limb surgery, but regional anesthesia may be technically difficult owing to limited joint mobility and closed interspinous spaces. Ossification of the ligamentum flavum is uncommon, however. A paramedian approach for spinal or epidural anesthesia may be easier than a midline approach.

Reactive Arthritis

Reactive arthritis is an inflammatory aseptic arthritis that occurs as a reaction to an extraarticular infection. Specific risk factors include HLA-B27 positivity and infection with *Chlamydia*, *Salmonella*, and *Shigella* species. Reiter syndrome refers to reactive arthritis that is accompanied by extraarticular inflammation such as urethritis, cervicitis, uveitis, conjunctivitis, and skin lesions. While most of the signs of Reiter syndrome persist for only a few days, the reactive arthritis progresses to sacroiliitis and spondylitis in approximately 20% of patients.

Cricoarytenoid arthritis can also occur. Hyperkeratotic skin lesions cannot be distinguished from those of psoriasis, and the two diseases frequently overlap. Management consists of antibiotic treatment for the initial infection and NSAIDs or sulfasalazine for symptomatic relief of the arthritis. Anesthetic management is related to arthritic lesions, especially the cricoarytenoid and spinal joints, extraarticular manifestations and side effects, and interactions of associated therapies.

Chronic Juvenile Polyarthropathy

The pathologic process in chronic juvenile polyarthropathy is similar to that in adult RA. An acute form of chronic juvenile polyarthritis that presents as fever, rash, lymphadenopathy, and splenomegaly in young children who test negative for rheumatoid factor and HLA-B27 is designated Still disease. These patients are the clinical equivalent of the systemic onset subtype of juvenile rheumatoid arthritis, but without the seropositivity for the rheumatoid factor. Complications include growth abnormalities, hepatic dysfunction, severe contractures, and skeletal deformities. Treatments consist of aspirin and corticosteroids, but the use of the latter is limited because of concerns about growth retardation. Anesthetic implications are related to airway management, patient positioning, and associated systemic manifestations.

Enteropathic Arthritis

Enteropathic arthritis is an arthritis that is encountered in patients with inflammatory bowel disease such as Crohn disease or ulcerative colitis. Enteropathic arthritis can be encountered in cases associated with HLA-B27 antigen or not. Enteropathic arthritis that is not associated with HLA-B27 antigen manifests mainly as a polyarthritis of the large joints of the lower extremities, and its activation and remission parallels that of the GI inflammatory disease. Enteropathic arthritis that is associated with HLA-B27 antigen manifests mainly as sacroiliitis and spondylitis, has a chronic course that may progress toward ankylosing spondylitis, and its activation and remission does not parallel that of the GI inflammatory disease. HLA-B27 antigen is found in 50% of these patients. Treatment of enteropathic arthritis is directed both toward the GI inflammatory disease and the associated arthritic manifestations. Anesthetic implications are related to systemic manifestations of the GI inflammatory disease and the associated arthritic manifestations as well as their associated complications and therapeutic interventions.

Paget Disease

Paget disease of bone is also known as osteitis deformans. It refers to excessive osteoblastic and osteoclastic activity that results in thick, weak, and deformed bones that are prone to fractures and associated arthritis. The cause is unknown but may include genetic and acquired factors, including excess parathyroid hormone, deficiency of calcitonin, and familial tendency. It is most commonly encountered in white men older than 40 years, with bone pain being the most common symptom. Complications include fractures, arthritis, neoplastic degeneration, nerve compression, paraplegia, irreversible hearing loss, hypercalcemia, and renal calculi. Radiographic features include bone enlargement combined with lytic and sclerotic changes. Radionuclide bone scan is the most reliable method of diagnosis. Laboratory testing reveals increased levels of serum alkaline phosphatase concentration (reflecting bone formation) and of urinary hydroxyproline excretion (reflecting bone resorption).

Treatment is aimed at alleviating bone pain and preventing disease progression. Bisphosphonates prevent disease progression by decreasing osteoclastic activity and bone resorption. Analgesics, antiinflammatory drugs, and drugs to treat neuropathic pain are used to alleviate pain, including pain due to nerve compression or concomitant osteoarthritis. Surgical treatment may be needed for fracture repair, joint replacement, osteotomy, or nerve decompression. Anesthetic implications are related to existing lesions and their complications, including metabolic, renal, and neurologic. Patients with paraplegia may have increased risk of excessive hyperkalemia after succinylcholine injection due to proliferation of extrajunctional acetylcholine receptors.

Dwarfism

Dwarfism in humans refers to short stature, which is sometimes defined as an adult height of less than 147 cm (4 ft 10 in). Dwarfism can be proportionate or disproportionate.

Proportionate dwarfism comprises about 30% of all cases and is due to growth hormone deficiency or insensitivity. Causes of growth hormone deficiency include genetic mutations, pituitary gland dysfunction, Turner syndrome, poor nutrition, or psychological stress. Disproportionate dwarfism comprises about 70% of all cases and is most commonly due to the genetic disorder of bone development known as achondroplasia.

Achondroplasia

Achondroplasia occurs predominantly in females, with an incidence of 1.5 per 10,000 births. Transmission is by an autosomal dominant gene, although an estimated 80% of cases represent spontaneous mutations. The basic defect is a decrease in the rate of endochondral ossification that, when coupled with normal periosteal bone formation, produces short tubular bones. The anticipated height of achondroplastic males is 132 cm (52 in) and that of females is 122 cm (48 in). Kyphoscoliosis and genu varum are common. Premature fusion of the bones at the base of the skull can result in a shortened skull base and a stenotic foramen magnum. In addition, there may be functional fusion of the atlantooccipital joint with odontoid hypoplasia, atlantoaxial instability, bulging disks, and severe cervical kyphosis. These changes may result in hydrocephalus or damage to the cervical spinal cord. Central sleep apnea in individuals with achondroplasia may be a result of brainstem compression due to foramen magnum stenosis. Pulmonary hypertension leading to cor pulmonale is the most common cardiovascular disturbance. Mental and skeletal muscle development is normal, as is life expectancy for those who survive the first year of life. Common surgical procedures in patients with achondroplasia include suboccipital craniectomy to correct foramen magnum stenosis, laminectomy to treat spinal stenosis or nerve root compression, and ventriculoperitoneal shunt placement to decompress obstructive hydrocephalus.

Management of anesthesia. Anesthetic implications are related to potential airway difficulties, cervical spine instability, and the potential for spinal cord trauma with neck extension (Box 24.5).

A history of obstructive sleep apnea increases the risk of upper airway obstruction after sedation or during emergence from anesthesia. Facial features, including a large protruding forehead, short maxilla, large mandible, flat nose, and large tongue, may result in difficulty obtaining a good mask fit and in maintaining a patent upper airway. Cervical kyphosis may result in difficulty in tracheal intubation due to inability to align the axes of the airway. Hyperextension of the neck during direct laryngoscopy should be avoided because of the likely presence of foramen magnum stenosis. Fiberoptic-guided tracheal intubation may be considered in selected patients. Weight rather than age is the best guide for selecting the proper size of endotracheal tube. Excess skin and subcutaneous tissue may make peripheral venous access technically difficult.

Suboccipital craniectomy procedures, especially in the sitting position, pose a risk of venous air embolism. Insertion of a right atrial catheter is desirable should an air embolism occur, but placing such a catheter may be technically difficult because of the short neck, difficulty of identifying the landmarks, and excessive soft tissue. Evoked potential monitoring is useful during surgery that may be associated with brainstem or spinal cord injury. Anesthetic techniques that permit rapid awakening may be desirable for prompt evaluation of neurologic function. Achondroplastic patients respond normally to anesthetic drugs and neuromuscular blockers.

Delivery by cesarean section is necessary in women with achondroplasia because a small, contracted maternal pelvis combined with an infant of near-normal birth weight leads to cephalopelvic disproportion. Regional anesthesia might be considered, but technical difficulties may occur secondary to kyphoscoliosis and a narrow epidural space and spinal canal. The small epidural space may make it difficult to introduce an epidural catheter. Osteophytes, prolapsed intervertebral disks, or deformed vertebral bodies can also contribute to difficulties with neuraxial blockade. There are no data confirming appropriate doses of local anesthetics for epidural or spinal anesthesia in these patients. Epidural anesthesia may be preferable to spinal anesthesia because it permits titration of the local anesthetic drug to achieve the desired level of sensory blockade.

BOX 24.5 Characteristics of Achondroplastic Dwarfism That May Influence Management of Anesthesia

- Difficulty exposing the glottic opening
- Foramen magnum stenosis
- Odontoid hypoplasia with cervical instability
- Kyphoscoliosis
- Restrictive lung disease
- Obstructive sleep apnea
- Central sleep apnea
- Pulmonary hypertension
- Cor pulmonale
- Hydrocephalus

Russell-Silver Syndrome

Russell-Silver syndrome is a form of primordial dwarfism, which refers to a proportionate dwarfism that begins in utero resulting in intrauterine growth restriction (IUGR), followed by birth of a neonate who is small for gestational age (SGA; i.e., birth weight ≤2.8 kg), continues during childhood, and stabilizes at adulthood with height approaching 150 cm (~60 in). Coexisting disorders and manifestations include feeding problems during infancy, hypoglycemia, excessive sweating during infancy, triangular face, micrognathia, facial hypoplasia, limb asymmetry, congenital heart defects, adrenocortical insufficiency, and hypogonadism.

Management of anesthesia. Preoperative evaluation should consider the serum glucose concentration, especially in neonates at risk of hypoglycemia. IV infusions containing glucose may be indicated preoperatively. Facial manifestations may make direct laryngoscopy and endotracheal intubation difficult. An endotracheal tube smaller than the predicted size may be needed. Obtaining a good mask fit may also be difficult because of facial asymmetry. Administration of some drugs (e.g., muscle relaxants) based on body weight rather than body surface area may result in relative underdosing. There is increased risk of intraoperative hypothermia because of large surface-to-volume ratio. During emergence, unexplained tachycardia, diaphoresis, or somnolence may indicate hypoglycemia.

Tumoral Calcinosis

Tumoral calcinosis is a nonneoplastic deposition of calcium in soft tissues outside the joint capsule. It can be either due to genetic mutation or as a complication of renal dialysis. It is most commonly encountered in the 6- to 25-year-old age group. Tumoral calcinosis is not painful per se, but it may continue to enlarge, interfere with skeletal muscle function, ulcerate the overlying skin, and extrude through the skin. The most commonly affected joints are the shoulders, elbows, and hips. Laboratory testing reveals normal serum calcium but elevated phosphate levels and (rarely) elevated alkaline phosphatase levels. Treatment consists of correction of serum phosphate levels and complete surgical excision of the lesions, since incomplete resection will lead to recurrence. Anesthetic implications are related to the rare occurrence of the disease process involving airway-related structures, including the hyoid bone, hypothyroid ligament, or cervical intervertebral joints, which would lead to difficult laryngoscopy and endotracheal intubation.

Disorders of the Shoulder

Shoulder pain ranks just behind back and neck pain as a cause of disability in workers. Common shoulder disorders include rotator cuff tear, adhesive capsulitis, and calcific tendinitis.

Rotator cuff tear is the most common, and its incidence increases with aging. Postmortem examinations reveal that up to 40% of adults aged more than 40 years have evidence of partial or full thickness rotator cuff tear. Arthrographic examinations reveal that up to 50% of adults aged more than 55 years have detectable rotator cuff tears. Other pathologic shoulder conditions are less common. Adhesive capsulitis (frozen shoulder) is encountered in approximately 2% of the adult population and

in 11% of the adult diabetic population. Calcific tendinitis is encountered in 3% to 7% of adults. Therapeutic interventions for shoulder disorder include corticosteroid injection into the subacromial space, arthroscopic release (manipulation) under anesthesia, and ultimately total shoulder replacement of the humeral and glenoid articular surfaces.

Management of Anesthesia

Anesthetic implications focus on providing adequate postoperative analgesia that allows early mobilization of the shoulder. Regional anesthesia via interscalene brachial plexus nerve block with catheter insertion for continuous infusion of local anesthetic can provide both intraoperative anesthesia as well as postoperative analgesia. Often general anesthesia with endotracheal intubation is provided in addition to regional anesthesia for airway control, since access to the patient's airway is limited during shoulder surgery. Ipsilateral hemidiaphragmatic paralysis is expected with interscalene block and is well tolerated in most patients. However, patients with severe COPD or neuromuscular diseases may not tolerate decrease in the capacity of respiratory effort that results from the unction of hemidiaphragmatic paralysis. Alternative adjunct analgesia methods include wound infiltration or joint lavage with long-acting local anesthetic solutions such as bupivacaine or ropivacaine.

Tracheomegaly

Tracheomegaly is also known as tracheobronchomegaly. It refers to marked dilatation (30 mm) of the trachea and bronchi either due to congenital defect in elastin and smooth muscle fibers or to destruction of these elements by radiotherapy. The dilated tracheobronchial tree is also flaccid and may collapse during vigorous coughing. Complications include chronic productive cough, frequent pulmonary infections, and eventual bronchiectasis. Anesthetic implications are related to increased risk of aspiration during or after general anesthesia, especially if inflation of the endotracheal tube cuff does not produce adequately effective seal.

Prader-Willi Syndrome

Prader-Willi syndrome is also known as Prader-Labhart-Willi-Fanconi syndrome. It is caused by genetic defect in chromosome 15 leading to muscular hypotonia that manifests since birth with breathing, coughing, and feeding difficulties. Later on, during childhood a different set of disorders becomes manifest, including little growth in height, intellectual deficit, behavioral problems, hyperphagia, obesity, hypogonadism, diabetes mellitus, obstructive sleep apnea, and possibly obesity hypoventilation syndrome (Pickwickian syndrome). Skeletal deformities may include micrognathia, high-arched palate, straight ulnar border, and congenital dislocation of the hip. Common associated disorders include dental caries, chronic regurgitation of gastric contents, strabismus, and seizures. Some patients may be treated with growth hormones during childhood to enhance height growth, but this therapy may worsen obstructive sleep apnea.

Management of Anesthesia

Anesthetic implications are mainly related to muscular hypotonia and altered metabolism of carbohydrates and fat. Muscular hypotonia decreases the ability to generate effective cough and increases the risk of postoperative atelectasis and pneumonia. Also, muscular hypotonia decreases muscle relaxant requirements and may obviate the need for their use. Succinylcholine has been administered without incident to these patients. Intraoperative monitoring of blood glucose concentration is necessary, and exogenous glucose administration may be needed because these patients use circulating glucose to manufacture fat rather than to meet basal energy needs. Calculating drug doses should take into consideration the decreased skeletal muscle mass and increased fat content in these patients. Disturbances in thermoregulation may manifest as intraoperative hyperthermia and metabolic acidosis.

Prune-Belly Syndrome

Prune-belly syndrome is named for the wrinkled appearance of abdomen due to a triad of congenital agenesis of abdominal wall musculature, cryptorchidism, and urinary tract anomalies, including ureteral dilatation, hypotonic bladder, and vesicoureteral reflux. Additional visceral anomalies include prostatic hypoplasia, malrotation of the gut, and ventricular septal defect. Musculoskeletal anomalies include pectus excavatum, scoliosis, club foot, and congenital joint dislocation, including the hip. The full syndrome appears only in males, but females constitute up to 3% of patients with an incomplete syndrome. Complications include frequent urinary tract infections due to vesicoureteral reflux and recurrent respiratory tract infections due to impaired cough. Anesthetic implications are related to associated visceral and skeletal anomalies. Abdominal wall muscular agenesis obviates the need for the use of muscle relaxation in many cases of abdominal surgery.

Meige Syndrome

Meige syndrome is also known as Brueghel syndrome and oral facial dystonia. It is an idiopathic dystonia that is a combination of blepharospasm and oromandibular dystonia. It most often affects middle-aged to elderly women. Facial muscle spasms are characterized by symmetric dystonic contractions of the facial muscles. Dystonia is aggravated by stress and disappears during sleep. The pathophysiology of this disease is unknown but may be related to dopamine hyperactivity or dysfunction of the basal ganglia. Medical treatments include antidopaminergics, anticholinergics, acetylcholine agonists, and ¯-aminobutyric acid (GABA) agonists. Facial nerve block with local anesthetics has been reported to provide sustained relief.

Spasmodic Dysphonia

Spasmodic dysphonia refers to abnormal phonation due to dystonic spasm of the vocal cords that is exacerbated by stress but rarely leads with respiratory distress. Common associated symptoms include muscle weakness, dystonia, and tremors. Treatments include botulinum toxin injections to affected areas, including the vocal cords, neck muscles, and eyelids.

Management of Anesthesia

Preoperative fiberoptic or direct laryngoscopy may be necessary to define anatomic abnormalities and estimate airway dimensions.

The presence of laryngeal stenosis may necessitate use of smaller-than-usual endotracheal tubes. The risk of pulmonary aspiration may be increased by vocal cord dysfunction caused by therapeutic interventions such as botulinum toxin injection or recurrent laryngeal nerve interruption. Continued monitoring during the postoperative period is important because these patients may experience respiratory difficulties.

Chondrodysplasia Calcificans

Chondrodysplasia calcificans is a rare congenital syndrome caused by dysfunctional peroxisomes, which are oxidative cellular organelles that generate hydrogen peroxide by scavenging reactive oxygen species. Peroxisomes play an important role in lipid metabolism and energy metabolism. Peroxisome dysfunction affects the formation and the function of many tissues and organs. Surviving children commonly have dwarfism, kyphoscoliosis, and subluxation of the hips. Tracheal cartilage may be involved by the disease process leading to tracheal stenosis. Additional malformations involve the heart, the skin, and the eye. Orthopedic procedures are often necessary to repair spine and limb malformations. Anesthetic implications are related to organ dysfunction and airway management complicated by tracheal stenosis.

Erythromelalgia

Erythromelalgia literally means "red, painful extremities." Erythema, intense burning pain, and increased temperature of the involved extremities are hallmarks of the disease. The feet, especially the soles, are most often involved, and males are affected twice as often as females. The pain is triggered by exposure to heat or exercise and is relieved with cooling. Primary erythromelalgia occurs more frequently than secondary erythromelalgia, which is associated with myeloproliferative disorders such as polycythemia vera. Intravascular platelet aggregation may be prominent. Aspirin is the most effective treatment for secondary erythromelalgia resulting from myeloproliferative diseases. Patients may seek relief by exposing the affected extremity to a cooler environment, such as immersing the extremity in cold water. Neuraxial opioids and local anesthetics may provide some symptom relief.

Farber Lipogranulomatosis

Farber disease is known by other names, including lipogranulomatosis, Farber lipogranulomatosis, ceramidase deficiency, and fibrocytic dysmucopolysaccharidosis. It is an extremely rare autosomal recessive lysosomal storage disease that is caused by deficiency of the enzyme ceramidase, which catalyzes the cleavage of ceramide from fatty acids to produce sphingosine, which is a component of the sphingolipids of the cell membranes. The enzyme deficiency leads to accumulation of ceramide and sphingolipids in all body tissues with most prominent abnormalities appearing in pleura, pericardium, synovial lining of joints, liver, spleen, and lymph nodes. Clinical manifestations include arthropathy, lipogranuloma formation in the pharynx or larynx, psychomotor retardation, renal failure, liver failure, respiratory failure, and nutritional failure that lead to premature death during early childhood, usually by the age of 2 years. Anesthetic implications are related to the various anatomic abnormalities and organ dysfunction. Tracheal intubation is best avoided in patients with upper airway involvement because laryngeal edema or bleeding from laryngeal granulomas is possible.

Klippel-Feil Syndrome

Klippel-Feil syndrome, also known as cervical vertebral fusion syndrome, is a rare congenital skeletal disorder that is characterized by fusion of two or more of the seven cervical vertebrae leading to a short neck with limited mobility that is commonly associated with spinal stenosis and kyphoscoliosis. Additional findings include mandibular malformation, micrognathia, cardiac anomalies, genitourinary anomalies, and obstructive sleep apnea. Anesthetic implications are related to difficulty in airway management, potential neuronal injury due to cervical spine instability and stenosis, and the presence of obstructive sleep apnea. Preoperative lateral neck radiographs help in evaluating cervical spine deformity and stability.

Osteogenesis Imperfecta

Osteogenesis imperfecta is a rare autosomal dominant hereditary disorder that impairs the production of type I collagen, with manifestations occurring mainly in the bones, sclera, and inner ear. It is more common in females. It has several types with different degrees of severity, with the most severe forms leading to death during infancy. Less severe forms have an age of onset of early childhood to early adolescence with manifestation, including gradual development of blue sclerae, brittle bones, proneness to bone fractures after minor trauma, kyphoscoliosis, bowlegs, otosclerosis, and deafness. Additional manifestations include platelet dysfunction, mild coagulopathy, hyperthermia, hyperhidrosis, increased serum thyroxine concentration, and increased oxygen consumption. Treatment with bisphosphonates increases bone strength and reduces bone pain and the number of fractures.

Management of Anesthesia

Management of anesthesia is influenced by the coexisting orthopedic deformities and the potential for additional fractures during the perioperative period. Patients with osteogenesis imperfecta often have a decreased range of motion of the cervical spine resulting from remodeling of bone. Tracheal intubation must be accomplished with as little manipulation and trauma as possible because cervical and mandibular fractures may easily occur. Awake fiberoptic intubation or video laryngoscopy may be prudent if orthopedic deformities suggest that it will be difficult to visualize the glottic opening with direct laryngoscopy. Dentition is often defective, and teeth are vulnerable to damage during direct laryngoscopy. Kyphoscoliosis and pectus excavatum decrease vital capacity and chest wall compliance and can result in arterial hypoxemia caused by ventilation/perfusion mismatching. Use of automated blood pressure cuffs may be hazardous, since inflation can result in fractures. Depolarizing muscle relaxation with succinylcholine is best avoided because fasciculations may produce fractures. Neuraxial regional anesthesia may obviate the need for endotracheal intubation but may be technically difficult because of kyphoscoliosis. The coagulation status should be evaluated before a regional

anesthetic technique is selected because osteogenesis imperfecta may be associated with platelet function abnormalities despite a normal platelet count. These may be due to impairment in platelet-endothelial cell adhesion. Desmopressin may be effective in normalizing this platelet dysfunction. These patients may have mild hyperthermia intraoperatively, but it is not a forerunner of malignant hyperthermia.

Fibrodysplasia Ossificans

Fibrodysplasia ossificans is a rare inherited autosomal dominant disease that usually presents before age 6. Fibrodysplasia ossificans refers to ossification of ligaments, tendons, and muscle tissues. Ossification of the muscles of the elbows, hips, and knees leads to serious limitations of joint movement. Ossification of the cervical spine is common and may lead to cervical fusion and atlantoaxial subluxation. Ossification of the temporomandibular joint is common and may lead to malnutrition. Ossification of chest wall structures may lead to a restrictive breathing pattern, pneumonia, and (rarely) respiratory failure. Ossification of ear bones may lead to deafness. Muscles that commonly escape ossification include those of the face, larynx, eyes, anterior abdominal wall, diaphragm, and heart. Deafness may occur, but intellectual disability is unlikely.

Fever and increased alkaline phosphatase activity may accompany ossification of skeletal muscles. ECG changes include ST-segment changes and right bundle branch block. There is no effective therapy. Anesthetic implications are related to various manifestations of ossifications and their systemic effects, including limitation in mouth opening, neck mobility, and lung expansion.

Deformities of the Sternum

Pectus carinatum refers to outward protuberance of the sternum, whereas pectus excavatum refers to inward concavity of the sternum. These deformities produce cosmetic problems but little functional impairment. Possible complications of pectus excavatum include obstructive sleep apnea in children, increased cardiac filling pressures, and dysrhythmias. Anesthetic implications are related to cardiopulmonary effects of the sternal deformity.

Macroglossia

Macroglossia is an infrequent but potentially lethal postoperative complication that is most often associated with posterior fossa craniotomy performed in the sitting position. Possible causes of macroglossia include arterial compression; venous compression resulting from excessive neck flexion or a head-down position; and mechanical compression of the tongue by the teeth, an oral airway, or an endotracheal tube. Macroglossia may also have a neurogenic origin. When the onset of macroglossia is immediate, it is easily recognized, and airway obstruction does not occur because tracheal extubation is delayed. In some patients, however, obstruction to venous outflow from the tongue leads to development of regional ischemia from compression of the lingual arteries. This is followed by a reperfusion injury that does not occur until the outflow obstruction is relieved. As a result, the development of macroglossia may be delayed for 30 minutes or longer. There is then the risk of complete airway obstruction occurring at an unexpected time during the postoperative period.

KEY POINTS

- Epidermolysis bullosa and pemphigus are characterized by bulla formation (blistering) that can involve extensive areas of skin and mucous membranes. Even minor frictional trauma can result in bulla formation. Airway management may be difficult because of bullae in the oropharynx. Airway manipulation, including direct laryngoscopy and endotracheal intubation, can result in acute bulla formation, upper airway obstruction, and bleeding.
- Patients with scleroderma can present several problems in anesthetic management. Decreased mandibular motion and narrowing of the oral aperture caused by taut skin may make endotracheal intubation difficult. Oral or nasal telangiectasias may bleed profusely if traumatized. Intravenous access may be impeded by dermal thickening. Systemic or pulmonary hypertension may be present. Hypotonia of the lower esophageal sphincter puts patients at risk of regurgitation and aspiration.
- Patients with disorders of elastin and collagen are at increased risk of vascular diseases and complications. These include premature arteriosclerosis, propensity to bleeding, and in the case of Marfan syndrome the well-recognized risk of thoracic aortic dissection. Other structures prone to injury include the intestines, lungs, and uterus.
- Muscular dystrophy is characterized by progressive symmetric skeletal muscle weakness and wasting but no evidence of skeletal muscle denervation. Sensation and reflexes are intact. Increased permeability of skeletal muscle membranes precedes clinical evidence of muscular dystrophy. Patients with muscular dystrophy are susceptible to malignant hyperthermia.
- The term *myotonic dystrophy* designates hereditary degenerative diseases of skeletal muscle characterized by persistent contracture (myotonia) after voluntary contraction of a muscle or electrical stimulation of the muscle. Peripheral nerves and the neuromuscular junction are not affected. This inability of skeletal muscle to relax after voluntary contraction or stimulation results from abnormal calcium metabolism.
- The clinical course of myasthenia gravis is marked by periods of exacerbation and remission. Muscle strength may be normal in well-rested patients, but weakness occurs promptly with exercise. Ptosis and diplopia resulting from extraocular muscle weakness are the most common initial signs. Weakness

of pharyngeal and laryngeal muscles results in dysphagia, dysarthria, and difficulty handling saliva. Patients with myasthenia gravis are at high risk of pulmonary aspiration.

- The acetylcholine receptor–binding antibodies of myasthenia gravis decrease the number of functional acetylcholine receptors, and this results in an increased sensitivity to nondepolarizing muscle relaxants. However, patients with myasthenia gravis demonstrate resistance to the effects of succinylcholine.
- Myasthenic syndrome (Eaton-Lambert syndrome) is a disorder of neuromuscular transmission that differs from myasthenia gravis. Myasthenic syndrome is an acquired autoimmune disease characterized by the presence of IgG antibodies to voltage-sensitive calcium channels, resulting in a deficiency of these channels at the motor nerve terminal. Anticholinesterase drugs effective in the treatment of myasthenia gravis do not produce an improvement in patients with myasthenic syndrome.
- In rheumatoid arthritis, cervical spine involvement is frequent and may result in pain and neurologic complications. The most significant abnormality of the cervical spine is atlantoaxial subluxation and consequent separation of the atlantoodontoid articulation. When this separation is severe, the odontoid process may protrude into the foramen magnum and exert pressure on the spinal cord or impair blood flow through the vertebral arteries.
- In rheumatoid arthritis, involvement of the cricoarytenoid joints is suggested by the presence of hoarseness or stridor or by the observation of erythema or edema of the vocal cords during direct laryngoscopy. Diminished movement of these joints can result in narrowing of the glottic opening and interference with passage of the endotracheal tube or an increased risk of cricoarytenoid joint dislocation.
- The spondyloarthropathies are a group of nonrheumatic arthropathies characterized by involvement of the spine, especially the sacroiliac joints; asymmetric peripheral arthritis; synovitis; and absence of rheumatic nodules or detectable circulating rheumatoid factor. These diseases have a shared predilection for new bone formation at sites of chronic inflammation, and joint ankylosis often results. Ocular inflammation is frequently present.
- Osteoarthritis is by far the most common joint disease, one of the leading chronic diseases of the elderly, and a major cause of disability. Osteoarthritis is a degenerative process that affects articular cartilage. Both the cervical and lumbar spine may be involved. This process is different from rheumatoid arthritis in that there is minimal inflammatory reaction in osteoarthritic joints. The pathogenesis is likely related to joint trauma from biomechanical stresses, joint injury, or abnormal joint loading resulting from neuropathy, ligamentous injury, muscle atrophy, or obesity. Pain is usually present on motion but relieved by rest.
- Kyphoscoliosis is a spinal deformity characterized by anterior flexion (kyphosis) and lateral curvature (scoliosis) of the vertebral column. Spinal curvature of more than 40 degrees is considered severe and is likely to be associated with physiologic derangements in cardiac and pulmonary function. Restrictive lung disease and pulmonary hypertension progressing to cor pulmonale are the principal causes of death in patients with kyphoscoliosis. During corrective surgery for scoliosis or kyphosis, spinal cord monitoring now utilizes measurement of evoked potentials (sensory and motor) much more frequently than the wake-up test.
- Malignant hyperthermia susceptibility is an inherited myopathy that can be triggered by drugs or physical stress into a muscular hypermetabolic state known as malignant hyperthermia crisis.
- Genetic, pathophysiologic, and therapeutic features of malignant hyperthermia susceptibility and crises are similar across affected species.
- Inquiry about malignant hyperthermia susceptibility should be part of every preanesthetic evaluation.
- A nontrigger technique and preparations to deal with malignant hyperthermia crisis should be implemented whenever there is personal or family history of potential malignant hyperthermia susceptibility.
- The Malignant Hyperthermia Association of the United States (MHAUS, www.mhaus.org) provides educational resources to patients and healthcare providers as well as real-time guidance during a malignant hyperthermia crisis.

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25

Infectious Diseases

Antonio Hernandez Conte

OUTLINE

Unknown illness … single infection … community spread … contagion … epidemic … pandemic. The recent year has demonstrated in full force that infectious diseases remain a major health concern. Infectious diseases jeopardize patient outcomes throughout the healthcare delivery system as well as in the perioperative sector. Additionally, new emerging infectious diseases stemming from special and novel pathogens pose great threats to the health and safety of persons in our local, national, and global communities, and new emerging pathogens can cause massive global disruption.

Multiple factors (i.e., overcrowding, poor sanitation, migration patterns, climate change, jet travel) in the past decade have led to fragile ecosystems that contribute to rapid disease spread. While many significant advances have been made in modern medicine in the treatment of cardiovascular disease and certain kinds of cancer, infectious organisms and their resultant diseases remain a major obstacle to worldwide health. The advent of antibiotics to treat some bacterial diseases was a major advance, as was the development of vaccines against a number of infectious diseases. But for every step forward, a substantial obstacle has appeared. For example, microorganisms have developed resistance to some antibiotic drugs, and they continue to mutate in ways that make their eradication ever more difficult. Development of vaccines to treat some of the most common and potentially deadly infectious diseases in the world have been stymied by the ability of some infectious agents to mutate much more quickly than lab personnel can change their vaccine formulations; malaria and human immunodeficiency virus (HIV) disease are examples of this. In addition, about one new infectious disease organism has been discovered annually over the past 50 years. Some have been discovered in regions far removed from our country, but easy travel has brought the opportunity for nearly anyone anywhere to become infected with what were formerly thought to be exotic diseases.

Healthcare facilities, long thought to be havens for the very ill, are now also reservoirs of multiple infectious diseases due to resistant microorganisms or to infection by microorganisms that can only manifest disease when other more virulent organisms have been reduced in number or eradicated. Thus the presence of infectious agents as a comorbid condition in patients presenting for surgery remains a significant issue for the perioperative physician. Additionally, the development of

hospital-acquired infections remains a significant cause of morbidity and mortality in the perioperative period. Patients may have coexisting infectious diseases that impact perioperative care when they come for surgery; these infections may be explicitly manifest or occult. Preexisting infectious diseases may be the indication for surgery or they may impact the risks associated with the surgery. In addition, every patient undergoing surgery is at risk of acquiring an infectious disease during the perioperative period. Patients undergoing surgery are vulnerable to infection both at the surgical site and where natural defenses are breached (i.e., respiratory tract, urinary tract, bloodstream, and sites of invasive monitoring). These infectious diseases can be passed on to other patients and to health professionals in the perioperative period, and healthcare workers themselves may serve as active agents in transmitting infectious diseases to patients.

INFECTION PREVENTION OVERVIEW

Antibiotic Resistance

Prior to the development of microscopic biology, humans had little understanding of infection and were subject to many devastating pandemics, such as the Black Death of the 14th century. Since the discovery of penicillin in 1928, bacteria have undergone thousands of mutations, resembling a Darwinian survival-of-the-fittest evolutionary response to antibiotic exposure that has perpetuated the need for ever-new antibiotics. Most classes of antibiotics were discovered in the 1940s and 1950s, and these drugs are directed at a few specific aspects of bacterial physiology: biosynthesis of the cell wall, DNA, and proteins. During the past 40 years, only two new chemical classes of antibiotics have been developed. One reason for the widespread drug resistance among bacterial pathogens is the limited choice of antibiotics that manipulate only a narrow range of bacterial functions. Another is overprescription and inappropriate use of current antibiotics.

Infectious diseases that were presumably eradicated (e.g., tuberculosis [TB]) are demonstrating a resurgence. Some re-emerging pathogens, such as multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB, have resistance to previously successful antimicrobial therapies. MDR organisms cause an increasing number of bacterial infections in hospitals, and bacteria are emerging with resistance to all available antibiotics. Much of the attention is presently focused on resistant gram-positive organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA). However, there is virtually no development of antibiotics active against resistant gram-negative pathogens. New antibiotic development has dramatically slowed owing to regulatory disincentives, market failures, and lack of profitability compared to other pharmacologic pursuits.

Surgical Site Infections

Surgical site infections (SSIs) have been the focus of much attention during the past 30 years, and the major emphasis has been on completely preventing the occurrence of surgery-related infections and their associated morbidity and mortality. In 2002, the Centers for Medicare and Medicaid Services (CMS), in collaboration with the Centers for Disease Control and Prevention (CDC), implemented the national Surgical Infection Prevention Project (SIPP). The key measures being monitored by this project are (1) the proportion of patients who receive parenterally administered antibiotics within 1 hour prior to incision (within 2 hours for vancomycin and fluoroquinolones), (2) the proportion of patients who receive prophylactic antimicrobial therapy consistent with published guidelines, and (3) the proportion of patients whose prophylactic antibiotic is discontinued within 24 hours after surgery.

Despite the implementation of numerous sets of drug and policy guidelines, SSIs continue to occur at a rate of 2% to 5% for extraabdominal surgery and up to 20% for intraabdominal surgery, and they affect approximately 500,000 patients annually. SSIs are among the most common causes of nosocomial infection, accounting for 14% to 16% of all nosocomial infections in hospitalized patients. SSIs are a major source of morbidity and mortality, rendering patients 60% more likely to spend time in the intensive care unit (ICU), five times more likely to require hospital readmission, and twice as likely to die. A recent resurgence in SSIs may be attributable to bacterial resistance, increased implantation of prosthetic and foreign materials, or the poor immune status of many patients undergoing surgery. Universal adoption of simple measures, including frequent handwashing and appropriate administration of prophylactic antibiotics, has been emphasized as a method of decreasing the incidence of SSIs.

SSIs are divided into superficial infections (involving skin and subcutaneous tissues), deep infections (involving fascial and muscle layers), and infections of organs or tissue spaces (any area opened or manipulated during surgery) (Fig. 25.1). *S. aureus*, including MRSA, is the predominant cause of SSIs. The increased proportion of SSIs caused by resistant pathogens and *Candida* species may reflect the increasing numbers of severely ill and immunocompromised surgical patients and the impact of widespread use of broad-spectrum antimicrobial drugs.

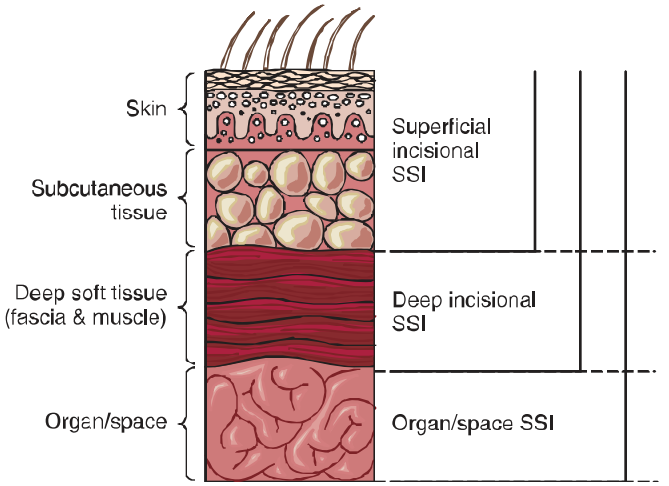

Fig. 25.1 Cross section of abdominal wall, showing the Centers for Disease Control and Prevention (CDC) classification of surgical site infection (SSI). (Adapted from Horan TC, Gaynes RP, Martone WJ, et al. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Infect Control Hosp Epidemiol*. 1992;13:606–608. PubMed:1334988.)

TABLE 25.1 Risk Factors for Surgical Site Infection

Patient-Related Factors	Microbial Factors	Wound-Related Factors
Extremes of age	Enzyme production	Devitalized tissue
Poor nutritional status	Polysaccharide capsule	Dead space
ASA physical status score >2	Ability to bind to fibronectin	Hematoma
Diabetes mellitus	Biofilm and slime formation	Contaminated surgery
Smoking		Presence of foreign material
Obesity		
Coexisting infections		
Colonization		
Immunocompromise		
Longer preoperative hospital stay		

ASA, American Society of Anesthesiologists.

Risk Factors for Surgical Site Infections

The risk of developing an SSI is affected by patient-related, microbe-related, and wound-related factors. Patient-related factors include chronic illness, extremes of age, baseline immunocompetence or inherent or acquired immunocompromise, diabetes mellitus, and corticosteroid therapy. These factors are associated with an increased risk of developing an SSI.

Microbial factors include pathogen enzyme production, possession of a polysaccharide capsule, and the ability to bind to fibronectin in blood clots. These are some of the mechanisms by which microorganisms exploit weakened host defenses and initiate infection. Biofilm formation is particularly important in the development of prosthetic material infections (i.e., prosthetic joint infection). Coagulase-negative staphylococci produce a glycocalyx and an associated component called slime that physically shield bacteria from phagocytes or inhibit antimicrobial agents from binding with or penetrating into the bacteria.

Devitalized tissue, dead space, and hematomas are wound-related features associated with the development of SSIs. Historically, wounds have been described as clean, contaminated, and dirty according to the expected number of bacteria entering the surgical site. The presence of a foreign body (i.e., sutures or mesh) reduces the number of organisms required to induce an SSI. Interestingly the implantation of major devices such as prosthetic joints and cardiac devices is not associated with a higher risk of SSIs. Risk factors for SSI are summarized in Table 25.1.

Signs and Symptoms

SSIs typically present within 30 days of surgery with localized inflammation at the surgical site and evidence of poor wound healing. Systemic features of infection, such as fever and malaise, may occur soon thereafter.

Diagnosis

There may be nonspecific evidence of infection, such as an elevated white blood cell count, poor blood glucose control, and elevated levels of inflammatory markers such as C-reactive protein. However, surgery is a great confounder because surgery itself causes inflammation and thus renders surrogate markers of infection less reliable. Purulence at the wound site is highly suggestive of infection. The gold standard in documenting a wound infection is growth of organisms in an aseptically obtained culture specimen. Approximately one-third of organisms cultured are staphylococci (*S. aureus* and *S. epidermidis*); *Enterococcus* species make up more than 10%, and Enterobacteriaceae make up the bulk of the remaining culprits. Table 25.2 lists the criteria for diagnosing an SSI.

Management of Anesthesia

Preoperative. Active infections should be treated aggressively before surgery; when possible, surgery should be postponed until infection has resolved. If a localized area of infection is present at the intended surgical site, surgery should be postponed until the localized infection is treated and/or resolves spontaneously. If a patient has clinical evidence of infection, such as fever, chills, or malaise, efforts should be made to identify the source of the infectious process. Several studies

TABLE 25.2 Criteria for Diagnosis of Surgical Site Infection (SSI)

Type of SSI	Time Course	Criteria (At Least One Must Be Present)
Superficial incisional SSI	Within 30 days of surgery	Superficial pus drainage Organisms cultured from superficial tissue or fluid Signs and symptoms (pain, redness, swelling, heat)
Deep incisional SSI	Within 30 days of surgery or within 1 yr if prosthetic implant present	Deep pus drainage Dehiscence or wound opened by surgeon (for temperature >38°C, pain, tenderness) Abscess (e.g., radiographically diagnosed)
Organ/space SSI	Within 30 days of surgery or within 1 yr if prosthetic implant present	Pus from a drain in the organ/space Organisms cultured from aseptically obtained specimen of fluid or tissue in the organ/space Abscess involving the organ/space

have shown that smoking may increase not only the incidence of respiratory tract infection but also the incidence of wound infections. Preoperative cessation of smoking for 4 to 8 weeks before orthopedic surgery decreases the incidence of wound-related complications. Significant preoperative alcohol consumption may result in generalized immunocompromise. One month of preoperative alcohol abstinence reduces postoperative morbidity in alcohol users.

Diabetes mellitus is an independent risk factor for infection, and optimization of preoperative diabetes treatment may decrease perioperative infection. Malnutrition, whether manifesting as cachexia or obesity, is associated with an increased perioperative infection rate. Appropriate diet and/or weight loss may be beneficial before major surgery.

S. aureus is the organism most commonly implicated in SSIs, and many individuals are carriers of *S. aureus* in the anterior nares. This carrier state has been identified as a risk factor for *S. aureus* wound infections. Topical mupirocin applied to the anterior nares has been successful in eliminating the carrier state of *S. aureus* and decreasing the risk of infection. However, there is concern that this practice may promote development of mupirocin-resistant *S. aureus*. Active surveillance programs to eliminate nasal colonization in hospital surgical personnel have controlled outbreaks of *S. aureus* SSIs.

Hair clipping at the planned surgical site is acceptable, but shaving increases the risk of SSI probably because microcuts serve as entry portals for microorganisms. Preoperative skin cleansing with chlorhexidine has been shown to reduce the incidence of SSIs.

Intraoperative

Prophylactic antibiotics. It was recognized many years ago that prophylactic administration of antimicrobial agents prevents postoperative wound infections. This is particularly true when the inoculum of bacteria is high, such as in colon, rectal, or vaginal surgery, or when the procedure involves insertion of an artificial implant such as a hip prosthesis or heart valve. The organisms implicated in SSIs are usually those carried by the patient in the nose or on the skin. Unless the patient has been in the hospital for some time before surgery, these are usually community organisms that have not developed multiple drug resistance. Timing of antibiotic prophylaxis (within 1 hour of surgical incision) is important, since these organisms are introduced into the bloodstream at the time of incision. For most procedures a single dose of antibiotic is adequate. Prolonged surgery (>4 hours) may necessitate a second dose. Prophylaxis should be discontinued within 24 hours of the procedure. For cardiac surgery, The Joint Commission has recommended that the duration of prophylaxis be increased to 48 hours. A first-generation cephalosporin, such as cefazolin, is effective for many types of surgery. In general, the spectrum of bacteria against which cephalosporins are effective, their low incidence of side effects, and the tolerability of these drugs have made them an ideal choice for prophylaxis. For high-risk patients and procedures, selection of another appropriate antibiotic plays a critical role in decreasing the incidence of SSIs.

When the small bowel is entered, coverage for gram-negative organisms is important; for procedures involving the large bowel and the female genital tract, the addition of coverage against anaerobic organisms is appropriate. Infections associated with clean surgery are caused by staphylococcal species, whereas infections associated with contaminated surgery are polymicrobial and involve the flora of the viscus entered. Guidelines for antimicrobial prophylaxis for those considered at risk of infective endocarditis are published by the American Heart Association. Additional treatment considerations are listed in Table 25.3.

TABLE 25.3 Surgical Infection Prevention Guidelines

1. Give prophylactic antibiotics within 30 minutes of surgical incision.
2. Stop prophylactic antibiotics at 24 hours (or 48 hours for cardiac surgery).
3. Increase dose of antibiotics for larger patients (>120 kg)
4. Repeat dose during surgery every 4 hours.
5. Administer antibiotic(s) appropriate for local resistance patterns.
6. Follow American Heart Association guidelines for patients at risk of infective endocarditis.
7. Adhere to procedure-specific antibiotic recommendations.

Physical and physiologic preventive measures. Several simple physical measures have been studied to determine their effects on the incidence of postoperative infection. Much of the work has focused on the oxygen tension at the wound site. Destruction of organisms by oxidation (oxidative killing) is the most important defense against surgical pathogens and depends on the partial pressure of oxygen in contaminated tissue. In patients with normal peripheral perfusion, the subcutaneous oxygen tension is linearly related to the arterial oxygen tension. An inverse correlation has been demonstrated between subcutaneous tissue oxygen tension and the rate of wound infections. Tissue hypoxia appears to increase the vulnerability to infection.

Hypothermia has been shown to increase the incidence of SSI. In a study in which patients were randomly assigned to hypothermia and normothermia groups, SSI was found in 19% of patients in the hypothermia group but in only 6% of those in the normothermia group. Radiant heating to 38°C increases subcutaneous oxygen tension. This may be one of the mechanisms for the decreased infection risk associated with increased body temperature.

Oxygen. An easy method of improving oxygen tension is to increase the concentration of inspired oxygen. Studies of patients undergoing colorectal resection have demonstrated that perioperative administration of 80% oxygen decreases the incidence of SSI in this patient group. It is unknown whether perioperative administration of 80% oxygen decreases the incidence of SSI in other surgical settings. Universal adoption of this treatment protocol remains controversial because a prolonged period of high inspired oxygen tension may cause pulmonary damage.

Analgesia. Superior treatment of surgical pain is associated with increased postoperative subcutaneous oxygen partial pressures at wound sites. Adequate analgesia may therefore be associated with a decreased incidence of SSI.

Carbon dioxide. Hypocapnia occurs frequently during anesthesia and can be deleterious for many reasons, particularly because of the vasoconstriction it causes. Such vasoconstriction could impair perfusion of vital organs. Hypercapnia causes vasodilation and increases skin perfusion. Intriguing research has shown that mild intraoperative hypercapnia increases the oxygen tension in subcutaneous tissue and the colon.

Glucose. The results of studies to date suggest that in the perioperative period, the ideal blood glucose goal should be in the normal range with minimal variability. A high blood glucose concentration is thought to inhibit leukocyte function and provide a favorable environment for bacterial growth. Interestingly the therapy for hyperglycemia may itself have beneficial effects. Administration of glucose, insulin, and potassium stimulates lymphocytes to proliferate and attack pathogens. Glucose, insulin, and potassium may play an important role in restoring immunocompetence to patients with immunocompromise.

Wound-probing protocols. Current studies suggest that infection of contaminated wounds can be decreased by following wound-probing protocols. Wound probing is a bedside technique that combines the benefits of primary and secondary wound closure. Use of this technique has been shown to decrease length of stay and SSIs, but the exact mechanism of its effect is not clearly understood.

BLOODBORNE INFECTIONS

Bloodstream Infections

Bloodstream infections (BSIs) are among the top three nosocomial infections in incidence. Anesthesiologists may play an important role in the prevention and often the treatment of BSIs. Although a 46% decrease in central line–associated bloodstream infections (CLABSIs) has occurred in hospitals across the United States from 2008 to 2013, an estimated 30,100 CLABSIs still occur in ICUs and wards of US acute care facilities each year. CLABSIs are serious infections typically causing a prolongation of hospital stay and increased cost and risk of mortality. CLABSIs are monitored by the National Healthcare Safety Network (NHSN) of the CDC. At every hospital, each institution should determine the CLABSI rate; this is calculated per 1000 central line days by dividing the number of CLABSIs by the number of central line days and multiplying the result by 1000. A central line utilization ratio is also calculated. Mortality risk related to these is estimated to be 12% to 25% for each bloodstream infection.

Signs and Symptoms

Patients typically have nonspecific signs of infection with no obvious source. There is no cloudy urine, purulent sputum, pus drainage, or wound inflammation. There is only an indwelling catheter. Inflammation at the catheter insertion site is suggestive of infection. A sudden change in a patient's condition, such as mental status changes, hemodynamic instability, altered tolerance for nutrition, and generalized malaise, can indicate a BSI.

Diagnosis

CLABSIs are defined as bacteremia or fungemia in a patient with an intravascular catheter with at least one blood culture positive for a recognized pathogen not related to another infection in that patient, clinical manifestations of infection, and no other apparent source for the BSI except the catheter. BSIs are considered to be associated with a central line if the line was in use during the 48-hour period before the development of the BSI. If the time interval between the onset of infection and device use is longer than 48 hours, other sources of infection must be considered. The diagnosis is more compelling if after catheter removal the same organisms that grew in the blood culture grow from the catheter tip. Table 25.4 lists pathogens commonly associated with BSI.

Treatment

The best treatment for CLABSIs is prevention. However, if infection is suspected, the source of the infection should be removed as soon as possible, and broad-spectrum antimicrobial therapy should be initiated. Once culture results are available, antibiotic therapy can be targeted to the specific organism. Because of antibiotic resistance patterns, it is difficult to strike a compromise between providing appropriate initial empirical coverage and not exhausting the last-line antimicrobial agents with the first salvo of antibiotic therapy. Treatment of patients with BSIs is similar to treatment of patients with sepsis.

Management of Anesthesia

Preoperative. Many central venous catheters are placed by anesthesiologists who may not be informed about BSIs that develop days later. Preventing BSIs related to central venous catheter use can be minimized by implementing a series of evidence-based steps shown to reduce catheter-related infection. A recent interventional study targeted five evidence-based procedures recommended by the CDC and identified as having the greatest effect in reducing the rate of catheter-related BSIs and the fewest barriers to implementation. The five interventions are (1) healthcare professional will perform hand hygiene

TABLE 25.4 Common Pathogens Associated With Bloodstream Infections

Gram-positive bacteria (55%)
Coagulase-negative staphylococci
Staphylococcus aureus
Enterococci
Streptococcus pneumoniae
Gram-negative bacteria (31%)
Escherichia coli
Enterobacter species
Klebsiella pneumoniae
Acinetobacter baumannii
Fungi (10%)
Candida species

Adapted from Orsini J, Mainardi C, Muzylo F, et al. Microbiological profile of organisms causing bloodstream infection in critically ill patients. *J Clin Med Res.* 2012;4:371–377.

prior to insertion, (2) adhere to aseptic technique and utilize full-barrier precautions (hat, mask, sterile gown, sterile area covering) during central venous catheter insertion, (3) cleaning the skin with 0.5% chlorhexidine with alcohol, (4) avoiding the femoral site if possible, and (5) using sterile chlorhexidine-impregnated dressing over the site, conducting routine daily inspection of catheters and removing them as soon as deemed unnecessary. In this study, use of these evidence-based interventions resulted in a large and sustained reduction (up to 66%) in rates of CLABSIs that was maintained throughout the 18-month study period. The subclavian and internal jugular venous routes carry less risk of infection than the femoral route, but the decision regarding anatomic location also has to consider the higher risk of pneumothorax with a subclavian catheter. During insertion, catheter contamination rates can be further reduced by rinsing gloved hands in a solution of chlorhexidine in alcohol before handling the catheter. Sterility must be maintained with frequent hand decontamination and cleaning of catheter ports with alcohol before accessing them. The same high standards of sterility should be applied with regional anesthetic catheters. Central venous catheters may be coated or impregnated with antimicrobial or antiseptic agents. These catheters have been associated with a lower incidence of BSIs. Concerns about widespread adoption of drug-impregnated catheters are based on increased costs and promotion of antimicrobial resistance. However, use of such catheters may be indicated for the most vulnerable patients, such as those with severe immunocompromise.

Intraoperative. Transfusion of red blood cells and blood components increases the incidence of postoperative infection via two mechanisms: direct transmission of organisms from the blood product and immunosuppression. Even autologous blood transfusion results in natural killer cell inhibition and is intrinsically immunosuppressive. The mechanism of immunosuppression may be related to infusion of donor leukocytes or their byproducts. Blood transfusion–associated immunosuppression may be decreased by leukodepletion.

Transfusion of cellular blood components has been implicated in transmission of viral, bacterial, and protozoal diseases. Over the past 20 years, reductions in the risk of viral infection from blood components have been achieved. Minipool nucleic acid amplification testing detects HIV and hepatitis B and C virus during the time before antibodies develop. This sensitive and specific test has decreased the risk of HIV-1 and hepatitis C virus transmission to 1 in 2 million blood transfusions.

Because of the success in detecting viral infection, bacterial contamination of blood products has emerged as the greatest residual source of transfusion-transmitted disease. Each year, approximately 9 million units of platelet concentrates are transfused in the United States. An estimated 1 in 1000 to 3000 platelet units is contaminated with bacteria. Platelets, to maintain viability and function, must be stored at room temperature, which creates an excellent growth environment for bacteria. The prevalence of episodes of transfusion-associated bacterial sepsis is approximately 1 in 50,000 for platelet units and 1 in 500,000 for red blood cell units. Implementation of bacterial detection methods will improve the safety and extend the shelf life of platelets. The best way to avoid infectious complications related to transfusion is simply to avoid or minimize the use of transfusions.

Postoperative. Several postoperative management strategies can decrease the incidence of catheter-related BSI: (1) removal of central lines and pulmonary artery catheters as soon as possible, and (2) avoidance of unnecessary parenteral nutrition and dextrose-containing fluid, since these may be associated with an increased risk of BSI. Food and glucose can usually be withheld for a short period or delivered into the gut rather than into a vein.

Sepsis

Sepsis is an umbrella term encompassing those conditions in which there are pathogenic microorganisms in the body. Sepsis may be life threatening because of complications precipitated by an organism, its toxins, and the body's own defensive inflammatory response. (A similar response may occur in the absence of infection, and this is sometimes called systemic inflammatory response syndrome [SIRS].) Sepsis is a spectrum of disorders on a continuum, with localized inflammation at one end and a severe generalized inflammatory response with multiorgan failure at the other (Fig. 25.2). Severe sepsis is defined as acute organ dysfunction secondary to infection, and septic shock is severe sepsis with hypotension not reversed by fluid administration.

Surgery and anesthesia should be postponed until sepsis is at least partially treated. However, sometimes the underlying cause of sepsis requires urgent surgical intervention. Such surgery may be termed *source control surgery*. Examples of septic sources are abscesses, infective endocarditis, bowel perforation or infarction, infected prosthetic device (e.g., intravenous [IV] catheter, intrauterine device, or pacemaker), endometritis, and necrotizing fasciitis.

Bacterial components such as endotoxin, through their action on neutrophils and macrophages, can induce a wide range of proinflammatory factors and counterregulatory host responses that turn off production of proinflammatory cytokines. As a result the proinflammatory reaction (SIRS) can become exaggerated by associated activation of the complement system and coagulation cascade, widespread arterial vasodilation, and altered capillary permeability. This may result in multiorgan dysfunction and death.

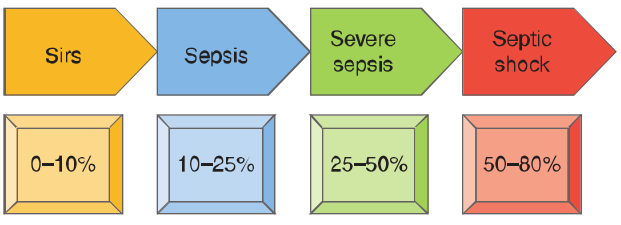

Fig. 25.2 Sepsis continuum and approximate mortality rates. *SIRS*, Systemic inflammatory reaction syndrome. (Adapted from Gotts GE, Matthay MA. Sepsis: pathophysiology and clinical management. BMJ. 2016;353. doi:10.1136/bmj.i1585.)

Signs and Symptoms

Signs and symptoms of sepsis are often nonspecific, and presentation varies according to the initial source of infection. SIRS is an important component of sepsis; however, sepsis is a continuum and can range from SIRS to septic shock (Table 25.5). Sepsis may result in multiorgan failure. Features of infection include fever, altered mental status, and encephalopathy. Hyperglycemia may be present. Septic shock refers to hemodynamic instability that may accompany sepsis and the perfusion abnormalities that may include (but are not limited to) lactic acidosis, oliguria, or a change in mental status. Classically, hypotension, bounding pulses, and a wide pulse pressure are present. These are characteristic signs of high-output cardiac failure and distributive shock, both of which may occur with sepsis. Patients who are receiving inotropic drugs or vasopressor support may not be hypotensive.

Diagnosis

A diagnosis of sepsis is surmised from history, signs, and symptoms. Confirmation is based on isolation of a specific causative pathogen. It is important to identify the culprit microbe to ensure that antimicrobial therapy is appropriate and targeted. Specimens for culture should be sent from all sources where organism growth is suspected. Blood, urine, and sputum specimens are a minimum. Tissue sampling from specific sources such as heart valves, bone marrow, and cerebrospinal fluid can also be important.

Treatment

Initial treatment of sepsis involves broad antimicrobial coverage coupled with supportive care of failing organs. The speed and appropriateness of therapy administered in the initial hours of sepsis can dramatically influence outcome. The replication of virulent bacteria can be so rapid that every minute may be crucial. As soon as specific microbiologic information is available, therapy should be tailored to the specific organism and its sensitivities. Choice of an antibiotic must also take into account the ability of the drug to penetrate various tissues, including bone, cerebrospinal fluid, lung tissue, and abscess cavities.

In addition to targeted antimicrobial therapy, supportive treatment relating to organ system dysfunction is essential. Early goal-directed optimization that targets oxygen delivery and cardiac output may improve outcome in sepsis.

Prognosis

Prognosis in sepsis depends on the virulence of the infecting pathogen(s), stage at which appropriate treatment is initiated, inflammatory response of the patient, immune status of the patient, and extent of organ system dysfunction. It is impossible to predict the outcome for any individual patient.

Management of Anesthesia

Preoperative. The most important considerations for a patient with sepsis requiring surgery are whether the surgery may be postponed pending treatment of sepsis and whether the patient's condition may be improved before surgery. A treatment algorithm for septic patients (Fig. 25.3) suggests goal-directed optimization of the patient's condition. Resuscitation should be targeted to achieve mean arterial pressure above 65 mm Hg, central venous pressure of 8 to 12 mm Hg, adequate urine output, a pH without a metabolic (lactic) acidosis, and a mixed venous oxygen saturation above 70%.

Intraoperative. Intraoperative management of patients with sepsis is challenging. Patients with sepsis may have limited

TABLE 25.5 The Sepsis Continuum

SIRS	Sepsis	Severe Sepsis	Septic Shock
Two or more SIRS criteria Temperature: >100.4°F or <96.8°F (>38.0°C or <36.0°C) Tachycardia: Heart rate >90 beats/min Tachypnea: Respiratory rate >20 breaths per minute White blood cell count: >12,000/mm^3, <4000/mm^3, or >10% immature cell	Two or more SIRS criteria Source of infection: Presumed or documented infectious focus Infiltrate on chest radiograph in patient with signs and symptoms consistent with pneumonia Infected fluid from a normally sterile site, including cerebrospinal fluid, joint fluid, and blood Urinalysis and microscopy consistent with infection Positive blood cultures Obvious cellulitis Purulent fluid drained from abnormal collection	Two or more SIRS criteria Source of infection Acute organ dysfunction: signs of microvascular compromise and poor perfusion Acute encephalopathy, presenting as altered mental status Renal dysfunction, presenting as oliguria Cardiac dysfunction, presenting as hypotension or myocardial depression Pulmonary dysfunction, presenting as severe hypoxia Tissue-level hypoperfusion, presenting as an elevated serum lactate level	Two or more SIRS criteria Source of infection Acute organ dysfunction Persistent hypotension: systolic blood pressure (SBP) <90 mm Hg or mean arterial blood pressure <65 mm Hg or a SBP reduction of >40 mm Hg from baseline, despite adequate fluid resuscitation (20–30 cc bolus over 30 min)

SIRS, Septic inflammatory reaction syndrome.

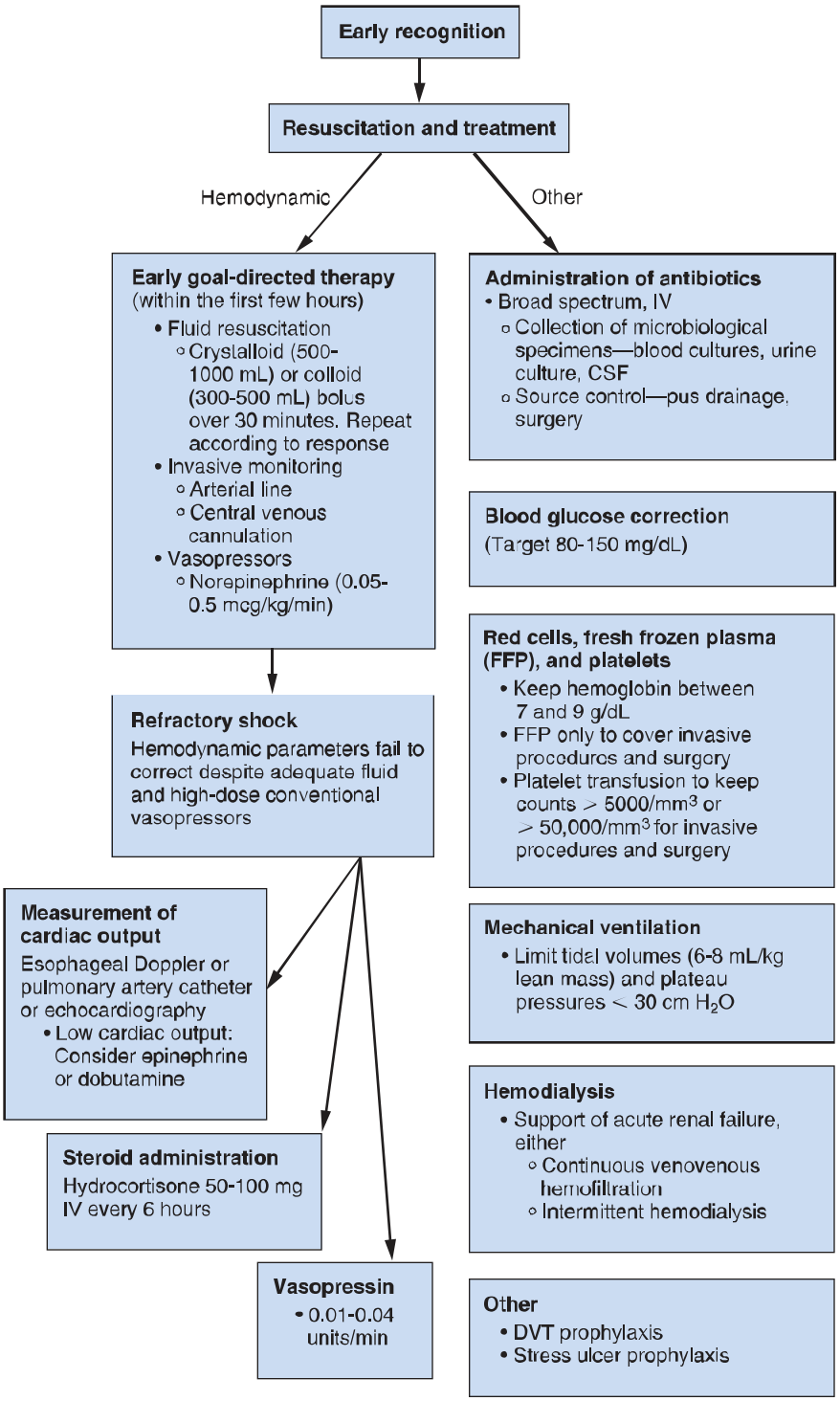

Fig. 25.3 Management of sepsis. *APACHE,* Acute Physiology and Chronic Health Evaluation II (score); *CSF,* cerebrospinal fluid; *DVT,* deep vein thrombosis; *IV,* intravenously.

physiologic reserve that renders them vulnerable to hypotension and hypoxemia with induction of anesthesia. Invasive monitoring, such as intraarterial blood pressure and central venous pressure monitoring, is usually indicated. Establishment of sufficient IV access to allow for volume resuscitation as well as transfusion of blood and blood components is essential. Antimicrobial prophylaxis appropriate for surgery is indicated. Ideally this would be combined with the treatment regimen for the pathogen thought to be responsible for the sepsis. Prophylactic antibiotics should be administered within 30 minutes of skin incision.

Postoperative. Patients with sepsis invariably require ICU admission after surgery. In the ICU the priorities include support of failing organ systems, targeted antimicrobial therapy, and minimizing the likelihood of new infections such as a fungal infection, infection with *Clostridium difficile,* or the emergence

of a resistant organism. Another important postoperative priority is continuation of antimicrobial therapy for only as long as it is indicated. Broad guidelines for treatment of patients with sepsis in the ICU have been published by the Society of Critical Care Medicine in the Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock.

GASTROINTESTINAL INFECTIONS

Clostridium Difficile Infection

C. difficile is an anaerobic, gram-positive, spore-forming bacterium that is the major identifiable cause of antibiotic-associated diarrhea and pseudomembranous colitis. It is clear today that most antibiotics can alter bowel flora, facilitating the growth of *C. difficile*. With the frequent use of broad-spectrum antibiotics, the incidence of *C. difficile* diarrhea has risen dramatically.

C. difficile infection is the most common cause of diarrhea in healthcare settings, resulting in increased hospital stays and higher morbidity and mortality among patients. The prevalence of asymptomatic colonization in the hospital, especially in older people, is over 20%. It is transmitted by spores that are resistant to heat, acid, and antibiotics. *C. difficile* is extremely hardy, can survive in the environment for prolonged periods of time, and is resistant to common disinfectants, which leads to transmission from contaminated surfaces and airborne spores. In approximately one-third of those colonized, *C. difficile* produces toxins that cause diarrhea. The two principal toxins are toxin A and toxin B. Toxin B is approximately 1000 times more cytotoxic than toxin A. Toxin A activates macrophages and mast cells. Activation of these cells causes production of inflammatory mediators, which leads to loss of intestinal barrier function and neutrophilic colitis. Toxin A is also an enterotoxin in that it loosens the tight junctions between the epithelial cells that line the colon, which helps toxin B enter these colonic cells.

A number of risk factors for *C. difficile*–associated diarrhea have been identified: advanced age (>65 years), severe underlying disease, gastrointestinal (GI) surgery, presence of a nasogastric tube, use of antiulcer medications such as proton pump inhibitors, admission to an ICU, long duration of hospital stay, long duration of antibiotic administration (risk doubles after 3 days), use of multiple antibiotics, immunosuppressive therapy or general immunocompromise, recent surgery, and sharing of a hospital room with a *C. difficile*–infected patient. Some antibiotics are frequently associated with *C. difficile* infection (Table 25.6).

TABLE 25.6 Antibiotic Therapy Most Commonly Associated With *Clostridium Difficile* Infection[a]

Clindamycin
Fluoroquinolones
Cephalosporins, carbapenems, monobactams
Macrolides
Sulfonamides
Penicillins
Tetracyclines

[a] Listed in order of highest to lowest risk.

Signs and Symptoms

The most frequent symptoms of *C. difficile* infection are diarrhea and abdominal pain. Patients may be febrile with abdominal tenderness and distention. With perforation, patients may have an acute abdomen.

Diagnosis

The gold standard for diagnosis *C. difficile* infection is detection of *C. difficile* toxins A and B in stool. The detection of *C. difficile* antibody does not indicate current infection.

Treatment

Therapy for patients with *C. difficile*–associated diarrhea consists of fluid and electrolyte replacement, withdrawal of current antibiotic therapy if possible, and institution of targeted antibiotic treatment to eradicate *C. difficile*. Antibiotic treatment should be given orally if possible. The first-line regimen is oral metronidazole 500 mg three times daily. An alternative is oral vancomycin 125 mg four times daily. Vancomycin has a theoretical advantage over metronidazole, since it is poorly absorbed and may therefore be present in higher concentrations at the site of infection. The major downside to vancomycin is that it may promote the growth of vancomycin-resistant enterococci. In 2011, fidaxomicin was approved by the US Food and Drug Administration (FDA) for treatment of *C. difficile* infection. It appears to be equivalent in effect to vancomycin in curing infection and is superior to vancomycin in reducing the risk of recurrent *C. difficile* infection. It is, however, even more expensive than vancomycin therapy. Fecal microbial transplantation is another treatment for *C. difficile* infection. Transplantation of feces from a healthy tested donor administered in a solution via a nasoduodenal tube and the cessation of all antibiotics are successful in treating over 90% of recurrent *C. difficile* infections.

Additional therapies might include probiotics to restore normal bowel flora, but their usefulness has yet to be defined.

Prognosis

C. difficile infection accounts for considerable increases in length of hospital stays and more than $1.1 billion in healthcare costs each year in the United States. The condition is a common cause of significant morbidity and even death in elderly, debilitated, and immunocompromised patients.

Management of Anesthesia

Preoperative. It is generally the sickest patients with *C. difficile* colitis, including those whose infection does not improve with conventional therapy, who come for surgery such as subtotal colectomy and ileostomy. If the patient is hemodynamically unstable, major surgery should be deferred and an ileostomy, cecostomy, or colostomy performed as a temporizing intervention. Surgery is associated with high mortality. Resuscitation and preoperative treatment of metabolic derangements may be needed. Patients with *C. difficile* infection should be scheduled for surgery at the end of the surgical day so the operating room can undergo additional cleaning to minimize the risk of transmission to subsequent patients.

Intraoperative. Patients with fulminant *C. difficile* colitis are very ill, and hemodynamic instability is likely during anesthesia. Invasive monitoring, including an intraarterial catheter and central venous catheter, may guide fluid administration and the use of inotropes and vasopressors. Dehydration, acid-base abnormalities, and electrolyte imbalances may be present because of the diarrhea. Opiates decrease intestinal motility, which may exacerbate toxin-mediated disease.

Postoperative. One of the most important considerations perioperatively is prevention of the spread of *C. difficile*. The spores are hardy and not destroyed by alcohol, so use of alcohol-based solutions for hand cleansing is not effective in removing *C. difficile* spores. Strict contact and isolation precautions, routine use of gloves and gowns, and vigorous handwashing with soap and water will remove spores and help prevent spread of this disease. Stethoscopes and neckties are potential repositories for spores.

CUTANEOUS INFECTIONS

Necrotizing Soft Tissue Infection

Necrotizing soft tissue infection is a nonspecific term that may encompass such diagnoses as gas gangrene, Fournier gangrene, severe cellulitis, and flesh-eating infections. One of the most important aspects of these infections is that the severity of the infection may be underappreciated at the time of presentation. The responsible organisms are highly virulent, the clinical course is fulminant, and mortality is high (up to 75%). Fournier gangrene was eponymously named for the French physician Jean Alfred Fournier, who described scrotal gangrene in five young men. He noted a sudden onset of symptoms, rapid progression to gangrene, and absence of a definite cause. Necrotizing soft tissue infections are surgical emergencies and represent a subclass of severe sepsis.

Signs and Symptoms

At presentation, patients may have general features of infection, including malaise, fever, sweating, and altered mental status. Pain is invariable and may be out of proportion to the physical signs. Specific features may include scrotal swelling and erythema, vaginal discharge, tissue inflammation, pus, or subcutaneous air (crepitus). The cutaneous signs are often surprisingly mild and do not reflect the extent of tissue necrosis, because necrotizing skin infections begin in deep tissue planes. Hypotension is an ominous sign and may presage progression to septic shock. Resolution of pain may also be ominous, since this may occur with progression to gangrene.

Diagnosis

History is important in suggesting a diagnosis. Older patients and patients with a history of alcohol use, malnutrition, obesity, trauma, cancer, burns, vascular disease, and diabetes are more susceptible, as are patients taking immunosuppressant medication or those infected with HIV. There may be a high white blood cell count, thrombocytopenia, coagulopathy, electrolyte abnormalities, acidosis, hyperglycemia, elevated levels of markers of inflammation such as C-reactive protein, and radiographic evidence of extensive necrotic inflammation/necrosis with subcutaneous air. Ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) may be used to delineate the extent of tissue necrosis. Blood, urine, and tissue samples should be sent to the laboratory for culture. Organisms most frequently grown from necrotic tissue include *Streptococcus pyogenes, S. aureus, S. epidermidis, Bacteroides* species, *Clostridium perfringens,* and gram-negative organisms, especially *Escherichia coli.* Polymicrobial infection is common.

Treatment

The definitive treatment is extensive débridement of necrotic tissue coupled with antimicrobial therapy, which typically includes coverage of gram-positive, gram-negative, and anaerobic organisms. Empirical broad-spectrum antibiotic coverage is provided initially, and treatment can subsequently be targeted to the specific organism(s) based on culture results.

Prognosis

Necrotizing soft tissue infection has a high mortality. If patients survive the initial insult, they remain vulnerable to secondary infection. They may require repeated anesthesia for débridements, skin grafts, and reconstructive surgery.

Management of Anesthesia

Preoperative. The anesthesiologist should treat patients with necrotizing soft tissue infection as having severe sepsis and should resuscitate preoperatively with goal-directed therapy, including administration of IV fluids and optimization of global oxygen delivery, with success reflected by resolution of lactic acidosis or an increase in mixed venous oxygen saturation. However, surgical débridement should not be postponed; any delay is associated with increased mortality.

Intraoperative. Concern has been raised about the use of etomidate for induction of anesthesia in patients with septic shock, since they may already have adrenal insufficiency, which theoretically may be worsened by even a single dose of etomidate. Major fluid shifts, blood loss, and release of cytokines occur intraoperatively. Good IV access is essential, and invasive intraarterial and central venous monitoring may provide valuable information. Blood should be cross-matched and readily available. Patients are at risk of developing both hypovolemic and septic shock.

Postoperative. Like patients with sepsis, patients with necrotizing soft tissue infection are at risk of multiple organ failure. Postoperative admission to an ICU is prudent. Antibiotic therapy and fluid resuscitation should be continued in the postoperative period.

Tetanus

Tetanus is caused by the gram-negative bacillus *Clostridium tetani* and occurs when a wound or entry site becomes contaminated with bacterial spores. Production of the neurotoxin tetanospasmin is responsible for the clinical manifestations of tetanus. With the exception of botulinum toxin, tetanospasmin is the most powerful microbe-produced poison known. Tetanospasmin, when absorbed into wounds, spreads centrally along

motor nerves to the spinal cord or enters the systemic circulation to reach the central nervous system (CNS). The toxin migrates into synapses, where it binds to presynaptic nerve terminals and inhibits or stops the release of certain inhibitory neurotransmitters such as glycine and γ-aminobutyric acid (GABA). Because the motor nerve has no inhibitory signals from other nerves, the chemical signal to the motor nerve of the muscle intensifies, causing the muscle to tighten up in a continuous contraction or spasm.

Tetanospasmin affects the nervous system in several areas. In the spinal cord, tetanospasmin suppresses inhibitory internuncial neurons, which results in generalized skeletal muscle contractions (spasms), and in the brain there is fixation of toxin by gangliosides. The fourth ventricle is believed to have selective permeability for tetanospasmin, which results in early manifestations of trismus and neck rigidity. Sympathetic nervous system hyperactivity may manifest as the disease progresses.

Signs and Symptoms

Trismus is the presenting symptom of tetanus in most patients. The greater strength of the masseter muscles compared with the opposing digastric and mylohyoid muscles results in lockjaw, and these patients may initially seek dental attention. Rigidity of the facial muscles results in the characteristic appearance described as risus sardonicus. Spasm of laryngeal muscles can occur at any time. Intractable pharyngeal spasms following tracheal extubation have been described in patients with unrecognized tetanus. Dysphagia may be due to spasm of the pharyngeal muscles. Spasm of the intercostal muscles and diaphragm interferes with adequate ventilation. The rigidity of abdominal and lumbar muscles accounts for the opisthotonic posture. Skeletal muscle spasms are tonic and clonic in nature and are excruciatingly painful. The increased skeletal muscle work is associated with dramatic increases in oxygen consumption, and peripheral vasoconstriction can contribute to hyperthermia.

External stimulation (e.g., sudden exposure to bright light, unexpected noise, tracheal suctioning) can precipitate generalized skeletal muscle spasms, leading to inadequate ventilation and death. Hypotension has been attributed to myocarditis. Isolated and unexplained tachycardia may be an early manifestation of hyperactivity of the sympathetic nervous system, but more often this hyperactivity is manifested as systemic hypertension. Sympathetic nervous system responses to external stimuli are exaggerated, as demonstrated by tachydysrhythmias and labile blood pressure. In addition, excessive sympathetic nervous system activity is associated with intense peripheral vasoconstriction and diaphoresis.

Treatment

Treatment of patients with tetanus is directed toward controlling the skeletal muscle spasms, preventing sympathetic hyperactivity, supporting ventilation, neutralizing circulating toxin, and surgically débriding the affected area to eliminate the source of the toxin. Diazepam or lorazepam is preferred for controlling skeletal muscle spasms. Administration of nondepolarizing muscle relaxants and mechanical ventilation may be necessary. Indeed, early protection of the upper airway is important because laryngospasm may accompany generalized skeletal muscle spasms. Overactivity of the sympathetic nervous system can be managed with IV administration of β blockers. The circulating exotoxin may be neutralized by intrathecal or intramuscular administration of human antitetanus immunoglobulin. This neutralization does not alter the symptoms already present but does prevent additional exotoxin from reaching the CNS. Penicillin or metronidazole can destroy the toxin-producing vegetative forms of *C. tetani*.

Management of Anesthesia

General anesthesia, including tracheal intubation, is a useful approach for surgical débridement. Surgical débridement is delayed until several hours after the patient has received antitoxin because tetanospasmin is mobilized into the systemic circulation during surgical resection. Invasive monitoring is indicated and should include continuous recording of systemic blood pressure and measurement of central venous pressure. Volatile anesthetics are useful for maintenance of anesthesia if excessive sympathetic nervous system activity is present. Drugs such as lidocaine, esmolol, metoprolol, magnesium, nicardipine, and nitroprusside should be readily available during the perioperative period.

RESPIRATORY INFECTIONS

Pneumonia

Community-Acquired Pneumonia

Combined with influenza, community-acquired pneumonia is one of the 10 leading causes of death in the United States. *Streptococcus pneumoniae* is by far the most frequent cause of bacterial pneumonia in adults. *S. pneumoniae* causes typical pneumonia. Influenza virus, *Mycoplasma pneumoniae*, chlamydia, legionella, adenovirus, and other microorganisms may cause atypical pneumonia. These latter pneumonias are considered atypical because the organisms are not common pneumonia-producing bacteria, do not respond to common antibiotics, and can cause uncommon symptoms.

Aspiration Pneumonia

Patients with depressed consciousness may experience aspiration that in the presence of underlying diseases that impair host defense mechanisms may manifest as aspiration pneumonia. Alcohol- and drug-induced alterations of consciousness, head trauma, seizures, other neurologic disorders, and administration of sedatives are most often responsible for the development of aspiration pneumonia. Patients with abnormalities of swallowing or esophageal motility resulting from placement of nasogastric tubes, esophageal cancer, bowel obstruction, or repeated vomiting are also prone to aspiration. Poor oral hygiene and periodontal disease predispose to development of pneumonia after aspiration because of the increased bacterial flora in the aspirate. Induction and recovery from anesthesia may place patients at increased risk of aspiration.

Clinical manifestations of pulmonary aspiration depend on the nature and volume of aspirated material. Aspiration of large volumes of acidic gastric fluid produces fulminant pneumonia

and arterial hypoxemia. Aspiration of particulate material may result in airway obstruction, and smaller particles may produce atelectasis. Infiltrates are most common in those areas of the lungs that were in a dependent position at the time of aspiration. Penicillin-sensitive anaerobes are the most likely cause of aspiration pneumonia. Hospitalization or antibiotic therapy alters the usual oropharyngeal flora, so aspiration pneumonia in hospitalized patients often involves pathogens that are uncommon in community-acquired pneumonia.

Postoperative Pneumonia

Postoperative pneumonia occurs in approximately 20% of patients undergoing major thoracic, esophageal, or upper abdominal surgery but is rare after other procedures in previously fit patients. Chronic lung disease increases the incidence of postoperative pneumonia threefold. Other risk factors include obesity, age older than 70 years, and operations lasting longer than 2 hours.

Lung Abscess

Lung abscess may develop after bacterial pneumonia. Alcohol abuse and poor dental hygiene are important risk factors. Septic pulmonary embolization, which is most often seen in IV drug abusers, may also result in formation of a lung abscess. The finding of an air-fluid level on the chest radiograph signifies rupture of the abscess into the bronchial tree. Foul-smelling sputum is characteristic. Antibiotics are the mainstay of treatment of a lung abscess. Surgery is indicated only when complications such as empyema occur. Thoracentesis is necessary to establish the diagnosis of empyema, and treatment requires chest tube drainage and antibiotics. Surgical drainage may be necessary to treat chronic empyema.

Diagnosis

An initial chill followed by abrupt onset of fever, chest pain, dyspnea, fatigue, rigors, cough, and copious sputum production often characterize bacterial pneumonia. Nonproductive cough is a feature of atypical pneumonia. A detailed history may suggest possible causative organisms. Hotels and whirlpools are associated with outbreaks of legionnaires' disease. Fungal pneumonia may occur with cave exploration and diving. *Chlamydia psittaci* pneumonia may follow contact with birds, and Q fever may follow contact with sheep. Alcoholism increases the risk of aspiration. Patients who are immunocompromised, such as those with acquired immunodeficiency syndrome (AIDS), are at risk of fungal pneumonia such as *Pneumocystis* pneumonia.

Chest radiography may be extremely helpful in diagnosing pneumonia. Diffuse infiltrates are suggestive of an atypical pneumonia, whereas a lobar opacification is suggestive of a typical pneumonia. Atypical pneumonia occurs more frequently in young adults. Radiography is useful for detecting pleural effusions and multilobar involvement. Leukocytosis is typical, and arterial hypoxemia may occur in severe cases of bacterial pneumonia. Arterial hypoxemia reflects intrapulmonary shunting resulting from perfusion of alveoli filled with inflammatory exudates.

Microscopic examination of sputum plus cultures and sensitivity testing may be helpful in suggesting the cause of the pneumonia and in guiding antibiotic treatment. Unfortunately, sputum specimens are frequently inadequate, and organisms do not always grow from sputum. Interpretation of sputum culture results may be challenging. If there is suspicion of TB, sputum specimens should be sent for testing for acid-fast bacilli. Antigen detection in urine is a good test for *Legionella*, whereas blood antibody titers are helpful in diagnosing *Mycoplasma* pneumonia. Sputum polymerase chain reaction (PCR) testing is useful for diagnosing *Chlamydia* infection. Blood cultures usually yield negative results but are important to rule out bacteremia. HIV infection is an important risk factor for pneumonia and should be ruled out when pneumonia is suspected.

Treatment

For severe pneumonia, empirical therapy is typically a combination of antibiotic drugs. However, local patterns of antibiotic resistance should always be considered before initiating therapy.

Therapy is advised for 10 days for pneumonia caused by *S. pneumoniae* and for 14 days for that caused by *M. pneumoniae* or *Chlamydia pneumoniae*. When symptoms resolve, therapy can be switched from the IV to the oral route. Inappropriate prescription of antibiotics for nonbacterial respiratory tract infections is common and promotes antibiotic resistance. It has recently been demonstrated that even brief administration of a macrolide antibiotic such as azithromycin to healthy subjects promotes resistance of oral streptococcal flora that lasts for months. Resistance of *S. pneumoniae* to antibiotics is becoming a problem. In 2013, 30% of pneumococcal bacteria were resistant to one or more antibiotics. Expanded use of pneumococcal vaccines may slow or reverse this emerging drug resistance.

Prognosis

The pneumonia severity index (Table 25.7) is a useful tool for aiding clinical judgment, guiding appropriate management,

TABLE 25.7 Elements of Pneumonia Severity Index

Age in years
Gender
Nursing home resident
Neoplastic disease history
Liver disease
Congestive heart failure
Cerebrovascular disease
Renal disease
Altered mental status
Respiratory rate >29 breaths/min
Systolic blood pressure <90 mm Hg
Temperature <35°C or >39.9°C
Pulse >124 beats/min
pH <7.35
Blood urea nitrogen >29 mg/dL
Sodium <130 mmol/L
Glucose >249 mg/dL
Hematocrit <30%
Pao_2 <60 mm Hg
Pleural effusion on radiograph

and suggesting prognosis. Old age and coexisting organ dysfunction have a negative impact. Physical examination findings associated with worse outcome are:

Temperature ≤35°C or ≥40°C
Respiratory rate ≥30 breaths/min
Altered mental status
Systolic blood pressure <90 mm Hg
Heart rate >125 beats/min

Laboratory findings and other test results indicative of a poorer prognosis are:

Hypoxia (Po_2 <60 mm Hg or saturation <90% on room air)
Effusion
Anemia (hematocrit <30%)
Renal: blood urea nitrogen >29 mg/dL
Glucose >250 mg/dL
Acidosis (pH <7.35)
Sodium <130 mmol/L

Management of Anesthesia

Anesthesia and surgery should ideally be deferred if acute pneumonia is present. Patients with acute pneumonia are often dehydrated and may have renal insufficiency. Fluid management can be challenging, since overhydration may worsen gas exchange and morbidity. If general anesthesia is used, a protective ventilation strategy is appropriate, with tidal volumes of 6 to 8 mL/kg ideal body mass and mean airway pressures of less than 30 cm H_2O. The anesthesiologist can perform pulmonary hygiene, including actively removing secretions during the period of intubation, even with bronchoscopy if needed. Endotracheal intubation offers the opportunity to obtain distal sputum specimens for Gram stain and culture.

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in the ICU and makes up one-third of all nosocomial infections. VAP is defined as pneumonia developing more than 48 hours after mechanical ventilation has been initiated via endotracheal tube or tracheostomy. Between 10% and 20% of patients who have endotracheal tubes and undergo mechanical ventilation for longer than 48 hours acquire VAP, with mortality rates ranging from 5% to 50%. VAP increases a patient's hospital stay by approximately 7 to 9 days and can increase hospital costs by an average of $40,000 per patient.

Several simple interventions may decrease the occurrence of VAP: ensuring meticulous hand hygiene for all caregivers, providing oral care, limiting patient sedation, positioning patients semiupright, performing repeated aspiration of subglottic secretions, limiting intubation time if feasible, and considering the appropriateness of noninvasive ventilatory support.

Diagnosis

VAP is difficult to differentiate from other common causes of respiratory failure such as acute respiratory distress syndrome (ARDS) and pulmonary edema. VAP is usually suspected when a patient develops a new or progressive infiltrate on chest radiograph, together with leukocytosis and purulent tracheobronchial secretions. An endotracheal tube or a tracheostomy tube provides a foreign surface that rapidly becomes colonized with upper airway flora. However, the mere presence of potentially pathogenic organisms in tracheal secretions is not diagnostic of VAP. A standardized diagnostic algorithm for VAP was developed in 2004, employing clinical and microbiologic data into a clinical pulmonary infection score (CPIS) to promote diagnostic consistency among clinicians and investigators. However, the sensitivity and specificity of the CPIS are lower than is desirable. As a result, the CPIS has been modified in various ways to both simplify data collection and improve its utility. One such modification is shown in Table 25.8. However, the accurate diagnosis of VAP remains elusive.

TABLE 25.8 Modified Clinical Pulmonary Infection Score

Parameter	Options	Score
Temperature (°C)	≥36.5 and ≤38.4	0
	≥38.5 and ≤38.9	1
	≥39 or ≤36	2
Blood leukocytes (per mm^3)	≥4000 and ≤11,000	0
	<4000 or >11,000	1
	+ Band forms >50%	Add 1
Tracheal secretions	No secretions	0
	Abundant secretions	1
	Abundant and purulent secretions	2
Oxygenation: Pao_2/Fio_2 (mm Hg)	>240 or ARDS	0
	≤240 and no ARDS	2
Pulmonary radiograph	No infiltrate	0
	Diffuse (or patchy) infiltrate	1
	Localized infiltrate	2
Culture of tracheal aspirate	Negative	0
	Positive	2

ARDS, Acute respiratory distress syndrome; *Pao_2/Fio_2*; ratio of arterial oxygen pressure to fraction of inspired oxygen.

Treatment and Prognosis

Treatment of VAP includes supportive care for respiratory failure plus antibiotics against the organism most likely to be implicated. The most common pathogens are *Pseudomonas aeruginosa* and *S. aureus*. Prognosis is improved if treatment is initiated early. Therefore, despite the high rate of false-positive diagnoses, broad-spectrum antibiotic therapy should be initiated to cover resistant organisms such as MRSA and *P. aeruginosa*. Treatment should be narrowed to target specific organisms once results of culture and sensitivity testing are available and should be stopped at 48 hours if culture results are negative. Fig. 25.4 presents an algorithm to guide treatment.

Management of Anesthesia

Patients with VAP frequently require anesthesia for tracheostomy. Major surgery should be deferred until the pneumonia has resolved and respiratory function has improved. Tracheostomy is not an emergency procedure, and it may be ill advised to proceed when the patient has minimal pulmonary reserve. One of the major goals for the anesthesiologist in this situation is to ensure that patients with VAP do not experience a setback

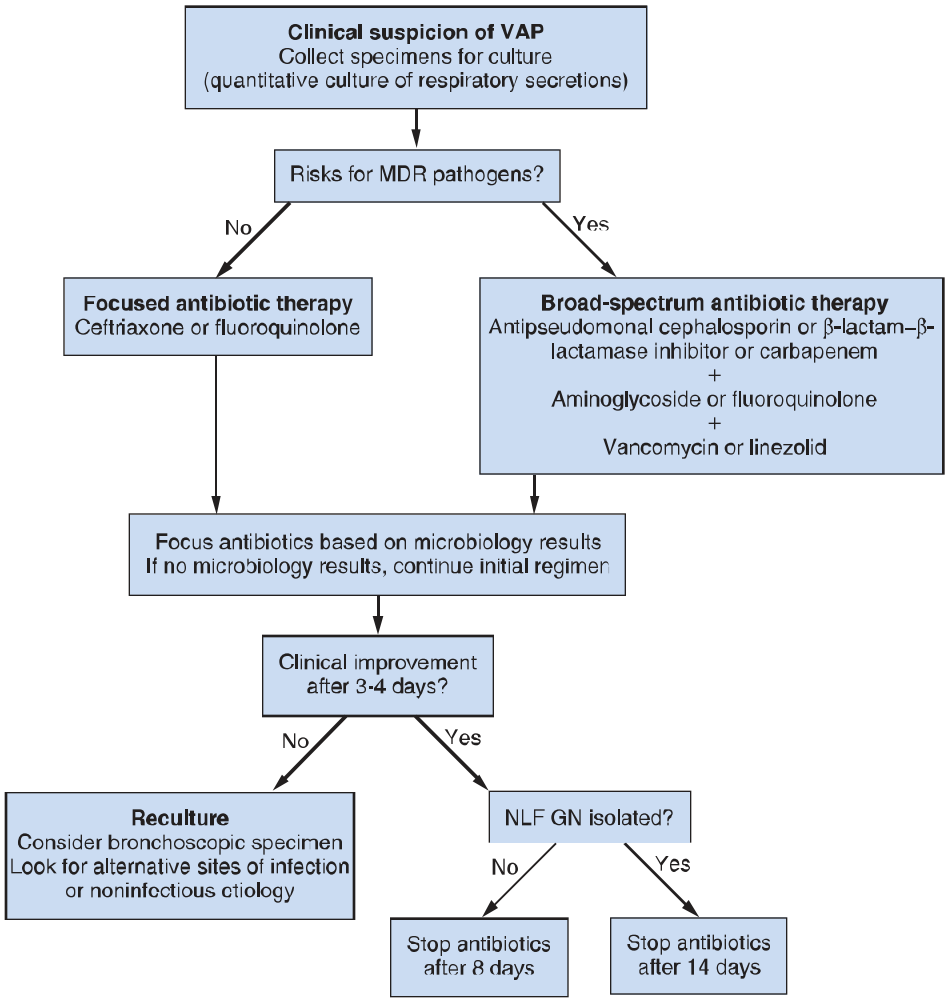

Fig. 25.4 Management of ventilator-associated pneumonia (VAP). *GN,* Gram-negative (organism); *NLF,* non–lactose fermenting; *MDR,* multidrug-resistant. (Adapted from Porzecanski I, Bowton DL. Diagnosis and treatment of ventilator-associated pneumonia. *Chest.* 2006;130:597–604.)

following anesthesia and tracheostomy. Because patients with respiratory failure may be positive end-expiratory pressure (PEEP) dependent, a PEEP valve should be used to decrease the likelihood of de-recruitment of alveoli during transport to the operating room. In the operating room, protective mechanical ventilation should be used. Ideally the same ventilator settings, mode of ventilation, and PEEP that were used in the ICU should be continued.

Severe Acute Respiratory Syndrome (SARS) and Influenza

Influenza pandemics have been described throughout history and typically occur several times each century. The influenza pandemic of 1918 was one of the major plagues to have affected humankind. It is estimated that this so-called Spanish flu infected as many as 500 million people worldwide and led to the deaths of as many as 50 to 100 million people in just 25 weeks. The Spanish flu was caused by an H1N1 strain of influenza virus that continues to cause human influenza pandemics. The 1957 and 1968 pandemics did not approach the catastrophic level of the 1918 pandemic.

H1N1 influenza (so named for the specific types of capsular peptides—hemagglutinin and neuraminidase—found on the virus) continues to impact society to this day; estimates by the CDC for the 2009 pandemic of influenza A (H1N1) in the United States from April 2009 to January 2010 resulted in 57 million total cases, 257,000 hospitalizations, and 11,700 deaths. In seasonal influenza the greatest mortality is among the very young and the very old. In contrast, the 1918 and 2009 epidemics affected children and younger adults.

Influenza A virus and the virus causing severe acute respiratory syndrome (SARS) are examples of respiratory viruses that may be associated with rampant courses, high virulence, and high mortality. From 2002 to 2003, SARS occurred without any warning and was a grim reminder of our vulnerability to new infectious diseases. SARS affected populations in Asia, the Pacific Rim, and Canada. The causative agent for SARS was thought to be an RNA coronavirus that was passed along through direct contact and droplet spread. This virus is viable ex vivo for 24 to 48 hours. Twenty percent of the victims of the 2003 SARS coronavirus outbreak were healthcare workers. There were over 8000 documented cases of SARS

coronavirus infection and approximately 700 deaths in 29 countries.

A new strain of avian influenza (bird flu), the H5N1 strain, which is a subtype of influenza A, is now threatening humankind. Avian influenza is an RNA orthomyxovirus, and like other RNA viruses it mutates at an alarming rate. The World Health Organization (WHO) has reported that 478 human cases of avian influenza occurred between 2003 and 2010, with 286 deaths. Many cases were in young children. Currently, H5N1 influenza A is passed from birds to humans. This virus has not developed a high affinity for human respiratory tract receptors. Therefore human-to-human transmission is not sustained, and cases have occurred only in small clusters.

Signs and Symptoms

Symptoms include nonspecific complaints of viral infection such as cough, sore throat, headache, diarrhea, arthralgias, and muscle pain. In more severe cases, patients may show respiratory distress, confusion, and hemoptysis. Signs may include fever, tachycardia, sweating, conjunctivitis, rash, tachypnea, use of accessory respiratory muscles, cyanosis, and pulmonary features of pneumonia, pleural effusion, or pneumothorax. A chest radiograph may show patchy infiltrates, areas of opacification, pneumothoraces, and/or evidence of pleural effusion. Both H5N1 influenza A virus and SARS coronavirus infection may cause acute lung injury and ARDS. Viruses that exhibit a propensity to bind to receptors in the lower respiratory tract may cause hemorrhagic bronchitis and pneumonia with diffuse alveolar damage and destruction. Complications include sepsis and multiple organ failure.

Diagnosis

In the context of an outbreak, history, symptoms, and presentation are usually sufficient to suggest the diagnosis. A definitive diagnosis is made by detection of the virus in sputum. The problem with serologic testing is that it may take 2 to 3 weeks for seroconversion (development of antibodies) after infection. PCR tests can detect genetic material from these viruses in various body fluids and tissues and are useful for diagnosing both SARS coronavirus infection and H5N1 influenza A.

Treatment

Vaccine development is a key component in preventing widespread viral infection and reducing morbidity and mortality associated with viral infection. Thus far there is no vaccine for either the SARS coronavirus or the H5N1 influenza A virus. For H5N1 influenza, neuraminidase inhibitors have been developed, including zanamivir and oseltamivir. These drugs may decrease the severity of infection, but sufficient quantities of these drugs are not likely to be available in the event of a major outbreak. Other pharmacologic treatments for influenza include amantadine and rimantadine. Antiviral drugs are of modest benefit and help only if administered within the first 48 hours of symptoms. There is no proven drug therapy that attenuates the course of SARS.

The mainstay of treatment for influenza and SARS is supportive care.

Prognosis

Prognosis depends on the virulence of the infecting virus as well as the susceptibility of the infected person. Influenza and SARS may trigger a marked inflammatory response and a cytokine storm. A clinical picture indistinguishable from severe bacterial sepsis may result. Superinfection with bacteria has been described and considerably worsens the outcome.

Management of Anesthesia

Preoperative. The anesthesiologist should assess the patient with an appreciation of the potentially deadly nature of the infection. Both patient and family should be counseled about the high risks associated with SARS coronavirus infection. Since primary transmission is via direct and indirect respiratory droplet spread, these viruses are highly contagious. Strict patient isolation should be enforced, and precautions to protect healthcare workers must be taken. Contact precautions are also necessary because the viruses can be spread via fomites such as clothing, contaminated surfaces, and exposed skin.

Ideally, infected patients should be cared for in rooms with negative pressure to decrease aerosolized spread and contagion. Barrier precautions include use of full-body disposable oversuits, double gloves, goggles, and powered air-purifying respirators with high-efficiency particulate air filters. If these are not available, N95 masks (which block 95% of particles) should be used rather than regular surgical masks.

Intraoperative. Aerosolized particles may be generated during all invasive airway procedures, ventilation with noninvasive and positive pressure ventilator support modes, suctioning, sputum induction, high-flow oxygen delivery, aerosolized or nebulized medication delivery, and interventions that stimulate coughing. If mechanical ventilation is required, protective ventilation is indicated. Tidal volumes should be limited to 6 to 8 mL/kg lean body mass, and mean airway pressure should be less than 30 cm H_2O. Sudden cardiorespiratory compromise could indicate an expanding pneumothorax. Drainage of pleural effusions may improve ventilation and gas exchange.

Postoperative. Precautions to prevent spread of infection should be ongoing. The same treatment principles as for ARDS and sepsis should apply.

Tuberculosis

Mycobacterium tuberculosis is the obligate aerobe responsible for TB. This organism survives and thrives in tissues with high oxygen concentrations, which is consistent with the increased presentation of TB in the apices of the lungs.

In the past, many cases of TB in the United States were due to reactivation of infection, especially in elderly individuals. However, from 1985 to 1992, the United States was confronted with an unprecedented resurgence in TB. This resurgence was accompanied by a rise in MDR TB, defined as TB caused by *M. tuberculosis* strains resistant to the most effective first-line drugs—isoniazid and rifampin. In addition, virtually untreatable strains of the TB organism are emerging worldwide. XDR strains of *M. tuberculosis* are resistant to second-line therapeutic agents, including fluoroquinolones and at least one of three injectables used to treat TB: amikacin, kanamycin, and

capreomycin. Mortality rates for patients with XDR TB are similar to those for TB patients in the preantibiotic era. Unfortunately, drug-resistant TB is a manmade problem resulting from poor adherence of infected patients to their medical regimens or improper treatment regimen designs. Worldwide, approximately 2 billion persons are infected with *M. tuberculosis*. In 2015, the WHO estimated that 480,000 new cases of MDR TB occurred worldwide.

At present most cases of TB in the United States occur in minority racial and ethnic groups, foreign-born individuals from areas where TB is endemic (Asia, Africa), IV drug abusers, and patients who are HIV seropositive or have AIDS. Any patient with TB should be tested for HIV, since there is a high association between the two infections. However, even in patients who are HIV negative, MDR TB has a 26% mortality rate. The epidemiologic increase in the incidence of TB coincided with the initial AIDS epidemic in the early 1980s.

Almost all *M. tuberculosis* infections result from inhalation of aerosolized droplets. It has been estimated that up to 600,000 droplet nuclei are expelled with each cough and that the expelled organisms remain viable for several days. Although a single infectious unit is capable of causing infection in susceptible individuals, prolonged exposure in closed environments is optimal for transmission of infection. An estimated 90% of patients infected with *M. tuberculosis* never become symptomatic and are identified only by conversion of the tuberculin skin test or by results on an interferon release assay. Often patients who acquire the infection early in life do not become symptomatic until much later. Patients who are HIV seropositive or immunocompromised with AIDS are at much higher risk of becoming symptomatic, especially after initiation of highly active antiretroviral therapy (HAART).

Diagnosis

The diagnosis of TB is based on the presence of clinical symptoms, the epidemiologic likelihood of infection, and the results of diagnostic tests. Symptoms of pulmonary TB often include persistent nonproductive cough, anorexia, weight loss, chest pain, hemoptysis, and night sweats. The most common test for TB is the tuberculin skin test (Mantoux test). The skin reaction is read in 48 to 72 hours, and a positive reaction is generally defined as induration of more than 10 mm. For patients with severe immunocompromise, including but not limited to AIDS, a reaction of 5 mm or more is considered positive. Because the skin test is nonspecific, its utility is limited. The tuberculin skin test result may be positive if the individual has received a bacille Calmette-Guérin (BCG) vaccine or has been exposed to TB or other mycobacteria, even if no viable mycobacteria are present at the time of the test. The CDC and WHO have now accepted two interferon release assays as equivalent to—and possibly even better than—the tuberculin skin test in sensitivity and specificity. These are the QuantiFERON TB Gold In-Tube test and the T-SPOT.TB test. Both are blood tests that measure release of interferon-γ (IFN-γ) from sensitized lymphocytes that are incubated with two peptides from the TB bacillus. Results of these tests are not affected by prior BCG immunization, nor do the tests cross-react with common environmental mycobacteria or *M. avium-intracellulare*.

Chest radiographs are important for the diagnosis of TB. Apical or subapical infiltrates are highly suggestive of TB. Bilateral upper lobe infiltration with cavitation is also common. Patients with AIDS may demonstrate a less classic picture on chest radiography, which may be further confounded by the presence of *Pneumocystis* pneumonia. Tuberculous vertebral osteomyelitis (Pott disease) is a common manifestation of extrapulmonary TB.

Sputum smears and cultures are used to diagnose TB. Smears are examined for the presence of acid-fast bacilli. This test is based on the ability of mycobacteria to take up and retain neutral red stains after an acid wash. It is estimated that 50% to 80% of individuals with active TB have positive sputum smear results. Although the absence of acid-fast bacilli does not rule out TB, a sputum culture positive for *M. tuberculosis* provides a definitive diagnosis.

Healthcare workers are at increased risk for occupational acquisition of TB; TB is twice as prevalent in physicians as in the general population. Nosocomial outbreaks of TB have occurred, especially among patients with AIDS. Anesthesiologists are at increased risk of nosocomial TB by virtue of events surrounding the induction and maintenance of anesthesia that may induce coughing (tracheal intubation, tracheal suctioning, mechanical ventilation). Bronchoscopy is a particularly high-risk procedure for anesthesiologists and has been associated with conversion of the tuberculin skin test. As a first step in preventing occupational acquisition of TB, anesthesia personnel should participate in annual tuberculin screening so that those who develop a positive skin test result may be offered chemotherapy. The decision to initiate TB chemotherapy is not trivial, since treatment may cause significant toxicity. A baseline chest radiograph is indicated at the time of the first positive tuberculin skin test result.

Treatment

Antituberculous chemotherapy has decreased mortality from TB by more than 90%. With adequate treatment, more than 90% of patients who have susceptible strains of *M. tuberculosis* have bacteriologically negative sputum smears within 3 months.

Some argue that for the protection of the community, people who have positive results on a skin test should receive chemotherapy with isoniazid. However, isoniazid is a potentially toxic drug; its toxicity is manifested in the peripheral nervous system and liver. Neurotoxicity may be prevented by daily administration of pyridoxine. Hepatotoxicity is most likely to be related to metabolism of isoniazid by hepatic acetylation. Depending on genetically determined traits, patients may be characterized as slow or rapid acetylators. Hepatitis appears to be more common in rapid acetylators, consistent with their greater production of hydrazine, a potentially hepatotoxic metabolite of isoniazid. Persistent elevations of serum transaminase concentrations mandate that isoniazid be discontinued, but mild transient increases do not.

Other first-line drugs used to treat TB include rifampicin, pyrazinamide, streptomycin, and ethambutol. Adverse effects of rifampicin include thrombocytopenia, leukopenia, anemia, and renal failure. Hepatitis associated with increases in serum

transaminase concentrations occurs in approximately 10% of patients being treated with rifampicin. To be curative, treatment for pulmonary TB should continue for 6 months. Extrapulmonary TB usually requires a longer course of antituberculous therapy.

Management of Anesthesia

Preoperative assessment of patients considered to be at risk of having TB includes taking a detailed history with questions concerning the presence of a persistent cough and tuberculin test status. Patients with HIV or AIDS should undergo a thorough review of systems to elicit a possible history of TB.

Elective surgical procedures should be postponed until patients are no longer considered infectious. Patients are considered noninfectious if they have received antituberculous chemotherapy, are improving clinically, and have had three consecutive negative findings on sputum smears. If surgery cannot be delayed, it is important to limit the number of involved personnel, and high-risk procedures (bronchoscopy, tracheal intubation, and suctioning) should be performed in a negative-pressure environment whenever possible. Patients should be transported to the operating room wearing a tight-fitting N95 face mask to prevent casual exposure of others to airborne bacilli. Staff should also wear N95 masks.

A high-efficiency particulate air filter should be placed in the anesthesia delivery circuit between the Y connector and the mask, laryngeal mask airway, or tracheal tube. Bacterial filters should be placed on the exhalation limb of the anesthesia delivery circuit to decrease the discharge of tubercle bacilli into the ambient air. Anesthesia equipment should be sterilized with standard methods, using a disinfectant that destroys tubercle bacilli. Use of a dedicated anesthesia machine and ventilator is recommended. Postoperative care should, if possible, take place in a negative-pressure isolation room.

INFECTIOUS DISEASES IN SOLID ORGAN TRANSPLANT RECIPIENTS

Each year, over 16,000 patients in the United States receive solid organ transplants, and this number is expected to continue rising. Patients who have received solid organ transplants (liver, kidney, heart, lung) present unique perioperative challenges to the anesthesiologist. Because of advances in surgical technique, immunosuppressive therapy, and medical management, this patient population has a 1-year survival rate of 80% to 90%, so these patients are coming for additional surgical procedures not necessarily related to their organ transplant.

To prevent allograft rejection, solid organ transplant recipients commonly receive a combination of immunosuppressive drugs. The mechanisms of action of immunosuppressants include blunting of general antibody responses, depression of cell-mediated immunity, down-modulation of lymphocyte and macrophage function, inhibition of cell proliferation, blocking of T-cell activation, and depletion of T cells. Regardless of the effect, immunosuppression is variable and depends on dosage, duration of therapy, and time since transplantation. Immunosuppression is most intense in the first few months after transplantation and becomes progressively less intense as immunosuppressive therapy is gradually withdrawn over time.

Immunosuppression in transplant recipients can also be affected by metabolic abnormalities, damage to mucocutaneous barriers, foreign bodies that interrupt these barriers (e.g., surgical incisions, chest tubes, biliary drains, endotracheal tubes, urinary catheters), and the possible presence of immunomodulating viruses such as cytomegalovirus and HIV. Therefore the resultant state of immunosuppression in the posttransplantation patient is a dynamic condition that impacts the development of infectious diseases and/or cancer.

Infectious Disease Occurrence

The best approach to infection control in the solid organ transplant recipient is prevention. If prevention is not possible, immediate diagnosis and treatment are essential. Challenges in managing infectious diseases in organ transplant recipients are many and include:

1. The spectrum of infective organisms is diverse and unusual.
2. The inflammatory response is blunted because of immunosuppressive therapy, so clinical and radiologic findings may be limited.
3. Antimicrobial coverage is complex and typically empirically based.

There are three major time periods during which specific infectious disease processes occur in the posttransplantation patient: the first month, the second through sixth months, and beyond the sixth month. In addition, these periods may be influenced by surgical factors, the net level of immunosuppression present, and environmental exposures. Defining the time period after transplantation will assist the clinician in determining likely infectious processes.

During the first month after transplantation, active infections can be harbored within the allograft and are typically bacterial or fungal. In addition, anatomic defects related to surgery (e.g., devitalized tissue, undrained fluid collections at high risk for microbial seeding) must be addressed if they foster infection. The only common viral infection during the first month after transplantation is reactivated herpes simplex virus infection in individuals positive for this virus before transplantation.

The period from the second through the sixth month after transplantation may be marked by unusual infections. These may be either community-acquired or opportunistic infections. Opportunistic pathogens possess very little virulence in healthy hosts but can cause serious infections in patients with immunocompromise. Trimethoprim-sulfamethoxazole is commonly given as prophylaxis for *Pneumocystis* pneumonia during the first 6 months after transplantation in all solid organ graft recipients and for longer periods in heart and lung transplant recipients.

In addition, high-dose immunosuppression may lead to reactivation disease syndromes caused by organisms present in the recipient before transplantation. TB has become especially common and occurs in 1% of the posttransplant population.

From 6 months after transplantation onward, most transplant recipients do fairly well from an infectious disease

standpoint and usually only sustain infections paralleling those seen in the community at large. However, another group of patients may have chronic or progressive viral infections with hepatitis B virus, hepatitis C virus, cytomegalovirus, or Epstein-Barr virus. The most commonly occurring viral infection is varicella-zoster virus infection manifesting as herpes zoster.

Patients with chronic or recurrent rejection are generally taking high dosages of immunosuppressants and are predisposed to acquiring the opportunistic infections typically seen in posttransplantation patients during the second to sixth months. In addition, posttransplantation patients with HIV and/or AIDS must be more closely followed for evidence of infections, both common and opportunistic. HIV HAART regimens must be maintained and can complicate immunosuppressive drug dosing.

Management of Anesthesia

Preoperative

Patients who have received solid organ transplants comprise a wide clinical spectrum, and it is difficult to make any generalizations about this patient population. Overall, the preoperative assessment should focus on determining the degree of immunosuppression and allograft function, examining for the presence of any infection, and evaluating any coexisting medical diseases. Laboratory evaluation should include a complete blood cell count (CBC), full metabolic panel, liver function tests, viral panels with viral loads as indicated, chest radiograph, and electrocardiogram (ECG). If patients are currently receiving immunosuppressants, blood levels of immunosuppressive agents should also be obtained when possible. Findings elicited on history taking, review of systems, and physical examination may serve as indicators for additional laboratory testing or further specialist evaluations. Evidence of active rejection is a contraindication to elective surgery. However, one may be faced with managing anesthesia in a posttransplantation patient with active rejection who requires explantation of the transplanted organ. This is considered an emergent procedure.

All medications and antimicrobial drugs taken by the patient should be noted, and these drugs should be continued during the perioperative period. If the posttransplantation patient manifests any active infection, surgery should be delayed or cancelled until additional consultation is obtained.

Intraoperative

All anesthetic techniques—general anesthesia, regional anesthesia, and sedation—have been used successfully in posttransplantation patients. Selection of anesthetic technique should be based on the type of surgery to be performed, the patient's associated comorbid conditions, the presence of contraindications for specific anesthetic techniques, and the potential for interactions between immunosuppressive and anesthetic drugs.

Use of regional anesthesia in immunosuppressed patients remains controversial, since studies have demonstrated that infections may occur secondary to neuraxial blockade. However, few studies have evaluated the frequency of epidural abscess or meningitis in the immunocompromised population. Information on the incidence of infection during peripheral nerve blockade and pain procedures in immunocompromised posttransplantation patients is scant. With regard to general anesthesia, nasal intubation should be avoided because it may introduce nasal bacterial flora into the systemic circulation. Overall, general anesthesia is considered to create more generalized immunosuppressant effects than regional anesthesia, although levels of specific and nonspecific biologic markers indicating immune suppression are not consistently depressed. Cyclosporine may delay the metabolism of neuromuscular blockers, specifically pancuronium and vecuronium. Invasive monitoring may be warranted, but strict use of aseptic technique during insertion of catheters is critical in this patient population.

Postoperative

Because of the high potential for further immunosuppression secondary to anesthesia and surgery, the posttransplantation patient must be observed for any clinical deterioration in graft function or any indication of an infectious process. All antibiotic regimens must be strictly followed and monitored closely. Because of the blunted inflammatory response in immunosuppressed patients, signs and symptoms of active infection are often difficult to detect.

HIV INFECTION AND AIDS

This immune disease syndrome was first described in 1981 and initially termed *gay-related immune disorder* because it was identified in a group of homosexual men in Los Angeles, California. The etiologic mechanism was initially unknown; however, severe immune dysfunction was present and was manifested clinically by the occurrence of unusual malignancies and opportunistic infections in previously healthy individuals. The disease was later reclassified as acquired immunodeficiency syndrome. In 1984, the cause of AIDS was elucidated and found to be a retrovirus that was named human immunodeficiency virus type 1 and type 2.

Thirty-seven years later, HIV infection and the associated AIDS pandemic continue to pose a major threat to global health. It is estimated that more than 50 million people worldwide (0.6% of the world's population) are infected with HIV, and AIDS is thought to have caused more than 26 million deaths worldwide. There are approximately 1.2 million people in the United States living with HIV infection and/or AIDS, and 1 in 8 is unaware of their HIV seropositive status. While HIV disease continues to spread, the incidence of infection in the United States is decreasing. In 2018, 37,832 people received an HIV diagnosis in the United States and dependent areas. The annual number of new diagnoses decreased 9% from 2010 to 2016 in the 50 states and the District of Columbia.

Worldwide, the most rapid increases in infection rates are being observed in southern and central Africa and in Southeast Asia. Throughout the world, the predominant mode of HIV transmission is via heterosexual sexual transmission, with women representing a large proportion of new infections. Other sources of infection globally include IV drug use, vertical transmission from pregnant mother to child, and blood

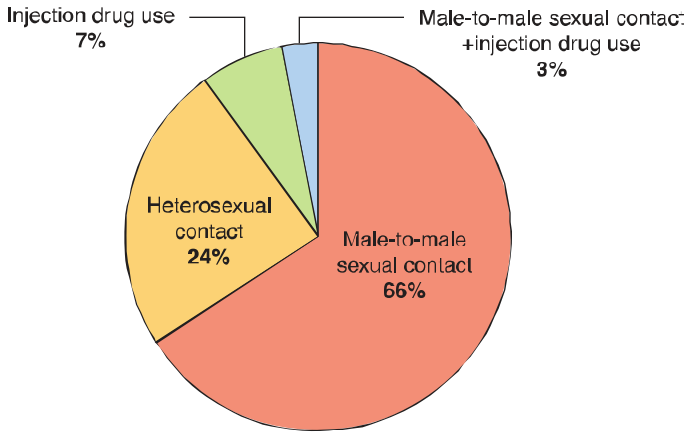

Fig. 25.5 New human immunodeficiency virus (HIV) diagnoses in the United States and dependent areas by transmission category, 2018. (Adapted from Centers for Disease Control and Prevention 2019 Statistics. https://www.cdc.gov/hiv/basics/statistics.html.)

transfusion. However, in the United States the largest population of persons infected with HIV is men who have sex with men (Fig. 25.5). In the United States, blacks are most affected by HIV. In 2018, black adults and adolescents accounted for 42% of all new HIV diagnoses. Additionally, Hispanics/Latinos are also strongly affected. They accounted for 27% of all new HIV diagnoses. HIV antiretroviral therapy has decreased the rate of disease progression, but there is no cure available. Research continues into development of a vaccine to prevent the acquisition of HIV infection.

Treatment modalities (HAART) have been effective in halting HIV replication and thereby delaying or preventing the transition from HIV infection to AIDS or eliminating the progression of AIDS itself. An increasing number of patients coming for surgery are HIV seropositive or may have had a diagnosis of AIDS in the past. Therefore anesthesiologists should be familiar with this infectious disease syndrome and its impact on anesthetic management. An understanding of the pathogenesis of HIV, the multiple organ system involvement of HIV and AIDS, the possible drug interactions occurring with HIV therapy, side effects related to HAART, and associated opportunistic infections will serve to better guide preoperative assessment and anesthetic planning.

Signs and Symptoms

Acute seroconversion illness occurs approximately 2 to 3 weeks after inoculation with the HIV virus. The acute viral phase is typically marked by a flulike illness associated with fever, fatigue, headache, night sweats, pharyngitis, myalgias, and arthralgias. Therefore signs and symptoms during the period after the initial infection may mimic those of any common flulike illness. Within 1 to 2 weeks after inoculation with HIV, the virus initiates rapid replication. After several months there is a gradual decrease in the viremia. As the immune system responds, viral replication decelerates, and a balance develops between host immune defenses and viral replication. The resulting viral level can be described as a steady-state rate of viral production equal to the rate of viral destruction and suppression. Generalized lymphadenopathy is a hallmark of HIV infection and may persist until HAART is initiated. An HIV-positive individual is not considered to have AIDS unless one of the AIDS-defining diagnoses is present.

As noted earlier, HIV belongs to the family of retroviruses. It is characteristically cytopathic (cell damaging), with a long latency period and a chronic course of infection. When the first cases of AIDS appeared, its pathogenesis was frustratingly elusive because the disease does not appear immediately after infection with HIV. It has been shown that the steady-state viral level is a reliable predictor of the rate of progression from HIV positivity to the development of AIDS. In general, higher basal viral levels correspond to more rapid disease progression. Weight loss and failure to thrive are among the first manifestations patients display as HIV infection progresses from the chronic latent phase to the development of AIDS.

Diagnosis

With the advent of HAART, the prognosis of those infected with HIV has dramatically improved. Therefore it is important that the stigma attached to HIV infection be removed so that high-risk individuals feel comfortable undergoing testing. The standard test to diagnose HIV infection is an enzyme-linked immunosorbent assay (ELISA), the results of which become positive when antibodies to HIV are present. This is typically 4 to 10 weeks after infection. This test is not a measure of viral load but simply indicates the presence of antibodies to HIV. During the initial period of infection there is significant viremia, and patients are highly infectious, but antibodies may not be present. Therefore a false-negative test result may occur. If a positive diagnosis is made, infection is confirmed with a Western blot test or by direct measurement of HIV viral load in the blood. HIV viral load is measured via PCR RNA analysis. If a patient is tested within a very short period after the initial infection, the ELISA test result may be negative or inconclusive. Nucleic acid testing of HIV RNA is the most specific and sensitive test for HIV.

Since HIV is lymphotropic and has a particular affinity for $CD4^+$ cells, measurement of these cells is useful in assessing the degree of HIV progression. $CD4^+$ cell levels are measured as cells per cubic millimeter (cells/mm^3). Ninety-eight percent of helper T lymphocytes ($CD4^+$ T cells) are located in lymph nodes, which are the major site of viral replication and T-cell destruction. During the acute infectious period, $CD4^+$ cell counts decline dramatically then rise again. Over the course of 8 to 12 years there is a gradual involution of lymph nodes, with a concomitant slow decrease in $CD4^+$ T-cell counts that is accompanied by an increase in viral load as the inexorable onset of AIDS occurs (Fig. 25.6).

After the diagnosis of HIV infection is confirmed, a patient will undergo further testing to determine viral genotype and phenotype. In addition, HIV sensitivity and resistance to existing HAART agents as well as coreceptor usage will be determined. These testing modalities have been extremely effective in minimizing resistance when HAART is initiated because selection of HAART agents is tailored to each individual patient. For the purposes of disease surveillance and disease severity

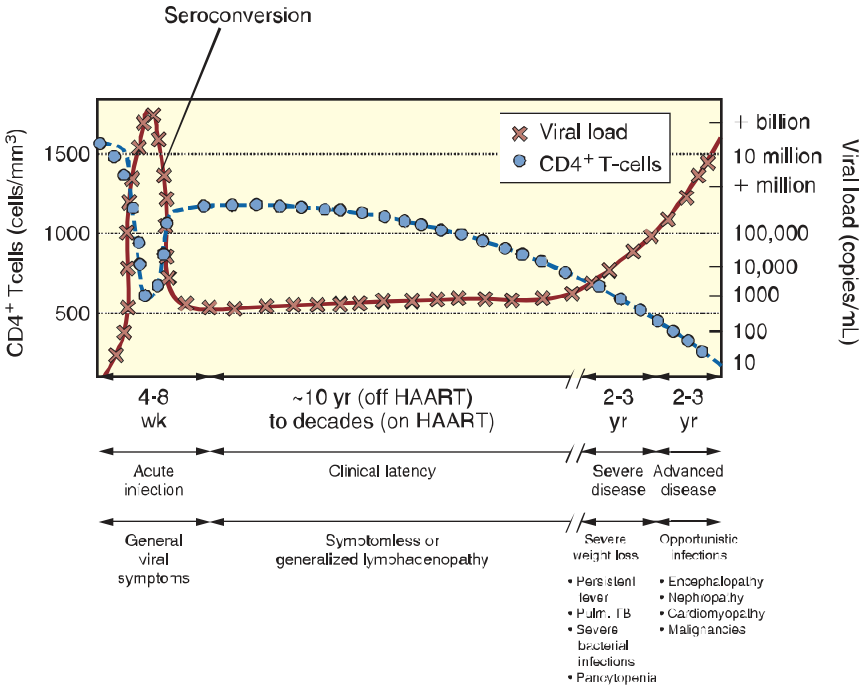

Fig. 25.6 Course of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) and the impact of highly active antiretroviral therapy (HAART). *Pulm. TB,* Pulmonary tuberculosis.

estimation and management, patients who are HIV positive are classified as having AIDS only when at least one of the AIDS-defining diagnoses is present (Table 25.9).

HIV Infection Clinical Continuum

Patients who are HIV positive are typically asymptomatic and will not demonstrate any external evidence of clinical immunosuppression. However, HIV infection is a disease that encompasses a continuum of clinical signs from acute infection to clinical latency, then to clinical progression, and eventually to development of AIDS with associated opportunistic infections and ultimately death. However, the clinical continuum from HIV infection to AIDS can be interrupted, delayed, or altered by the institution of HAART. Opportunistic infections are caused by pathogens with no intrinsic virulence and require a compromised or defective immune system to proliferate. Because subclinical and clinical multiple organ system involvement is a hallmark of HIV infection, the anesthesiologist should be adept at eliciting a history and reviewing systems to detect any of the myriad coexisting diseases that can be present, as well as performing a thorough physical examination to detect pertinent pathologic conditions.

Cardiac Manifestations

Cardiac involvement in the course of HIV infection is common but often subclinical. Up to 50% of HIV-positive patients have abnormal echocardiographic findings at some point during their disease. HIV is an extremely trophic virus with a high affinity for the myocardium, and evidence has demonstrated the presence of HIV in myocardial cells. Left ventricular dilatation and cardiac dysfunction may result. In addition, pulmonary

TABLE 25.9 AIDS-Defining Diagnoses in HIV-Seropositive Patients

Bacterial infection, multiple or recurrent
Burkitt lymphoma
Candidiasis of the bronchi, trachea, lungs, or esophagus
$CD4^+$ T-lymphocyte cell count <200 cells/mm^3
Cervical cancer, invasive
Coccidiomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 mo)
Cytomegalovirus retinitis or cytomegalovirus infection (with loss of vision)
Herpes simplex with chronic ulcers (>1 mo), bronchitis, pneumonitis, or esophagitis
HIV-related encephalopathy
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic (>1 mo)
Kaposi sarcoma
Immunoblastic lymphoma
Lymphoma of the brain, primary
Mycobacterium avium-intracellulare complex or *M. kansasii* infection, disseminated or extrapulmonary
M. tuberculosis infection, any site
Mycobacterium infection, any other species, pulmonary or extrapulmonary
Pneumocystis jiroveci pneumonia (PCP)
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy (PML)
Recurrent *Salmonella* septicemia
Toxoplasmosis of the brain
Wasting syndrome due to HIV

AIDS, Acquired immunodeficiency syndrome; *HIV,* human immunodeficiency virus.

hypertension is present in about 1% of patients with HIV infection or AIDS. Cardiac disease may be exacerbated by HAART, especially when protease inhibitors are used. Protease inhibitors may cause premature atherosclerosis and diastolic dysfunction leading to heart failure. Myocardial infarction has been reported even in young patients with HIV infection. Approximately 25% of patients with HIV infection have a pericardial effusion. Myocarditis, which is more common in advanced disease, may be caused by toxoplasmosis, disseminated cryptococcosis, coxsackievirus B infection, cytomegalovirus infection, lymphoma, aspergillosis, and HIV infection itself. In addition, HIV is trophic for vascular structures and has been implicated in the development of multifocal abdominal aortic aneurysms in adults and children, as well as aortic arch aneurysms and aortic dissection in adults.

Central and Peripheral Nervous System Manifestations

Neurologic disease, ranging from AIDS dementia to infectious and neoplastic involvement, may be common, especially as AIDS progresses. HIV enters the CNS early in the course of infection, and the CNS is considered a reservoir for HIV. Three diagnoses comprise the majority of predominantly focal cerebral diseases complicating AIDS: cerebral toxoplasmosis, primary CNS lymphoma, and progressive multifocal leukoencephalopathy. *Cryptococcus neoformans*, HIV, and the TB bacillus can cause meningitis. Aggressive generalized cerebrovascular disease may occur as a complication of HAART. Increased intracranial pressure may develop with active HIV infection, resulting from the presence of intracranial masses or opportunistic infections. Peripheral neuropathy is the most frequent neurologic complication in HIV-positive patients. Approximately 35% of patients with AIDS show clinical evidence of polyneuropathy or myopathy. Autonomic nervous system dysfunction may also appear with or without the presence of CNS involvement.

Pulmonary Manifestations

Pulmonary manifestations in HIV-positive patients are typically caused by opportunistic infections. Complications include respiratory failure, pneumothorax, and chronic pulmonary disease. Cavitary lung disease can be due to pyogenic bacterial lung abscess, pulmonary TB, fungal infection, or *Nocardia* infection. Kaposi sarcoma and lymphoma can also affect the lungs. Adenopathy can lead to tracheobronchial obstruction or compression of the great vessels. Endobronchial Kaposi sarcoma may cause massive hemoptysis. HIV directly affects the lungs and may cause a destructive pulmonary syndrome similar to emphysema.

Pneumocystis jiroveci pneumonia (PCP) does not usually occur until the $CD4^+$ count falls below 200 cells/mm^3 and fortunately has become less common with the use of HAART. With PCP, an AIDS-defining illness, the chest radiograph can be normal but typically shows bilateral ground-glass opacities. Pneumothoraces may be evident, or there may be several pneumatoceles. High-resolution CT scans reveal a ground-glass appearance even when chest radiograph findings appear normal. Pulmonary function tests show reduced lung volumes with decreased compliance and diminished diffusing capacity. Measurements of oxygen saturation during exercise may be more helpful than pulmonary function tests. If PCP is suspected, fiberoptic bronchoscopy and bronchoalveolar lavage should be performed. The advantage of an early diagnosis compensates for the high frequency of negative examination findings.

Disseminated TB is a potential cause of severe respiratory failure, and respiratory secretions should be examined routinely for acid-fast bacilli in HIV/AIDS patients with pulmonary infiltrates. Bacterial pneumonia may also be the cause of severe acute respiratory failure. Bacteria may be detected in sputum or bronchial washings.

Endocrine Manifestations

Adrenal insufficiency should be considered, since this may occur with advanced HIV infection. Random measurement of cortisol levels and tests of adrenal stimulation may reveal absolute or relative adrenal insufficiency. This is the most serious endocrine complication in HIV-positive patients. In HIV-positive patients taking protease inhibitor therapy, glucose intolerance, disorders of lipid metabolism, and fat redistribution are common.

Hematologic Manifestations

The hematopoietic system is widely affected by HIV infection, and the most common early finding of HIV infection is anemia. Lymphocytosis, with an increase mainly in $CD8^+$ T lymphocytes, may appear within 2 weeks of initial HIV infection. Bone marrow involvement can occur secondary to HIV infection itself and/or to opportunistic infection. This can produce leukopenia, lymphopenia, and thrombocytopenia. In addition, bone marrow suppression may develop after initiation of zidovudine therapy. Thrombocytopenia typically worsens as $CD4^+$ counts diminish to less than 250 cells/mm^3. HIV-positive patients may be prone to either hypercoagulable states or coagulation abnormalities.

Renal Manifestations

HIV-positive patients may develop renal disease secondary to HIV infection, viral hepatitis, associated drug use, or HAART. Protease inhibitor therapy has been specifically implicated in both toxic acute tubular necrosis and nephrolithiasis. In addition, nephrotic syndrome may occur as a result of HIV-associated nephropathy. HIV-associated nephropathy is especially common in black men and commonly leads to end-stage renal disease.

Treatment

HAART targets and blocks various steps in the HIV replication cycle (Fig. 25.7). Six major classes of antiretroviral drugs are currently in use, and another two groups of drugs are undergoing clinical investigation. There is continued interest in developing treatment regimens that have a higher safety profile, lower rates of adverse effects, and easier dosing regimens. Antiretroviral drugs used to treat HIV infection are always employed in combinations of at least two drugs with different mechanisms of action. Patients who have developed resistance to commonly used HAART regimens or have advanced AIDS

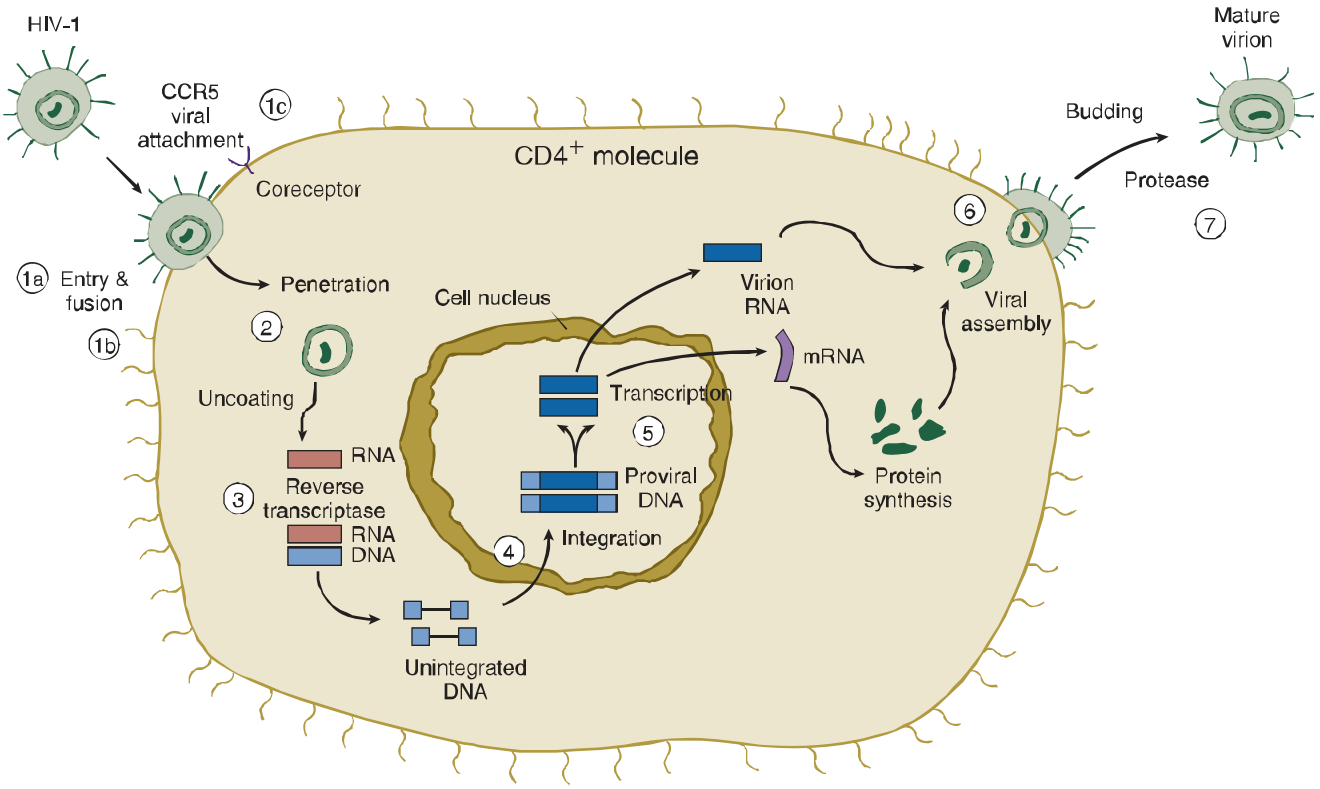

Fig. 25.7 Life cycle of HIV and targets of action of antiretroviral therapy *(indicated by circled numbers)*. 1a, Fusion inhibitors; 1b, entry inhibitors; 1c, chemokine receptor 5 (CCR5) antagonists/blockers; 2, no antivirals available for "uncoating"; 3, nucleoside and nonnucleoside reverse transcriptase inhibitors; 4, integrase strand transfer inhibitors; 5, no antivirals available for RNA transcription; 6, maturation inhibitors; 7, protease inhibitors. *mRNA*, Messenger RNA.

may require four drugs and possibly additional booster medications designed to increase drug bioavailability.

The decision to initiate HAART is based on several factors, and once begun, treatment entails a lifelong commitment. Nonadherence to the medical regimen for any reason is one of the main causes of the development of viral resistance and treatment failure. Initiation of HAART is not necessarily a benign process, and implementation of HAART may result in a host of drug-related complications. Some patients who are in the early phase of HIV infection may decide, in conjunction with their physicians, not to immediately implement therapy and choose simply to be monitored.

In the past, patients infected with HIV typically only began HAART when there was evidence that $CD4^+$ cell counts are diminishing rapidly, counts have already fallen below 200 cells/mm^3, or a patient with newly diagnosed HIV infection already meets AIDS-defining criteria. However, current recommendations advocate that HAART be instituted as soon as possible after the diagnosis of HIV infection is made regardless of $CD4^+$ count. Early institution of HAART is linked to lowered inflammatory states, less impact on $CD4^+$ count, greater long-term survival, and lower morbidity.

A typical antiretroviral regimen consists of at least two drugs, and drug selection is based on viral sensitivity, resistance patterns, coreceptor subtypes, and virulence subtypes. Some HAART regimens may require three or more agents based upon organism sensitivity or viral strain type. In some circumstances, combinations of four or more drugs are used, such as when drug resistance patterns are evident with a patient undergoing a rapid clinical decline. The aim of therapy in treatment-naïve patients is to achieve an undetectable viral load in 24 weeks, halt $CD4^+$ cell decline, restore immune competence, and improve and extend the length and quality of life. Numerous side effects and drug interactions complicate such regimens and decrease adherence. Patients may develop a myriad of adverse drug reactions, and some are potentially fatal (Table 25.10).

Patients who begin HAART may also develop a reaction known as immune reconstitution inflammatory syndrome (IRIS). IRIS occurs as a result of restoration of basic immune competence with HAART and the gradual improvement and strengthening of the immune system. IRIS leads to a paradoxical deterioration of general clinical symptoms in the context of improving $CD4^+$ counts and a reduced viral load. IRIS is marked by the appearance and/or exacerbation of previously silent clinical diseases such as hepatitis A, B, and C, PCP, TB, and any other dormant opportunistic infection.

Concurrent use of zidovudine and corticosteroids may result in severe myopathy and respiratory muscle dysfunction. In addition, reports have documented several cases of respiratory failure related to HAART initiation. Of particular importance to anesthesiologists is that patients receiving HAART are subject to long-term metabolic complications, including lipid

TABLE 25.10 Highly Active Antiretroviral Therapy (HAART) Drug Interactions

Class	Common Drug-HAART Interactions	Anesthetic-Specific Drug-HAART Interactions
Nucleoside reverse transcriptase inhibitors (NRTIs)	Interactions with: *Anticonvulsant:* phenytoin *Antifungals:* ketoconazole, dapsone *Alcohol* *H_2 blocker:* cimetidine	NRTIs potentially change drug clearance and effects of: *Opiate:* methadone
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	Interactions with: *Anticoagulant:* warfarin *Anticonvulsants:* carbamazepine, phenytoin, phenobarbital *Anti-TB drug:* rifampin *Herbal:* St. John's wort	NNRTIs prolong half-life and/or effects of: *Sedatives:* diazepam, midazolam, triazolam *Opiates:* fentanyl, meperidine, methadone
Protease inhibitors (PIs)	Interactions with: *Anticoagulant:* warfarin *Anticonvulsants:* carbamazepine, phenytoin, phenobarbital *Antidepressant:* sertraline *Calcium channel blockers* *Anti-TB drug:* rifampin *Herbal:* St. John's wort *Immunosuppressant:* cyclosporine	PIs prolong half-life and/or effects of: *Antidysrhythmics:* amiodarone, digoxin, quinidine *Sedatives:* diazepam, midazolam, triazolam *Opiates:* fentanyl, meperidine, methadone *Local anesthetic:* lidocaine
Integrase strand transfer inhibitors (INSTIs)	Interactions with: *Proton pump inhibitor:* omeprazole *Anti-TB drug:* rifampin	None
Entry inhibitors	Interactions with: *Anticonvulsant:* carbamazepine *Anti-TB drug:* rifampin *Oral contraceptives* *Proton pump inhibitor:* omeprazole *Herbal:* St. John's wort	HAART potentially changes drug clearance and effects of: *Sedative:* midazolam

TB, Tuberculosis.

abnormalities and glucose intolerance, which may result in development of diabetes, coronary artery disease, and cerebrovascular disease. HAART has also been implicated in fat redistribution to the neck, back of the neck, and abdomen. This phenomenon may make airway management more difficult or increase intraabdominal pressure.

Protease inhibitors, particularly ritonavir and saquinavir, act as inhibitors of cytochrome P450. In contrast, drugs such as nevirapine are inducers of hepatic microsomal enzymes. These variable effects on liver enzyme mechanics further complicate the dosing of HAART drugs and other drugs that undergo hepatic metabolism, including anesthetic and analgesic drugs. Therefore caution must be used when administering pharmacologic agents that may be metabolized via these pathways because drug duration and anticipated effect may be highly variable.

Prognosis

Before 1995 the prospects for successful treatment of HIV infection were dismal, and a diagnosis of HIV infection was inevitably followed by death. Several independent factors dramatically changed the situation: (1) improved understanding of the pathogenesis of HIV infection, (2) availability of surrogate markers of immune function and plasma viral burden to determine whether HAART is effective (specifically $CD4^+$ cell counts and HIV viral load quantification), (3) use of $CD4^+$ cell counts and viral load determinations by researchers to determine minimal effective concentrations of HAART and thereby improve its risk/benefit profile, (4) development of viral genotype/phenotype profiling, coreceptor subtyping, and sensitivity and resistance pattern analysis, which has enabled optimal selection of specific HAART regimens, (5) continued development of new and more powerful drugs, and (6) completion of several large clinical end-point trials that have conclusively demonstrated that antiretroviral combinations significantly delay the progression of HIV disease and improve long-term survival.

Management of Anesthesia

Preoperative

Patients with HIV infection and/or AIDS are usually managed by an internist, primary care provider, or infectious disease specialist. Although a medical evaluation by one of these physicians immediately before surgery is not mandatory, it may be helpful to obtain a consultation if the patient is unable to delineate pertinent medical history and management specifically related to HIV infection and/or AIDS. Additional information from primary care and infectious disease specialists may be especially pertinent in patients who present with advanced AIDS.

Not all patients with HIV/AIDS are receiving HAART, and it is important to understand what current treatment strategies are being used for a specific patient. Some patients may be waiting for further deterioration in clinical and immune status

before initiating HAART, whereas a subset of patients may be on physician-approved "drug holidays," and other patients may simply be unable to tolerate the adverse effects of HAART. HAART treatment strategies in the 21st century typically include initiation of antiviral therapy immediately after diagnosis and confirmation of genotype/phenotype.

Whether or not a patient is receiving HAART and has an undetectable viral load, patients with HIV/AIDS should always be considered a potential source of disease transmission with adherence to universal precautions. In patients who are not receiving HAART, initiating HAART to minimize viral load and improve overall clinical condition in the period immediately before surgery is not indicated. Studies have indicated that HAART has no protective effect in reducing perioperative risk, and initiation of HAART within 6 months of surgery actually increases overall morbidity and mortality in patients with HIV infection. The occurrence of IRIS after HAART is begun may paradoxically worsen the patient's overall condition and further delay surgery.

Since HIV infection, AIDS, and HAART can all potentially impact multiple organ systems, it is advisable to order a CBC, basic metabolic panel (including renal function studies), liver function tests, and coagulation studies. A chest radiograph and ECG are also useful preoperatively regardless of age or evidence of cardiopulmonary disease. If a patient with HIV infection or AIDS has any signs or symptoms of cardiac dysfunction, echocardiography or stress testing may also be indicated, with additional consultation by a cardiologist as indicated.

There is little specific information concerning the overall risk of anesthesia and surgery in the HIV-positive patient. The American Society of Anesthesiologists (ASA) physical status assessment and the inherent surgical risk probably provide a measure of global risk assessment. An ASA status of 2 is typically assigned to HIV-positive patients without any clinical evidence of immunocompromise or acute deterioration; these patients may or may not be receiving HAART. Patients with AIDS may be classified as having an ASA status of either 3 or 4 depending on the severity of coexisting disease processes either related or unrelated to HIV infection. In addition, patients with advanced AIDS may be receiving HAART but for all practical purposes may be minimally responsive to it; $CD4^+$ cell counts may be low and viral load may range from undetectable to low, moderate, or high. This information, when combined with the stage of the HIV infection, degree of clinical immunosuppression, and presence and severity of opportunistic infections or neoplasms, may offer the best predictor of global perioperative risk in the HIV-positive patient.

The utility of obtaining a $CD4^+$ cell count and viral load determination before surgery has not been demonstrated. Studies have shown that there is no significant difference in perioperative outcomes in HIV-positive or AIDS patients whose $CD4^+$ cell counts are higher than 50 cells/mm^3 compared with outcomes in patient populations without HIV/AIDS matched for the same surgery, comorbid conditions, and ASA status. Viral load level is not a predictor of perioperative outcome unless viral load exceeds 30,000 copies/mL. Owing to the overall improved effectiveness of HAART, $CD4^+$ cell counts and viral load are usually monitored every 6 months. HAART does not offer any real protective effects or decrease the overall morbidity and mortality associated with surgery and anesthesia. However, patients with HIV infection and AIDS do demonstrate a higher overall mortality 1 year after surgery than similar cohorts without HIV/AIDS. This has been attributed to HIV infection and/or AIDS itself and not to the surgical procedure performed or the anesthetic used.

In general, if a patient is HIV seropositive and has never met AIDS-defining criteria, one can presume the patient's $CD4^+$ cell count is higher than 200 cells/mm^3. However, patients with AIDS-defining diagnoses or a history of AIDS (with or without HAART) may have widely varying $CD4^+$ cell counts. Not all HIV-positive patients receiving HAART have undetectable viral loads, so viral load quantification does not necessarily assist the anesthesiologist in any meaningful way during the perioperative period. In addition, even if viral load is undetectable, universal precautions should still be employed to ensure maximal safety. Recent CDC communications do acknowledge that a person with undetectable viral loads have almost zero risk of HIV transmission to another individual. HIV persistence is a known phenomenon, and HIV can remain dormant in lymph nodes and CNS reservoirs.

Since patients with HIV infection or AIDS can manifest a wide array of coexisting diseases, every patient should undergo a thorough history, review of systems, and physical examination focused particularly on subclinical or clinical manifestations of cardiac, pulmonary, neurologic, renal, and hepatic disorders related to HIV or AIDS. With regard to selection of anesthetic method, any anesthetic technique is acceptable unless there is a specific contraindication to regional anesthesia. Consideration should be given to addressing potential HAART-drug interactions when selecting anesthetic drugs and analgesics in the perioperative period.

Overall, HIV infection and AIDS do not increase the risk of postsurgical complications, including death, up to 30 days postoperatively. Thus surgical intervention should not be restricted because of HIV status and concern for subsequent complications. During anesthesia, however, tachycardia is more frequently seen in HIV-positive patients; postoperatively, fever, anemia, and tachycardia are more frequent.

Intraoperative

Selection of a particular anesthetic technique should take into account both HIV/AIDS-related comorbidities and any other clinical issues. Overall, no specific anesthetic technique has been shown to be superior or inferior in patients with HIV infection or AIDS. Specifically in patients with AIDS, focal neurologic lesions may increase intracranial pressure, which precludes neuraxial anesthesia. Spinal cord involvement, peripheral neuropathy, and myopathy may occur with cytomegalovirus or HIV infection itself. Therefore succinylcholine could conceivably be hazardous in this setting. HIV infection may be associated with autonomic neuropathy, and this can produce hemodynamic instability during anesthesia or in the ICU. Invasive hemodynamic monitoring may be helpful in patients with severe autonomic dysfunction. Steroid supplementation may

decrease hemodynamic instability and should be considered in cases of unexplained persistent hypotension.

Several studies indicate that general anesthesia and opiates may have a negative effect on immune function. Although this immunosuppressive effect may be of little clinical importance in healthy individuals, the implications for the HIV-infected patient are uncertain. Immunosuppression resulting from general anesthetics occurs within 15 minutes of induction and may persist for as long as 3 to 11 days. The psychological stress of undergoing anesthesia and surgery may also lead to some degree of generalized immunosuppression. However, no studies have been undertaken to determine specific effects in HIV-positive patients. Aside from $CD4^+$ cell count and viral load, there are no specific markers of immune status in this patient population.

The prevalence of HIV infection and AIDS is increasing in women of childbearing age, and there has been much study of this patient population. Although research has demonstrated the effectiveness of zidovudine in parturient women, monotherapy has limited long-term benefit because HIV resistance develops rapidly. Therefore, during pregnancy, combination therapy is preferable, and acceptable multidrug regimens are available. Data suggest that cesarean section decreases the incidence of vertical transmission of HIV from mother to child. A combination of antiretroviral therapy and elective cesarean section reduces the rate of vertical transmission to 2%. However, cesarean section is a major surgical intervention with many potential complications. Many practitioners in the past did not recommend elective cesarean section for HIV-infected women who were adherent to antiretroviral treatment regimens and had undetectable HIV viral loads. However, studies demonstrate that cesarean section can proceed safely. Unfortunately, HIV-positive women with low $CD4^+$ counts whose infants would likely benefit most from caesarean delivery are also the women who are most likely to experience perioperative complications.

HIV-positive parturient women who are given regional anesthesia have not had neurologic or infectious complications related to the anesthetic or obstetric course. In the immediate postpartum period, immune function has remained essentially unchanged, as has the severity of the preexisting HIV disease. There have been concerns that access to the epidural space and lumbar puncture in HIV-positive patients might allow entry of the virus into the CNS. However, the natural history of HIV infection includes CNS involvement early in its clinical course. The safety of epidural blood patches for treatment of postdural puncture headache has been reported in HIV-positive patients. Fear of disseminating HIV from the bloodstream into the CNS is not warranted.

Postoperative

A limited number of retrospective studies have evaluated the long-term consequences of undergoing anesthesia and surgery in HIV-positive and AIDS patients, but many of the studies conducted in the pre-HAART era yielded conflicting results. Current studies are examining surgical and anesthetic-related morbidity and mortality in HIV-positive patients who had been receiving HAART. Therefore it is important to understand the impact HAART has had on overall well-being in the HIV-positive population.

It appears that patients with HIV infection and AIDS do not experience any statistically significant increases in perioperative complications compared with similar cohorts who are not HIV positive. No statistically significant differences have been noted with regard to wound healing, SSI rates, wound dehiscence, number of complications, length of hospital stay, number of follow-up visits to the surgeon, or need for further operative procedures to treat surgical complications. However, 1-year mortality is higher overall in patients who are HIV positive and/or have AIDS; this is felt to be due to HIV infection itself. Patients with $CD4^+$ cell counts of less than 50 cells/mm^3 and patients with viral loads of more than 30,000 copies/mL fare the worst in terms of postoperative mortality. Patients with HIV infection may have a higher incidence of postoperative pneumonia than non–HIV-positive patients. Proper diagnosis and treatment typically lead to resolution of the pulmonary infection without sequelae.

Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring significantly underestimates mortality risk in HIV-positive patients admitted to the ICU with a total lymphocyte count below 200 cells/mm^3. This is particularly true of patients admitted with pneumonia or sepsis. There is a diverse range of indications for critical care in patients with HIV infection. Historically, respiratory failure caused by PCP was the most common reason for ICU admission and accounted for a third of ICU admissions in HIV-positive patients. The need for mechanical ventilation for PCP and other pulmonary disorders is associated with a mortality rate over 50%. In contrast, admission to the ICU and mechanical ventilation for nonpulmonary disorders is associated with a mortality rate below 25%. In patients with septic shock, however, HIV infection is an independent predictor of poor outcome. In the era of HAART, fewer patients with HIV infection are admitted to the ICU with AIDS-defining illnesses. Many patients are now admitted to the ICU with unrelated critical illnesses and are found coincidentally to be infected with HIV.

EMERGING AND UNUSUAL INFECTIOUS DISEASE THREATS

As the guardians of patients in the perioperative sector, we are often faced with managing clinical scenarios that arise rapidly and require deployment of bold precautionary, supportive, and treatment measures developed by local, regional, and national infection control teams. Recent infectious disease outbreaks have impacted the perioperative sector that have led to infection control algorithms that are tailored to each particular pathogen. These clinical care paradigms often share many common features; however, they may also vary significantly based on each respective clinical situation or pathogen. It is important to keep in mind that healthcare leaders and front-line providers actively monitor and develop plans to contain infectious diseases so that spread is minimized, and healthcare personnel attending to ill patients are properly trained to ensure their safety.

Ebola Virus Disease

Ebola virus disease (EVD), also called Ebola hemorrhagic fever or simply Ebola, is a disease of humans and other primates caused by Ebola viruses. The disease was first identified in 1976 in two simultaneous outbreaks, one in Nzara and the other in Yambuku, a village near the Ebola River from which the disease takes its name. EVD outbreaks occur intermittently in tropical regions of sub-Saharan Africa. Between 1976 and 2013 the WHO reported a total of 24 outbreaks involving 1716 cases. The largest outbreak ever reported was the epidemic that began in 2014 in West Africa. As of January 17, 2016, this outbreak had resulted in 28,638 reported cases and 11,316 deaths.

Some healthcare experts astutely predicted that Ebola fever would appear in patients outside the original epidemic zone because of the importation of healthcare workers from Europe and the United States for treatment and control maneuvers. Although the incidence and presence in the United States is quite rare, identification and containment of patients with Ebola virus is absolutely essential to infection control.

EVD in humans is caused by four of five viruses of the genus *Ebolavirus*. The four are Bundibugyo virus, Sudan virus, Taï Forest virus, and one simply called *Ebola virus* (formerly Zaire Ebola virus). Ebola, species *Zaire ebolavirus*, is the most dangerous of the known EVD-causing viruses and is responsible for the largest number of outbreaks. The fifth virus, Reston virus, is not thought to cause disease in humans but has caused disease in other primates.

Early diagnosis is difficult, since signs and symptoms of fever and flulike illness are nonspecific and similar to early findings in malaria and typhoid fever (Table 25.11). Diagnosis of Ebola infection can be made via antigen-capture ELISA, immunoglobulin M (IgM) ELISA, PCR testing, and/or virus isolation.

Infection Control

Because of the small group of patients (who were healthcare workers infected with Ebola virus) who were medically evacuated to the United States for treatment during the 2014 Ebola outbreak, the majority of healthcare institutions in the United States had to reevaluate their infectious disease identification measures, as well as their prevention strategies, to deal with persons potentially exposed to Ebola virus during travel. Healthcare institutions initiated a three-point screening process aimed at identifying patients possibly infected with Ebola virus. Patients being admitted to a hospital or healthcare facility are currently asked (1) if they have traveled in the last 21 days to an area associated with EVD, (2) if they have been directly exposed to a person (or the human remains of any person) with known or suspected Ebola virus infection, and (3) if they have had recent clinical symptoms of high fever, nausea, and/or vomiting. If patients respond "yes" to any of the listed questions, appropriate steps are taken to perform further testing to determine whether exposure to Ebola virus is likely. Any suspected cases are immediately reported to the epidemiology department of the institution.

To minimize the risk of EVD, existing standard precautions should be strengthened and carefully applied when providing care to any patient, regardless of the presenting signs and symptoms. Hand hygiene is the most important measure. Gloves should be worn for any contact with blood or bodily fluids. Medical masks and goggles or face shields should be used if there is any potential for splashes of blood or bodily fluids to the face, and cleaning of contaminated surfaces is paramount. These same precautions should also be taken for contact with corpses.

During EVD outbreaks, every healthcare facility should have a dedicated and well-equipped triage area at the building entrance to evaluate any patients presenting with high fever who are seeking care in the facility. This area should be staffed with healthcare professionals trained in basic infection control principles and specific precautions for EVD, and on the use of a standard algorithm to identify EVD cases. Staff in the triage area should wear a scrub suit, a gown, examination gloves, and

TABLE 25.11 Symptoms of Ebola Virus Disease (EVD) Infection

Symptoms

Fever
Severe headache
Muscle pain
Weakness
Fatigue
Diarrhea
Vomiting
Abdominal pain
Unexplained hemorrhage (bleeding or bruising)

Diagnosis

There must be a combination of symptoms suggestive of EVD AND a possible exposure to EVD within 21 days before the onset of symptoms. An exposure may include contact with:

- Blood or body fluids from a person sick with or who died from EVD
- Objects contaminated with blood or body fluids of a person sick with or who died from EVD
- Infected fruit bats and nonhuman primates (apes or monkeys)
- Semen from a man who has recovered from EVD.

Polymerase chain reaction (PCR) is one of the most commonly used diagnostic methods because of its ability to detect low levels of Ebola virus. PCR methods can detect the presence of a few virus particles in small amounts of blood, but the ability to detect the virus increases as the amount of virus increases during an active infection.

Treatment

- Providing fluids and electrolytes (body salts) through infusion into the vein (intravenously)
- Offering oxygen therapy to maintain oxygen status
- Using medication to support blood pressure, reduce vomiting and diarrhea, and manage fever and pain
- Treating other infections if they occur

Specific EBV Treatment

- There is currently no antiviral drug licensed by the US Food and Drug Administration (FDA) to treat EVD in people.
- During the 2018 eastern Democratic Republic of the Congo outbreak, four investigational treatments were initially available to treat patients with confirmed Ebola. For two of those treatments, called regeneron (REGN-EB3) and mAb114, overall survival was much higher. These two antiviral drugs currently remain in use for patients with confirmed Ebola.

a face shield. The area should be large enough to keep the potentially infected EVD patient at a 1-m distance from staff and should be equipped with an easily accessible hand hygiene facility (alcohol-based disinfectant dispensers; sink with running water, liquid soap, and single-use towels), thermometer, bin with lid and infectious waste plastic bags, and a sharps container (if rapid diagnostic testing is meant to be performed there). Triage staff should follow a no-touch process while interviewing patients.

Suspected or confirmed cases must be placed in single isolation rooms with an adjoining dedicated toilet or latrine, showers, sink (equipped with running water, soap, and single-use towels), alcohol-based handrub dispensers, stocks of personal protective equipment (PPE), stocks of medicines, adequate ventilation, closed doors, and restricted access. If single isolation rooms are unavailable, EVD patients should be put together in confined areas while rigorously keeping suspected and confirmed patients separated.

It is important to ensure that clinical and nonclinical personnel are assigned exclusively to EVD patient care areas and do not move freely between the EVD isolation areas and other clinical areas during the outbreak. All nonessential staff must be kept from EVD patient care areas. If a patient with EVD were to require surgery, a specifically designated operating room should be used and maintained for this patient population, with only designated staff accompanying the patient to the operating room. After the procedure, additional cleaning measures should include terminal cleaning of all devices and surfaces, including the anesthesia machine, with bleach/chlorine. PPE should be worn according to current WHO guidelines for Ebola outbreaks. All waste material, linens, and nondisposable materials should be decontaminated according to WHO guidelines. Fortunately to date there are no reported cases of patients infected with the Ebola virus who have undergone surgery in the United States.

Treatment

Symptoms of Ebola and complications are treated as they appear. The following basic interventions, when used early, can significantly improve the chances of survival: (1) providing IV fluids and creating electrolyte balance, (2) maintaining satisfactory oxygen saturation and blood pressure, and (3) treating other infections if they occur. Experimental vaccines and treatments for Ebola are under development, but they have not yet been fully tested for safety or effectiveness. Recovery from Ebola depends on strong supportive care and an adequate immune response by the patient. Those who recover from Ebola infection develop antibodies that last for at least 10 years, possibly longer. It is not known whether people who recover are immune for life or if they can become infected with a different species of Ebola. Some patients who have recovered from Ebola infection have developed long-term complications such as joint and vision problems.

Mycobacterium Chimaera

Background

Mycobacterium chimaera, a non-TB mycobacterium found in soil and water, was first described in 2004. *M. chimaera* has been associated with pulmonary infections but appears to be less infectious and/or virulent compared to *M. avium* or *M. intracellulare*. In early 2013 medical centers worldwide began reporting outbreaks of *M. chimaera* in patients who had undergone open heart surgery; the outbreak was limited to patients exposed to Stockert-3T heater cooler units (HCUs) attached to cardiopulmonary bypass circuits. In 2016, the CDC documented a series of *M. chimaera* infections in patients having undergone cardiac surgery in the United States in multiple centers. Epidemiologic and laboratory evidence suggested that inoculation and contamination of the HCUs occurred during manufacturing of Stockert-3T units manufactured by LivaNova (formerly Sorin); whole-genome sequencing data suggested a single point source. Growth of biofilm and subsequent aerosolization of *M. chimaera* dispersed by the HCU fan was demonstrated to have compromised the sterile surgical field and was the likely route of transmission. Despite ultraclean ventilation systems, *M. chimaera* aerosolization with resulting infection occurred. Patients typically present several years after cardiac surgery due to the long incubation period associated with *M. chimaera* infection. The latency period for *M. chimaera* infection is very long and can present months to years after cardiac surgery with either localized endocarditis, graft infection, wound infections, and/or disseminated (distal site and/or bloodstream) infection. Definitive identification of *M. chimaera* requires a molecular diagnostic laboratory for 16S ribosomal RNA gene sequencing and homology analysis. Molecular techniques for rapid identification of *M. chimaera* are currently evolving. Limitations to their use include high cost and need for third-party payor approval.

Identification of Patients

After reports of *M. chimaera* outbreaks began to occur, many medical centers began identifying all patients who had undergone cardiac surgery with use of Stockert-3T HCUs. Patients were contacted and asked to report any possible signs or symptoms associated with infection. Additionally, "possible *M. chimaera*" alerts were embedded in the electronic medical record so that any healthcare provider or physician caring for a patient who was "at risk" could perform a risk assessment analysis. Due to the long incubation period for active infection, surveillance was otherwise quite limited.

Prevention

After reports confirmed that a particular Stockert HCU was the causative source for *M. chimaera* infections, the HCUs were either decontaminated following manufacturer instructions or removed entirely and replaced with a different product. The majority of medical centers did not change operating rooms or alter airflow mechanics in the respective operating rooms. Per CDC isolation guidelines, patients infected with non-TB mycobacterium do not require isolation or contact isolation and can be safely managed with standard precautions.

Treatment

By the time a definitive diagnosis is made, patients infected with *M. chimaera* may possess a wide variety of symptoms, including

fatigue, malaise, weight loss, and failure to thrive. Treatment primarily consists of antimycobacterial agents based on phenotypic and genotypic analysis. Reoperation may be needed to remove infected grafts or valves respective for the initial cardiac surgery; however, mortality rates have been high in patients undergoing reoperations. Prevention of further infections has been eliminated by removal of all contaminated HCUs by each respective institution.

Coronavirus (COVID-19)

Background

In 2019, reports of a novel outbreak of an influenza virus were emanating from Wuhan, China. The virus was named SARS-CoV-2, and the disease it causes has been named coronavirus disease 2019 (COVID-19). COVID-19 is an RNA retrovirus and shares characteristics with MERS-CoV and SARS-CoV (Fig. 25.8). By March 2020, over 150 countries, including the United States, were impacted by COVID-19, and the WHO characterized this contagion as a global pandemic. As of May 2021, COVID-19 has impacted nearly every country in the world and has resulted in 159 million global infections, with new infections continuing to occur daily. Additionally, COVID-19 has resulted in over 3.3 million global deaths and climbing. The United States, India, and Brazil have been the hardest hit nations with regard to overall infections and deaths.

Coronaviruses are a large family of viruses that are common in people and many different species of animals, including camels, cattle, cats, and bats. Rarely, animal coronaviruses can infect people and then spread between people such as with MERS-CoV and SARS-CoV. The gene sequences from American patients are similar to the one that China initially posted, suggesting a likely single, recent emergence of this virus from an animal reservoir.

Transmission

The epicenter of the initial outbreak has been linked to the city of Wuhan (Hubei Province), China. Early epidemiology of infected patients demonstrated linkage to a large seafood and live animal market, suggesting animal-to-person spread. Later, a growing number of patients reportedly did not have exposure to animal markets, indicating person-to-person spread. Person-to-person spread was subsequently reported outside Hubei and in countries outside China, including in the United States. International destinations experienced community spread fairly rapidly presumably due to mobile populations enabled by jet travel. Community spread implies that persons have become infected, but it is not known how or where they became exposed.

The major form of transmission occurs through person-to-person spread via respiratory droplets. It is now known that airborne aerosolized particles are also infectious. Spread is exacerbated by close proximity (<6 ft) to others. Contaminated surfaces and objects (steel, plastic, resins) may harbor viral particles that can remain viable for a range of hours to several days.

Infectious persons may be completely asymptomatic carriers, and these persons may never develop any disease symptoms. Several studies have documented SARS-CoV-2 infection in patients who never develop symptoms (asymptomatic) and in patients not yet symptomatic (presymptomatic).

Clinical Picture

At the time of this writing, the full clinical paradigm and clinical sequelae with regard to COVID-19 is not fully known. Initial signs of infection may be extremely subtle and manifest as GI distress and/or diarrhea. Limited reports have indicated that patients with precursor GI symptoms may fare worse than patients with GI distress. As infection proceeds, the most common

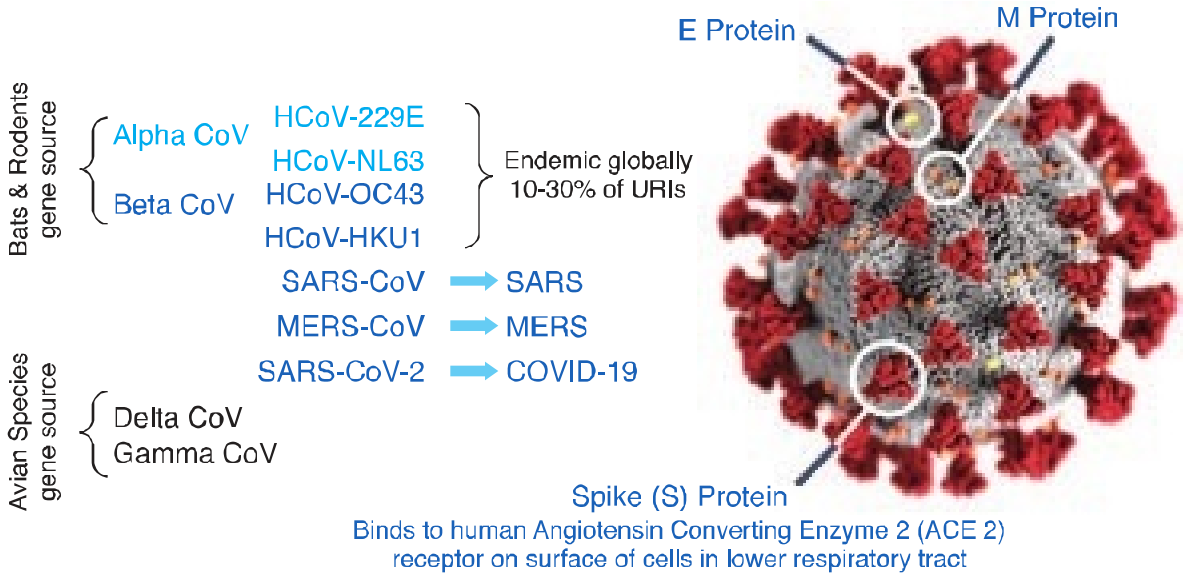

Fig. 25.8 COVID-19 viral particle with surface protein designations; COVID-19 gene sources, and similar viral strains causing respiratory infections.

hallmarks are fever, dry nonproductive cough, and progressive shortness of breath. COVID-19 infection may range from very mild (including some persons with no reported symptoms) to severe. Infection can proceed rapidly with 2 to 14 days and require respiratory support, intubation, and ICU admission.

While information thus far suggests that most COVID-19 illness is mild, reports from China suggest that serious illness occurs in 16% of cases. Older people and people of all ages with severe chronic medical conditions (i.e., heart disease, lung disease, and diabetes) appear to be at higher risk for developing serious COVID-19 illness. Patients who are black and Latinx are disproportionally affected in the United States. Additionally, patients with refractory COVID-19 were older in age, male, had more underlying comorbidities, had a lower incidence of fever (higher levels of maximum temperature among fever cases), and had a higher incidence of shortness of breath and anorexia. Patients with refractory disease also had high levels of neutrophils, aspartate aminotransferase, lactate dehydrogenase, and C-reactive protein; lower levels of platelets and albumin; and higher incidence of bilateral pneumonia and pleural effusion. Differential diagnosis should include influenza, parainfluenza, adenovirus, rhinovirus, respiratory syncytial virus, and human metapneumovirus.

Severe Infection

Patients who experience significant respiratory deterioration are transferred to the ICU and may require ventilator support. Reports suggest that among those infected with severe ARDS, up to 20% develop severe disease requiring hospitalization. Among those who are critically ill, profound acute hypoxemic respiratory failure from ARDS is the dominant finding. Hypercapnia is rare. Fevers tend to wax and wane during ICU admission. The need for mechanical ventilation in those who are critically ill is high, ranging from 30% to 100%. Clinical reports suggest that length of ICU stay appears to be long, with many patients remaining intubated for 1 to 2 weeks or longer. Sepsis, shock, and multiorgan failure do occur but appear to be less common when compared with non-COVID-19–related ARDS. Strategies that have been shown to be effective include low-tidal volume ventilation, pulmonary vasodilators (nitric oxide, epoprostenol), recruitment, and high PEEP; patient positioning with proning maneuvers are also effective in alleviating pulmonary congestion.

Testing and Identification

Guidelines for testing are evolving as the nature of COVID-19 infection is further characterized. During the early course of the pandemic, scarcity of testing kits led to limited testing and was only indicated for persons with symptoms consistent with COVID-19 and a high index of suspicion for acquisition from community spread. However, persons who were elderly or immune compromised were tested more aggressively. Testing detects for COVID-19 viral genetic material utilizing real-time PCR. The WHO test detects E gene, whereas the CDC test detects the N gene; the cobas SARS-CoV-2 test (Roche Laboratories) is a qualitative assay that allows the detection of nucleic acids, is extremely rapid, and can yield results in less than 4 hours. Additionally, antibody testing will reveal if you have had a prior exposure; however, antibodies to COVID-19 typically disappear within 3 to 4 months after the initial infection. Therefore antibody testing has limited utility.

Since asymptomatic persons are not routinely tested, the prevalence of asymptomatic infection and detection of presymptomatic infection is not yet well understood. One study found that as many as 13% of reverse transcription PCR (RT-PCR)–confirmed cases of SARS-CoV-2 infection in children were asymptomatic. Another study of skilled nursing facility residents who were infected with SARS-CoV-2 after contact with a healthcare worker with COVID-19 demonstrated that half of the residents were asymptomatic or presymptomatic at the time of contact tracing, evaluation, and testing. Increasing numbers of epidemiologic studies have documented SARS-CoV-2 transmission during the presymptomatic incubation period. Virologic studies using RT-PCR detection have reported tests with low cycle thresholds, indicating larger quantities of viral RNA and viable virus have been cultured from persons with asymptomatic and presymptomatic SARS-CoV-2 infection. The relationship between SARS-CoV-2 viral RNA shedding and transmission risk is not yet clear. The proportion of SARS-CoV-2 transmission due to asymptomatic or presymptomatic infection compared to symptomatic infection is unclear. Detection of SARS-CoV-2 viral RNA is better in nasopharynx samples compared to throat samples. Lower respiratory samples may have better yield than upper respiratory samples. SARS-CoV-2 RNA has also been detected in stool and blood, and detection of SARS-CoV-2 RNA in blood may be a marker of severe illness.

Treatment

Part of treatment is initially based on containment. Isolation (if sick) is key, and the goal is to keep infected people away from uninfected people. Self-quarantine (if exposed) is the next most important measure for disease containment. Potentially infected persons should also stay home for 14 days with no visitors, maintain a minimum distance of 6 feet from others in the household, and perform standard hygiene with frequent handwashing.

COVID-19 specific vaccines were approved by the U.S. Food and Drug administration in December, 2020. Multiple manufacturers (i.e. Pfizer, Moderna, AstraZeneca, Jansen) produced both single dose and multiple dose vaccines. The COVID-19 vaccines have shown to be extremely effective at preventing COVID-19 disease and/or reducing severity and progression leading to death. Unlike other vaccines that commonly use live whole virus or attenuated virus, the COVID vaccines that are currently approved utilize either viral vectors or messenger RNA to induce an antibody response. Fig. 25.9 denotes the process by which messenger RNA vaccines effectuate an immune response. Antibiotics are ineffective because COVID-19 is a viral infection and not bacterial. If symptoms become more severe, supportive treatments may be initiated by your doctor or at a hospital. Treatment may involve (1)

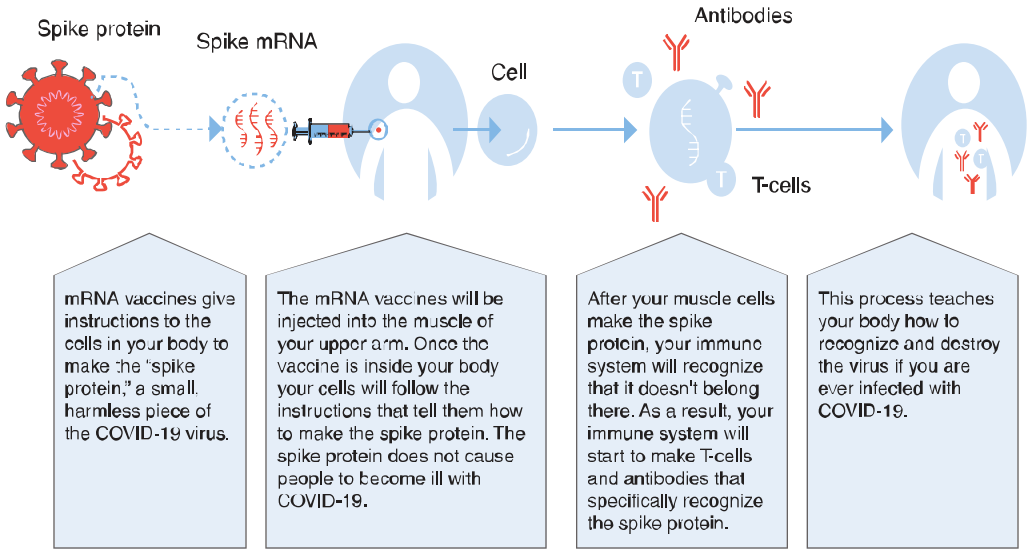

Fig. 25.9 Mechanism of Action for mRNA COVID-19 Vaccine.

fluids to reduce the risk of dehydration, (2) medication to reduce a fever, and (3) supplemental oxygen and/or intubation with ventilator support in more severe cases leading to ARDS and/or sepsis. While vaccines are currently the most effective means of preventing COVID-19 infection, there is no definitive treatment or antiviral to treat COVID-19 infection. Some countries have initiated use of other medications with no final results or outcomes to date. Current treatment guidelines are continually being revised as studies demonstrate effectiveness. The mainstay of treatment for COVID-19 currently includes the use of convalescent plasma and remdesivir; new therapies are continually being evaluated. The CDC does not recommend the use of chloroquine, hydroxychloroquine, lopinavir-ritonavir, and ivermectin.

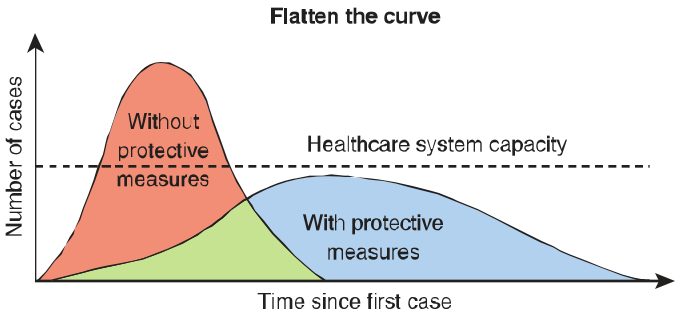

Fig. 25.10 "Flatten the curve" campaign demonstrating impact of social distancing and isolation efforts to contain spread and distribute over a longer period of time to allow healthcare absorption of cases.

Impact on Perioperative Sector

Due to the rapidly evolving spread of COVID-19, extreme measures were implemented throughout global communities to reduce the incidence of community spread. Both social isolation and social distancing were utilized to minimize exposure and possible community spread of the coronavirus. This campaign was designated "flatten the curve" to diminish or spread the impact of infection so that healthcare systems could slowly accommodate infected patients over a longer period of time (Fig. 25.10).

Exponential increases in active infection in affected countries require large allocation of hospital resources, most notably use of ICU beds, ventilators, respiratory therapists, anesthesiologists, and critical care personnel. Rapid and large-scale use of PPE, medical supplies, and blood products yields a huge strain on existing resources. Additionally, stringent infection control policies were implemented in hospital sectors that were based on standard precautions with additional layers of protection (Table 25.12).

Additionally, health resource consumption in highly affected countries led to drastic measures to preserve medical supplies and PPE, reduce blood consumption, and increase bed capacity specifically with ICU and respirator capability. Elective and nonurgent surgical cases were cancelled in most countries, and only urgent/emergent cases were performed. COVID-19 continues to significantly impact persons on a global scale. While vaccine therapies are the most effective means of prevention, challenges include persons who refuse vaccine administration, health care disparities limiting vaccine distribution and new evolving COVID-19 variants that may demonstrate resistance patterns.

Scheduling COVID-Positive Patients for Surgery

Patients infected with COVID-19 will require either emergent, urgent or elective surgery will require surgery and surgical scheduling timelines based upon status of COVID disease have become better understood. Based upon large multi-center data collection, centers typically group COVID-positive patient into three major groupings: 1) asymptomatic 2) symptomatic and 3)

TABLE 25.12 Symptoms, Risk Factors, and Precautions for Coronavirus Disease (COVID-19) Infection

Screening for COVID-19 Symptoms

Documentation from direct encounter, telehealth communication, or self-reporting via electronic medical record alert

Diarrhea/gastrointestinal distress
Fever
Cough (nonproductive, excessive)
Shortness of breath at rest
Fatigue
New loss of taste or smell
Sore throat
Congestion

Risk Factors

Immune compromised
Persons >60 yr of age
Global travel in country or countries of originating illness
Has the patient been in close contact with infected person?

General Infection Precautions

Hand washing with soap and water (<20 sec)
Decontamination of surfaces with antiviricidal agents
Limitation of large person groups
Self-isolation (14 days or until testing) if criteria above or high index of suspicion for COVID-19
Every hospital should institute central command monitoring with direct communication action plan to healthcare providers.

If interaction with known COVID-19 patient:

Put a mask on yourself (N95 if possible).
Provide the patient a mask.
Keep a distance of 6 ft from patient when possible.
Accompany patient to a negative pressure exam room (or regular exam room with door closed).

Operating Room Precautions:

Team huddle prior to direct care of COVID-19 infected patient.
Patient to be placed in a negative pressure operating room for anesthesia induction.
Healthcare providers performing intubation/extubation should utilize powered air purifying respirator (PAPR).
After airway secured, patient can be transported to regular operating room; PAPRs may be removed and replaced with N95 mask.
When case is complete, the patient should be transferred back to the isolation room for extubation.
Providers performing extubation should don PAPRs, all other team members should wear N95 masks.

Treatment

Supportive measures
Respiratory support as indicated, including intubation and isolation
Antiviral medications (recommendations as per CDC): remdesivir

Adapted from Centers for Disease Control Advisory Statements, 2020; COVID-19 Clinical Care Guidelines, Kaiser Permanente Health System California.

TABLE 25.13 Recommended Timeline for COVID-19 Positive Patients Requiring Surgery

Case Classification		Peak Covid Severity	Minimum Recovery Time[1]
Emergent/Urgent	Balance disease risk vs infectious risk (10 days)[2]		
Elective[3]	Class A	Asymptomatic	>= 1 month
	Class B	Symptomatic with or without diabetes, and/or immunocompromised	>= 2 months
	Class C	Hospitalized	>= 3 months

[1]Recommended timelines only. Clinical judgement, risk assessment and individual timelines may be necessary.
[2]Case by case consideration of surgical disease, COVID symptoms, physiologic effects of COVID and infectious risk.
[3]Elective classification systems assumes full recovery or establishments of a new stable, clinical baseline.

hospitalized. Table 25.13 denotes the recommended minimum recover time for the various groups of COVID-positive patients. For patients requiring emergent or urgent surgery, the anesthesiologist and surgeon/proceduralist must balance the need for surgery versus COVID disease impact and possible sequelae. Whenever possible, recovery time after COVID-19 infection should be maximized in order to mitigate any potential negative effects, including subclinical impact. Additionally, testing prior to surgery is recommended in all patients who were previously COVID-positive. Fig. 25.11 describes the testing and surgical scheduling timeline algorithm. In summary, elective surgery should be delayed for >= 7 weeks following COVID infection to reduce the risk of postoperative mortality and pulmonary complications. In addition, COVID-positive patients who are still symptomatic >= 7 weeks after COVID infection may benefit from a further delay until their symptoms resolve.

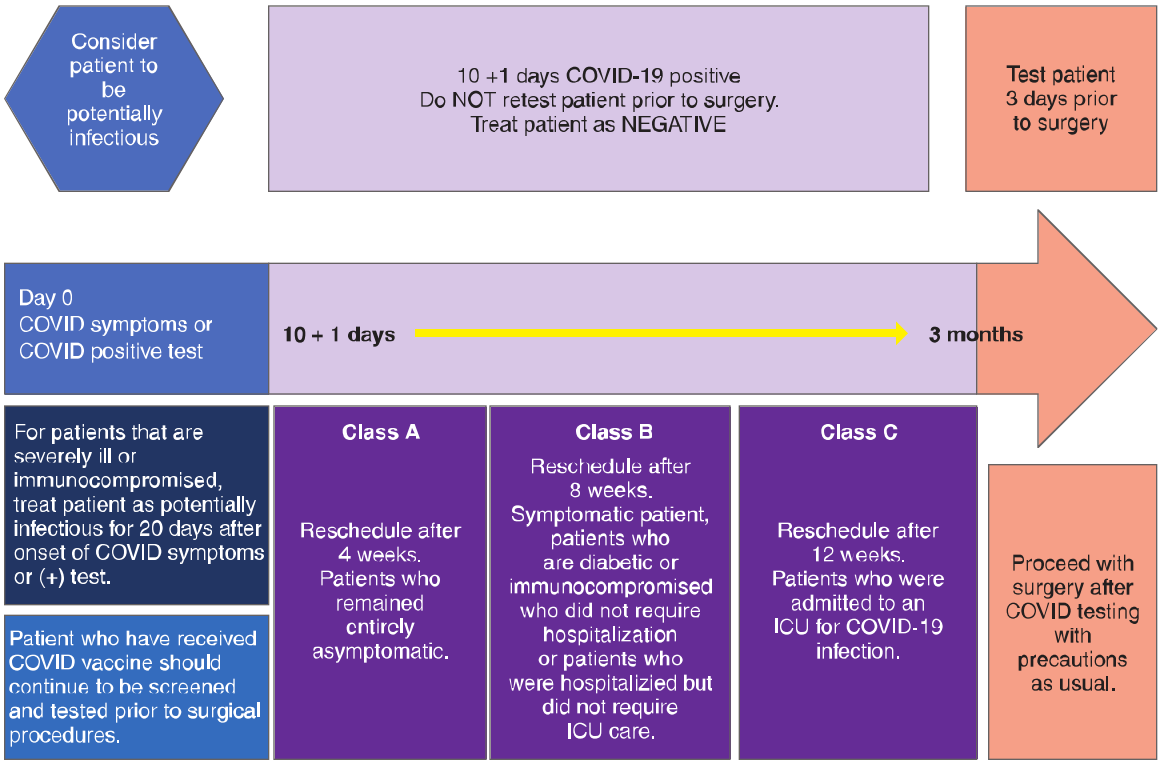

Fig. 25.11 Elective Surgical Scheduling Timeline & Considerations for COVID-19 Positive Patients. (Adapted from Gasparini G, Sapcnaro G, Patini R, Nepogodiev D. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. *Anaesthesia.* 2021;76(6):748–758. doi:10.1111/anae.15458. https://www.asahq.org/about-asa/newsroom/news-releases/2020/12/asa-and-apsf-joint-statement-on-elective-surgery-and-anesthesia-for-patients-after-covid-19-infection.)

KEY POINTS

- The 21st century has become noteworthy for a proliferation of infectious diseases caused by various new viral organisms.
- There are few new antibiotics under development to combat resistant gram-negative organisms.
- Multidisciplinary protocols focusing on preoperative, intraoperative, and postoperative prevention of SSI decrease the likelihood of patients developing such perioperative infections.
- Frequent hand decontamination with either alcohol or soap and water is likely the single most effective intervention in decreasing nosocomial infection.
- Administration of antibiotics at the right time, in the right dosage, and for an appropriate duration of time effectively treats infection and retards development of antibiotic drug resistance.
- The growing epidemic of virulent *C. difficile*–associated diarrhea among hospitalized patients may be associated with widespread use of broad-spectrum antibiotics.
- To minimize widespread resistance of organisms to all antimicrobial agents, therapy must be narrowed as soon as organisms are identified and susceptibility testing is completed.
- Specimens for culture should be obtained from all likely sources if sepsis is suspected.
- With necrotizing soft tissue infections, superficial cutaneous signs typically do not reflect the extent of tissue necrosis.
- Between 10% and 20% of patients requiring endotracheal intubation and mechanical ventilation for longer than 48 hours develop ventilator-associated pneumonia, which involves significant mortality.
- Respiratory viruses usually have high virulence, a fulminant infectious course, and high mortality; prevention measures and treatment should be initiated as rapidly as possible.
- Allogeneic red blood cell transfusion creates generalized immunosuppression and can reactivate latent viruses.
- The development of extremely drug-resistant (XDR) TB, caused by *M. tuberculosis* strains that are not only resistant to antibiotic therapy but also more virulent and more frequently lethal, has become a large public health problem.
- Posttransplantation patients are especially susceptible to infectious diseases, and strict adherence to immunosuppression regimens, antimicrobial prophylaxis, and surgical infection prophylaxis is critical in preventing new infections.
- HIV infection is a modern pandemic and has acute, latent, and end-stage phases. HAART has transformed HIV into a manageable chronic disease; however, significant HAART-induced and/or HIV-related morbidity continues to exist.
- Healthcare workers must recognize that they are potential agents of infection transmission and maintain high infection

control vigilance and report any unusual patterns related to possible nosocomial or hospital-acquired infections.
- New emerging pandemics continue to threaten the safety of our communities and require high vigilance, insight and knowledge integration from multiple disciplines, rapid precautionary and possible extreme measures, and flexibility in managing diverse situations.
- COVID-19 is a new viral pathogen that has impacted communities across the globe. Effective transmission prevention consists of washing hands, maintaining social distancing (6 ft), and wearing a mask. Multiple COVID-19 vaccines are available and currently in the distribution phase to persons aged 16 and older.
- Children between the age of 12 to 16 will be eligible for vaccine by mid 2021.

RESOURCES

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WORLD WIDE WEB LINKS

Facts about antibiotic resistance:
http://www.idsociety.org/AR_Facts/
Information about surgical site infection:
https://www.cdc.gov/infectioncontrol/guidelines/ssi/index.html
Facts about bloodstream infections:
https://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf
Facts about HIV:
http://www.hivguidelines.org
https://www.cdc.gov/hiv/default.html
Facts about Ebola virus disease
https://www.cdc.gov/vhf/ebola/clinicians/index.html
Facts about influenza
https://www.cdc.gov/flu/index.htm
Facts about coronavirus (COVID-19)
https://www.cdc.gov/coronavirus/2019-ncov/index.html
https://coronavirus.jhu.edu/
https://www.asahq.org/about-asa/newsroom/news-releases/2020/12/asa-and-apsf-joint-statement-on-elective-surgery-and-anesthesia-for-patients-after-covid-19-infection

26

Diseases Related to Immune System Dysfunction

Natalie E. Holt

OUTLINE

INTRODUCTION

The human immune system is traditionally divided into two pathways: innate immunity and adaptive (also known as acquired) immunity. Each is comprised of a series of unique components, all of which function to protect the host against invading microorganisms. The innate immune response is rapid and nonspecific (i.e., recognizes targets that are common to many pathogens and requires no prior exposure to a target antigen). Its noncellular elements include physical barriers (tight junctions in the skin, epithelial and mucous membrane surfaces), complement factors, acute-phase proteins, and proteins of the contact activation pathway. Cellular elements include neutrophils, macrophages, monocytes, eosinophils, basophils, mast cells, and a subset of lymphocytes called natural killer (NK) cells (Fig. 26.1). The adaptive immune response is an evolutionarily more mature system present only in vertebrates. Adaptive immunity has a more delayed onset of activation but is capable of developing memory and more specific antigenic responses. It consists of a humoral component mediated by B lymphocytes that produce antibodies and a cellular component composed of T lymphocytes. T cells are divided into two main subsets: cytotoxic (Tc) cells and helper/modulatory (Th) cells, distinguished by their different combinations of surface antigens. Tc cells express a predominance of CD8 antigen, while Th cells express a predominance of CD4 antigen. Precursor helper T lymphocytes differentiate into several distinct subsets, including Th1, Th2, Th9, Th17, regular T cells (Tregs), and follicular T cells (Tfh). Th1 cells produce interferon-γ (IFN-γ) and interleukin-2 (IL2) and promote cell-mediated immune responses. Th2 cells produce specific interleukins, including IL4, IL5, and IL13, which favor a humoral immune response and suppress cell-mediated immunity. Th9 cells produce IL9 and IL10 and have a role in tumor immunity, allergy, and autoimmune disease. They also help to protect against parasitic infections. Th17 cells are proinflammatory and influence the development of chronic inflammatory conditions, including some cell-mediated autoimmune diseases. In contrast, Treg cells promote tolerance and minimize autoimmune and allergic or inflammatory responses. Finally, Tfh cells play a role in the maturation of B-cell germinal centers, which ultimately lead to the production of antibodies. As a general rule, cytotoxic and helper T-cell responses are important in the effective response to trauma, infection, and tumorigenesis (Table 26.1).

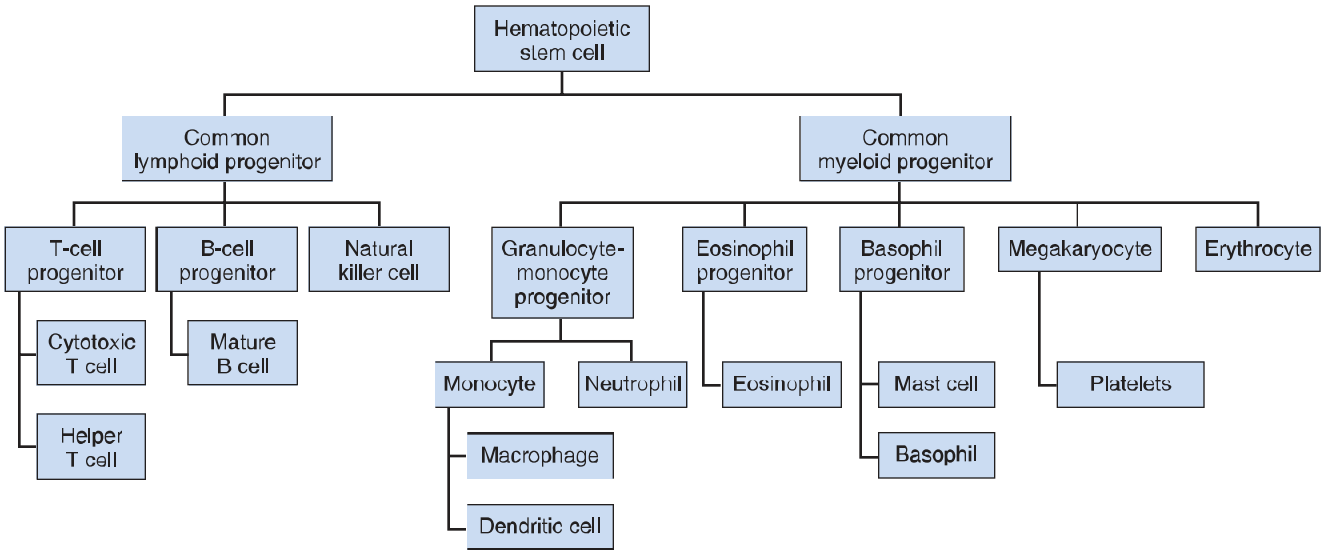

Fig. 26.1 Hematopoietic stem cell differentiation. A pluripotent hematopoietic stem cell gives rise to all blood cell types via two main lineages: lymphoid and myeloid. A common myeloid progenitor differentiates into the granule-containing cells of the immune system (monocytes, macrophages, neutrophils, eosinophils, basophils) as well as megakaryocytes and erythrocytes. A common lymphoid progenitor differentiates into the nongranule-containing cells of the immune system (T cells, B cells, and natural killer cells).

TABLE 26.1 T-Lymphocyte Differentiation

Subset	Main Functions	Cytokines Produced
Helper T cells		
Th1	Macrophage activation	IFN-γ
	Cellular cytotoxicity	IL2
	Protection against intracellular microorganisms	
	Delayed hypersensitivity reactions	
Th2	IgE production	IL4
	Eosinophil proliferation	IL5
	Protection against parasitic infection	IL13
Th9	Tumor immunity	IL9
	Resistance to parasites	IL10
Th17	Chronic inflammation, allergy, autoimmune diseases	IL17
	Protection against extracellular bacteria and fungi	IL22
		IL26
Th22	Chronic inflammation, allergy, autoimmune diseases	IL22
Regulatory T cells (Tregs)	Prevention of allergic and autoimmune disease	TGFβ
	Downregulation of immune response/development of tolerance	IL10
Follicular T cells (Tfh)	Germinal center B-cell development and maturation	
Cytotoxic T cells	Induction of cellular toxicity in infected or tumor cells	
	Inhibition of microbial replication	

IFN-γ, Interferon; *IL*, interleukin; *TGFβ*, transforming growth factor β.

Immune dysfunction can be divided into three categories: (1) injury caused by an inadequate immune response, (2) injury caused by an excessive immune response, and (3) injury caused by a misdirection of the immune response.

INADEQUATE INNATE IMMUNITY

Neutropenia

Neutropenia is defined as a neutrophilic granulocyte count of less than 1500/μL. Normal neutrophil counts vary somewhat by age and ethnicity. For example, newborns tend to have higher granulocyte counts in the first few days of life, and Blacks tend to have lower average granulocyte counts compared to whites. It is not until the granulocyte count decreases to less than 500/μL that a patient is at significantly increased risk of pyogenic infections. Common infecting organisms include *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli,* and *Klebsiella* species, producing infections of the skin, mouth, pharynx, and lung. Broad-spectrum parenteral antibiotics are indicated in the management of these patients.

Neutropenia in Pediatric Patients

Several neutropenic syndromes can occur in newborns and children. Neonatal sepsis is the most common cause of severe neutropenia within the first few days of life. A transient neutropenia may occur in children born to mothers with autoimmune diseases or as a result of maternal hypertension or drug ingestion. Persistent neutropenia can occur due to defects in neutrophil production, maturation, or survival.

The autosomal dominant disorder cyclic neutropenia is a particularly well-studied cause of childhood neutropenia. It is

characterized by recurrent episodes of neutropenia (not always associated with infection) that occur in regular cycles every 3 to 4 weeks. Each episode is characterized by a brief phase of reduced granulocyte production, followed by a period of reactive mastocytosis and then spontaneous recovery of normal granulocyte production. A characteristic feature is the presence of chronic mouth ulcers and gingival disease. In most cases, the condition is caused by a defect in the elastase gene, which halts myelocyte maturation in the bone marrow. Patients respond well to treatment with granulocyte colony-stimulating factor (G-CSF).

Kostmann syndrome is an autosomal recessive disorder of neutrophil maturation. Patients with Kostmann syndrome appear to have a normal population of early progenitor cells that somehow become suppressed, inhibiting normal maturation. If untreated, mortality in the first year of life approaches 70%. Treatment with G-CSF is effective in 90% of patients; in patients who do not respond to G-CSF, bone marrow transplantation may be considered.

Wiskott-Aldrich syndrome is another form of congenital neutropenia with an X-linked inheritance pattern seen almost exclusively in males. The pathophysiology relates to impaired T-cell signaling and an inability of NK cells to mount a cytotoxic response. In addition to susceptibility to infections, these patients also present with thrombocytopenia and eczema.

With the advent of G-CSF leading to increased survival in children with congenital neutropenic syndromes, it has become clear that these patients are at increased risk for the development of myelodysplastic syndrome (MDS) and leukemia in later life.

Neutropenia in Adults

Acquired defects in the production of neutrophils in adults are very common. Typical causes include cancer chemotherapy and treatment of human immunodeficiency virus (HIV) with zidovudine. Neutropenia usually reflects the impact of a drug on stem cell and early myelocytic progenitor proliferation. In most cases, the marrow recovers once the drug is withdrawn. Many drugs have been associated with neutropenia. Among the most prominent of these are the injectable gold salts, chloramphenicol, antithyroid medications (carbimazole and propylthiouracil), analgesics (indomethacin, acetaminophen, and phenacetin), tricyclic antidepressants, and phenothiazines. However, virtually any drug can, on occasion, produce severe life-threatening neutropenia. Therefore, when neutropenia occurs in the course of medical treatment, the possibility that it is drug induced must be considered.

Autoimmune-related neutropenia can be observed as an isolated disorder or in the context of another known autoimmune condition. Antineutrophil antibodies are sometimes present. The two most common associations are with systemic lupus erythematosus (where the neutropenia can occur alone or be accompanied by thrombocytopenia) and rheumatoid arthritis. Conditions associated with splenomegaly often lead to granulocytopenia due to white cell sequestration. Felty syndrome is the triad of rheumatoid arthritis, splenomegaly, and neutropenia. Other causes of splenomegaly and neutropenia include lymphoma, myeloproliferative disease, and severe liver disease with portal hypertension. In these latter situations, it is often difficult to decide whether the granulocytopenia is caused simply by splenic sequestration or whether it also has an autoimmune component. In some patients, splenectomy may improve neutrophil production.

Acute, life-threatening neutropenia can occur as a result of certain infections. A decreasing white cell count in a patient with sepsis is a negative prognostic indicator. It reflects a rate of granulocyte use that exceeds the marrow's ability to produce new cells. Alcoholic patients are especially susceptible to infection-induced neutropenia. Both folic acid deficiency and direct toxic effects of ethanol on marrow precursor cells compromise the host's ability to produce new neutrophils in response to infection. HIV infection is a common cause of T-cell dysfunction. In these patients, loss of the Th subset and overexpression of the T-suppressor subset is associated with abnormalities of neutrophil production and function.

Benign ethnic neutropenia is an inherited condition most often seen in individuals of African descent, but also certain other ethnic groups (e.g., Sephardic Jews, Greeks, and Arabs). It is rare for the neutrophil count to drop below 1000/μL. The clinical course is benign for most patients.

Abnormalities of Phagocytosis

Chronic granulomatous disease is a genetic disorder in which granulocytes lack the ability to generate reactive oxygen species. The granulocytes can migrate to a site of infection and ingest organisms but are unable to kill them. *Staphylococcus aureus* and certain gram-negative bacteria such as *Serratia marcescens* and *Burkholderia cepacia* that are normally killed by phagocytosis and lysosomal digestion are responsible for most infections in these patients. The condition is usually diagnosed during childhood or early adult life when patients present with recurrent microabscesses and chronic granulomatous inflammation. Persistent inflammation and granuloma formation can lead to multiorgan dysfunction, including intestinal obstruction, glomerulonephritis, and chorioretinitis. Aggressive treatment of infectious complications, prophylaxis with antibiotics and antifungal agents, and the use of recombinant IFN-γ has significantly improved survival in patients with this disease.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an inherited disorder caused by a genetic defect in the enzyme G6PD. This enzyme is mostly present in red blood cells (RBCs), where it generates nicotinamide adenine dinucleotide phosphate (NADPH) and protects RBCs against oxidative injury. G6PD is also present in neutrophils. Patients with severe G6PD deficiency exhibit an impaired ability to generate the oxidase needed to kill ingested microorganisms. As with chronic granulomatous disease, neutrophil G6PD-deficient patients are at lifelong risk of infection with catalase-positive microorganisms.

Leukocyte adhesion deficiency is a relatively rare deficiency of a subunit of the integrin family of leukocyte adhesion molecules. This subunit is critical for cellular adhesion and chemotaxis. Although clinical severity varies, patients with

leukocyte adhesion deficiency experience a higher risk of recurrent bacterial infections. Persistent granulocytosis is often present; however, the absence of pus is the most characteristic feature of the disease.

Chédiak-Higashi syndrome is an uncommon multisystem disease characterized by partial oculocutaneous albinism, frequent bacterial infections, mild bleeding diathesis, progressive neuropathy, and cranial nerve defects. The neutrophils of these patients contain characteristic giant granules. Patients exhibit multiple defects of immune function, including impairment in neutrophil chemotaxis, phagocytosis, NK-cell activity, and T-cell cytotoxicity. Many white blood cells (WBCs) are destroyed before leaving the bone marrow. In most patients, an accelerated lymphoproliferative syndrome leads to death; however, bone marrow transplantation can reverse immunologic dysfunction in some patients.

Neutrophil-specific granule deficiency syndrome is another rare congenital disorder characterized by neutrophils that exhibit impaired chemotaxis and bactericidal activity. Patients are prone to recurrent bacterial and fungal infections with abscess formation. Skin and pulmonary infections appear to predominate and most of these respond well to aggressive antibiotic therapy.

Management of Patients With Neutropenia or Abnormalities of Phagocytosis

Patients with neutropenia or a qualitative disorder of granulocyte function often benefit significantly from treatment with G-CSF. Recombinant G-CSF reduces the duration of absolute neutropenia in patients receiving ablative chemotherapy and autologous bone marrow transplantation. It also shortens the length of antibiotic therapy and reduces the risk of life-threatening bacteremia and fungal infections. G-CSF therapy has been approved for the reversal of the neutropenia associated with HIV infection and the prevention of worsening neutropenia in patients on HIV therapy. Neutropenic patients undergoing elective surgery may benefit from a course of G-CSF preoperatively to reduce the risk of perioperative infection.

Deficiencies in Components of the Complement System

Complement refers to a family of serum proteins that are critical to the host response to infection. Complement activation may occur by pathogen-dependent (classical or lectin) or pathogen-independent (alternative) pathways (Fig. 26.2). Complement proteins assist in the clearing of microorganisms by coating infectious agents with proteins that facilitate phagocytosis. Complement proteins also promote the inflammatory response. Certain complement components are unique to a particular pathway, but all pathways lead to the formation of C3 and the membrane attack complex. Deficiencies in virtually all the soluble complement components have been described. Defects in early components of the classical pathway of complement activation (C1q, C1r, C1s, C2, and C4) predispose to autoimmune inflammatory disorders resembling systemic lupus erythematosus. Deficiencies in the common pathway component C3 are often fatal in infancy. Deficiencies in the terminal complement components C5 through C9 are associated with recurrent neisserial infections, but these infections are usually mild, and the mortality rate is low. The liver is the primary organ of complement protein synthesis; therefore patients with advanced liver disease are often at increased risk of infection, especially pneumonia and sepsis caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Escherichia coli*. Prompt recognition and treatment of infection and careful maintenance of routine vaccinations are the hallmarks of treating these patients.

Tight regulation of complement activation prevents misdirected activation of the inflammatory and immune responses. The main inhibitor compound is C1 inhibitor. Deficiency of C1 inhibitor is responsible for hereditary angioedema, an autosomal dominant condition marked by episodes of subcutaneous and submucosal edema, caused primarily by excessive concentrations of bradykinin, which increases vascular permeability. Factor H is another regulatory protein of the complement cascade. Deficiency in factor H predisposes patients to hemolytic uremic syndrome and macular degeneration.

Hyposplenism

The spleen is a lymphopoietic organ involved with the removal of senescent RBCs, encapsulated bacteria, and other particulates from the circulation. The spleen is capable of enlarging significantly in response to infection. The spleen also normally contains about one-third of the total platelet mass. Splenectomy is the most common cause of splenic dysfunction, although various clinical conditions may lead to impaired splenic function (functional asplenia). Perhaps the most common of these is sickle cell anemia, which causes autoinfarction of the spleen due to vasoocclusive disease. *Streptococcal pneumoniae* is the most common cause of bacterial sepsis in postsplenectomy patients. Splenic dysfunction also increases risk of infection with *Neisseria meningitides*, *Escherichia coli*, *Haemophilus influenzae*, and malaria. As recommended for patients with complement deficiencies, management of hyposplenic patients relies heavily on prevention, mainly through vaccination against *S. pneumoniae*, *H. influenza* b, and *N. meningitides*. Daily penicillin prophylaxis is often administered postsplenectomy to children until the age of 5.

EXCESSIVE INNATE IMMUNITY

Neutrophilia

The earliest response to an infection is the migration of leukocytes out of the circulation and into the site of bacterial invasion. The rapidity and magnitude of the increase in the number of circulating leukocytes in response to infection is remarkable. Within hours of the onset of a severe infection, the leukocyte count increases two- to fourfold. This increase represents a change in the marginated and circulating pools of leukocytes as well as the delivery of new leukocytes from the bone marrow. The most common cause of leukocytosis is neutrophilia, since 60% to 70% of circulating leukocytes are neutrophils. Neutrophilia is defined as an absolute neutrophil count greater than 7700/μL, which is typically seen in patients with leukocyte

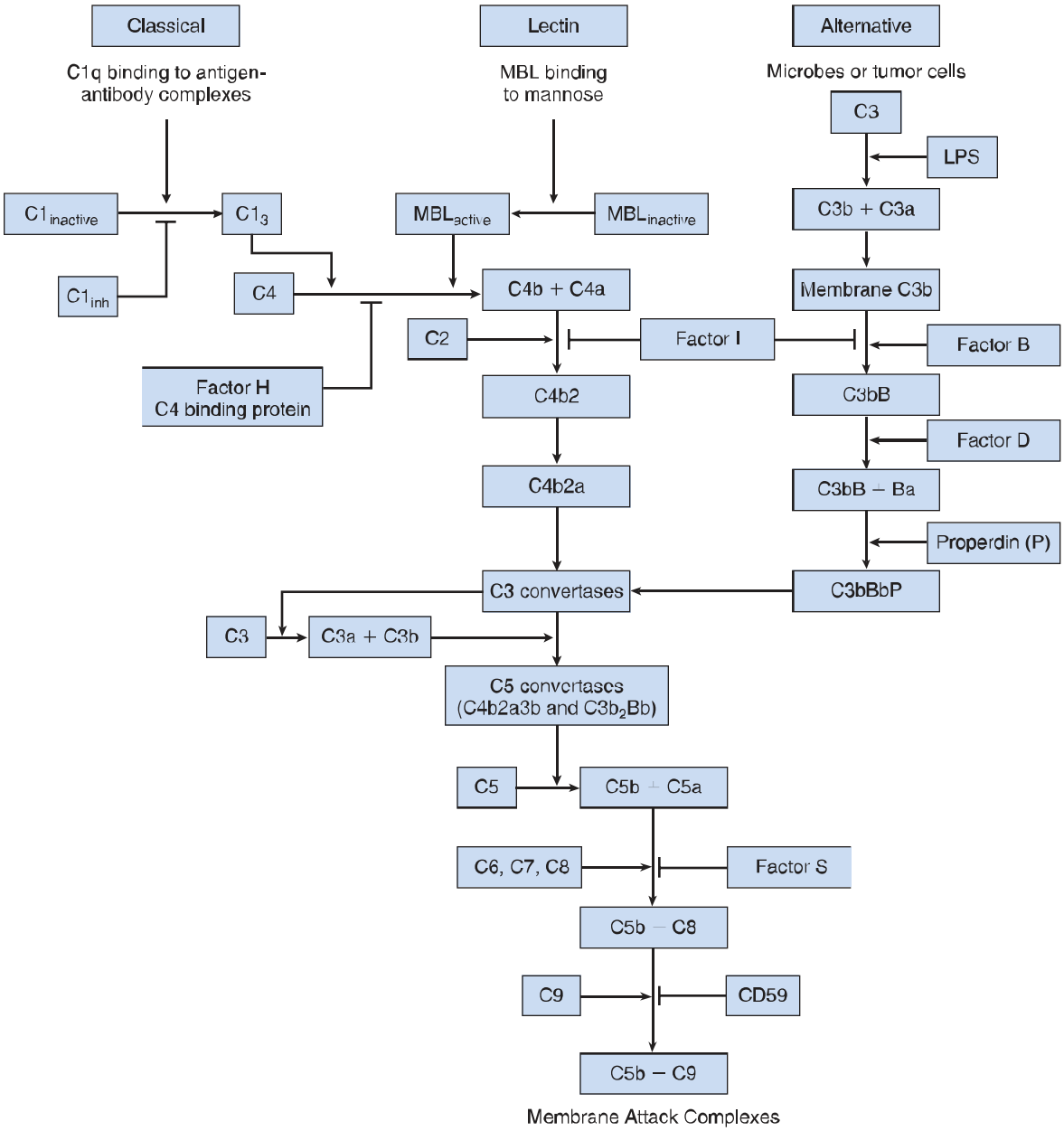

Fig. 26.2 Activation of the complement cascade. Complement activation can occur via classical and lectin pathways or by alternative pathways. In the classical pathway, binding of an antigen-antibody complex to C1q is the triggering event. In the lectin pathway, mannose residues on bacteria bind to mannose binding lectin *(MBL)*, setting off complement activation. The alternative pathway can be activated by microbes or tumor cells. All pathways lead to formation of C3, which is important in immune complex modification, opsonization, and lymphocyte activation. The terminal common pathway that flows from all three activation pathways leads to production of the membrane attack complex C5b-9, which lyses cells. *C1 inh*, C1 inhibitor; *LPS*, lipopolysaccharide.

counts greater than 11,000/μL. Major causes of neutrophilia are listed in Table 26.2.

Leukocytosis does not produce specific symptoms or signs unless the count exceeds 100,000/μL. Such marked leukocytosis can produce leukostasis resulting in infarction of the spleen and a reduction in the oxygen-diffusing capacity of the lungs. Leukocytes can also accumulate in the skin to produce nontender, purplish nodules called chloromas (also called myeloid sarcoma or leukemia cutis). Unlike immature blasts, mature granulocytes do not invade brain tissue, so neurologic complications do not result from reactive leukocytosis.

The clinical features associated with moderate leukocytosis vary depending on the primary disease underlying the condition. Deep-seated infections and peritonitis are associated with leukocyte counts of 10,000 to 30,000/μL or more. Parasitic infestations are typically associated with an elevated eosinophil count, whereas basophilia is seen in patients with chronic myelogenous leukemia. As a general rule, sustained leukocyte

TABLE 26.2 Clinical Conditions Associated With Neutrophilia

Primary
Myeloproliferative disorders
Leukemias
Down syndrome
Secondary
Infection/inflammation
Cigarette smoking
Stress
Metabolic disorders (preeclampsia, diabetic ketoacidosis, thyroid storm)
Drugs (steroids, lithium, catecholamines)
Splenectomy

counts of 50,000/μL or higher are suggestive of a noninfectious malignant disease process such as a myeloproliferative disorder. The appearance of very immature myelocytic cells in the circulation and accompanying changes in other cell lines (increased or decreased platelets or RBCs) are also signs of a hematologic malignancy.

Neutrophilia is an expected side effect of glucocorticoid therapy because glucocorticoids interfere with the egress of granulocytes from the circulation into tissues. Patients receiving a prednisone dose of 60 mg/day or higher often have WBC counts of 15,000 to 20,000/μL. Other causes of neutrophilia include physiologic stress, drugs, and cigarette smoking (see Table 26.2).

Monocytosis

Monocytosis occurs in conjunction with inflammatory disorders such as systemic lupus erythematosus, rheumatoid arthritis, and sarcoidosis and in the context of certain infections, including tuberculosis, syphilis, and subacute bacterial endocarditis. Monocytosis can also be seen in patients with primary neutropenic disorders or hematologic malignancies. Although important components of the immune system, the association between the circulating monocyte count and the propensity to infection is not as clear as in the case of neutrophils.

Asthma

Asthma is characterized by an exaggerated bronchoconstrictor response to certain stimuli (see also Chapter 2). Triggers for bronchospasm unrelated to the immune system produce intrinsic asthma. Placement of an endotracheal tube may trigger this type of asthma; other common triggers are cold, exercise, stress, or inhaled irritants. Mediators of intrinsic asthma are components of the innate immune system. By contrast, triggers that activate the immune system and release IgE produce extrinsic asthma and are part of adaptive immunity. Inhaled allergens such as pollen and pet dander are common causes of extrinsic asthma. Symptoms of extrinsic or allergic asthma are highly variable and can include cough, dyspnea, and wheezing. Treatment consists of administration of β agonists, corticosteroids, leukotriene inhibitors, and anticholinergics.

MISDIRECTED INNATE IMMUNITY

Angioedema

Angioedema may be hereditary or acquired. It is characterized by episodic, asymmetric subcutaneous, and submucosal edema formation, often involving the face, extremities, and gastrointestinal tract, that occurs rapidly and often resolves spontaneously. Two types of angioedema are recognized. One is caused by release of mast cell mediators and is associated with urticaria, bronchospasm, flushing, and even hypotension. The other results from bradykinin release and does not cause allergic symptoms. The most common hereditary form of angioedema results from an autosomal dominant deficiency or dysfunction of C1 esterase inhibitor. This serine protease inhibitor (serpin) regulates complement, contact activation, and fibrinolytic pathways. The absence of C1 esterase inhibitor leads to a release of vasoactive mediators that increase vascular permeability and produce edema via bradykinin. Patients deficient in this regulatory enzyme experience repeated bouts of facial and/or laryngeal edema lasting 24 to 72 hours. These attacks usually begin in the second decade of life and may be triggered by menses, trauma, infection, stress, or estrogen-containing oral contraceptives. Dental surgery can be an important trigger of laryngeal attacks. Abdominal attacks usually present with excruciating pain, nausea, vomiting, and/or diarrhea. The diagnosis of C1 esterase inhibitor deficiency is suggested by a low C4 level.

C1 esterase inhibitor deficiency can be acquired by patients with lymphoproliferative disorders. These patients have antibodies to C1 inhibitor, and this gives rise to a syndrome that closely mimics hereditary angioedema. Angiotensin-converting enzyme (ACE) inhibitors used for the treatment of hypertension and heart failure can also precipitate angioedema in about 0.2% of patients. This drug-induced angioedema is thought to result from increased availability of bradykinin made possible by the ACE inhibitor–mediated blockade of bradykinin catabolism. Interestingly, angioedema provoked by ACE inhibitors may develop unexpectedly after prolonged drug use. It is more commonly seen in Blacks, females, patients with a history of allergies, and smokers. Other drugs implicated in the development of angioedema include nonsteroidal antiinflammatory drugs (NSAIDs) and estrogens.

Treatment of angioedema depends on the suspected mechanism. Mast cell–mediated angioedema is treated with drugs typically used to treat allergy and anaphylaxis, including epinephrine, antihistamines, and glucocorticoids. For bradykinin-mediated angioedema, the preferred treatment for an acute attack is C1 inhibitor concentrate, a kallikrein inhibitor, or a bradykinin-receptor antagonist. Fresh frozen plasma has in the past been administered to replace the deficient enzyme, but this approach should only be employed if other alternatives are not available. For ACE inhibitor–induced angioedema, treatment is to stop the offending drug and administer supportive care. Glucocorticoids have been shown to increase the expression of ACE, which may accelerate bradykinin metabolism. C1 inhibitor concentrate, kallikrein, or a bradykinin-receptor antagonist have been used with variable results. Should upper airway

obstruction develop during acute attacks, tracheal intubation may be lifesaving until the edema subsides. When performing laryngoscopy, it is important to have personnel and equipment available to perform tracheostomy if needed, but tracheostomy itself may be extremely difficult or impossible in the face of massive airway edema.

Management of Anesthesia

Patients experiencing recurrent angioedema, whether hereditary or acquired, require prophylaxis before a stimulating procedure such as dental surgery or any surgery requiring endotracheal intubation. It is prudent to ensure the ready availability of C1 inhibitor concentrate for intravenous infusion should an acute attack occur. In the past, androgens and transexamic acid have been used to prevent attacks of angioedema, but these drugs are used less frequently now, owing to the availability of more specific and effective therapies. Incidental trauma to the oropharynx, such as that produced by suctioning, should be minimized. Regional anesthetic techniques and intramuscular injections are well tolerated.

INADEQUATE ADAPTIVE IMMUNITY

Defects of Antibody Production

Antibody disorders are the most common type of primary immunodeficiency disease. X-linked agammaglobulinemia is an inherited defect in the maturation of B cells. Mature B cells are missing or reduced in the circulation, and lymphoid tissues have no plasma cells; therefore functional antibody is not produced. Affected boys have recurrent pyogenic infections during the latter half of their first year of life as maternal antibodies wane. Therapy with intravenous immunoglobulin every 3 to 4 months to maintain plasma IgG levels near 500 mg/dL allows most of these children to survive into adulthood.

Selective IgA deficiency occurs in 1 of every 600 to 800 adults, making it the most common B-cell disorder in the United States. With this condition, plasma IgA concentrations are less than 5 mg/dL, but the concentrations of other immunoglobulins are normal. Recurrent sinus and pulmonary infections are common, although many patients remain asymptomatic. Some patients with IgA deficiency produce IgA antibodies. This subset of patients may experience life-threatening anaphylaxis when transfused with blood products containing IgA. Therefore these patients should receive blood or blood components that have been washed to remove as much IgA as possible or that come from IgA-deficient donors.

Waldenström macroglobulinemia is due to proliferation of a malignant plasma cell clone that secretes IgM, resulting in marked increases in plasma viscosity. The bone marrow is infiltrated with malignant lymphocytes, as are the liver, spleen, and lungs. Anemia and an increased incidence of spontaneous hemorrhage are common findings in these patients. In contrast to multiple myeloma, Waldenström macroglobulinemia rarely involves the skeletal system. As a result, renal dysfunction due to hypercalcemia is uncommon. Treatment consists of plasmapheresis to remove the abnormal proteins and reduce plasma viscosity. Chemotherapy may be instituted in attempts to decrease proliferation of the cells responsible for production of the abnormal immunoglobulins.

Cold autoimmune diseases are characterized by the presence of abnormal circulating proteins (usually IgM or IgA antibodies) that agglutinate in response to a decrease in body temperature. They include cryoglobulinemia and cold hemagglutinin disease. Hyperviscosity of the plasma is prominent, and microvascular thrombosis may cause acute end-organ damage during a period of hypothermia. Symptoms normally do not occur until body temperature falls below 33°C. Management of anesthesia in these patients includes strict maintenance of normothermia. Patients scheduled for surgery requiring cardiopulmonary bypass present significant challenges. Use of systemic hypothermia may be contraindicated, and cold cardioplegia solutions may precipitate intracoronary hemagglutination with consequent thrombosis, ischemia, or infarction. Alternatives to cold cardioplegia include fibrillatory arrest for brief time periods. Plasmapheresis may also be helpful for reducing plasma concentrations of immunoglobulins.

Amyloidosis encompasses several disorders characterized by the accumulation of insoluble fibrillar proteins (amyloid) in various tissues, including the heart, vascular smooth muscle, kidneys, adrenal glands, gastrointestinal tract, peripheral nerves, and skin. Primary amyloidosis is a plasma cell disorder marked by the accumulation of immunoglobulin light chains. Secondary amyloidosis is observed in association with several other conditions, including multiple myeloma, rheumatoid arthritis, and a prolonged antigenic challenge such as may be produced by chronic infection.

Macroglossia is a classic feature of patients with amyloidosis, occurring in about 20% of patients. The enlarged, stiff tongue may impair swallowing and speaking; involvement of the salivary glands and adjacent tissue may cause upper airway obstruction that mimics angioedema. Cardiac involvement is fairly common and may cause intraventricular conduction delays, including heart block. Sudden death is not uncommon. Cardiac dysfunction classically involves right heart failure, with relative sparing of left heart function until late in the disease. Accumulation of amyloid in the kidneys may produce nephrotic syndrome. Deposition in joint spaces may lead to limited range of motion as well as peripheral nerve entrapments such as carpal tunnel syndrome. Amyloidosis of the gastrointestinal tract may lead to malabsorption, ileus, and impaired gastric emptying. Hepatomegaly is common, although hepatic dysfunction is rare. The diagnosis is based on clinical suspicion with confirmatory tissue biopsy. Potential sites for biopsy include subcutaneous fat or rectal mucosa.

Treatment of amyloidosis is generally directed toward symptomatic improvement rather than cure; however, in hereditary forms of amyloidosis in which the amyloid protein is produced by the liver, liver transplantation may be considered to prevent further amyloid deposition. Biologic agents, such as those used for diseases like rheumatoid arthritis, may occasionally be helpful also. Airway management in patients with amyloidosis may be challenging due to an enlarged tongue. Perioperative management of these patients requires careful preoperative evaluation for signs of end-organ dysfunction such as renal insufficiency

and heart failure or conduction defects. Gastric motility drugs may be useful in some patients. Of note, amyloid deposits have the potential to trap factor X or evoke fibrinolysis, predisposing these patients to hemorrhagic complications.

Defects of T Lymphocytes

DiGeorge syndrome (thymic hypoplasia) is the result of a gene deletion. Features include absent or diminished thymus development, hypoplasia of the thyroid and parathyroid glands, cardiac malformations, and facial dysmorphisms. The degree of immunocompromise correlates with the amount of thymic tissue present. Complete absence of the thymus produces a severe combined immunodeficiency syndrome-like phenotype with associated bacterial, fungal, and parasitic infections. Complete DiGeorge syndrome is treated by thymus transplantation or infusion of mature T cells. Partial DiGeorge syndrome requires no therapy.

Combined Immune System Defects

Severe combined immunodeficiency syndromes are caused by a number of genetic mutations that affect T-, B-, or NK-cell functions. The most common form of severe combined immunodeficiency syndrome is the X-linked form, which has a prevalence of approximately 1 in 58,000 live births. The disease is caused by a defect in a receptor that modulates lymphocyte responses to interleukins. In some cases, the molecular defect results in only T-cell deficiency; however, since B-cell development requires signals from T cells, B-cell and immunoglobulin levels are often low as well. The only treatment that substantially prolongs life expectancy is bone marrow or stem cell transplantation from a human leukocyte antigen (HLA)–compatible donor.

Adenosine deaminase deficiency (ADA) is another form of severe combined immunodeficiency syndrome, accounting for approximately 10% to 15% of cases. The adenosine deaminase enzyme is most abundant in lymphocytes, and deficiency allows for accumulation of toxic levels of purine intermediates leading to T-cell death. Patients with ADA deficiency typically have severely reduced numbers of T, B, and NK cells. Other physical examination findings include absence of palpable lymph nodes and skeletal abnormalities of the ribs. Enzyme replacement with bovine adenosine deaminase enzyme is advised as immediate treatment. Normal ADA gene expression can be achieved via gene therapy. Hematopoietic cell transplantation is an alternative to gene therapy.

Ataxia telangiectasia is a syndrome consisting of cerebellar ataxia, oculocutaneous telangiectasias, chronic sinopulmonary disease, and immunodeficiency. The genetic basis of this disorder is a gene mutation in the surveillance system that monitors DNA for double-strand breaks. With this syndrome, DNA damage that occurs during cell division is missed, and defective cells are released into the circulation. One consequence of this defect is the production of dysfunctional lymphocytes. Progressive pulmonary disease, including recurrent infections, bronchiectasis, and interstitial fibrosis, is a significant cause of morbidity and mortality. Approximately 10% to 25% of these patients will eventually develop a malignancy, especially leukemia or lymphoma. Ataxia telangiectasia patients are so susceptible to radiation-induced injury that bone marrow transplantation is not possible. Supportive therapy includes intravenous immunoglobulin administration.

EXCESSIVE ADAPTIVE IMMUNITY

Allergic Reactions

Immune-mediated allergic reactions are classified according to their mechanism. Type I allergic reactions are IgE-mediated and involve mast cells and basophils. Most cases of anaphylaxis are IgE-mediated events. Type II reactions are rare. They typically arise when drugs bind to surfaces of certain cell types and act as antigens. Subsequent binding of antibodies (usually IgG) causes these cells to be cleared by macrophages. Type II reactions usually manifest as hemolytic anemia, thrombocytopenia, or neutropenia. Clinical presentation and severity vary widely; interestingly, symptoms often appear several days after the initiating drug exposure. Type III reactions produce tissue damage via immune complex formation or deposition. Glomerulonephritis, urticaria, vasculitis, and arthralgias are common presenting symptoms. Type IV reactions are marked by T-lymphocyte–mediated delayed hypersensitivity. Cutaneous symptoms are the most common physical manifestation. Clinical severity ranges from simple contact dermatitis to Stevens-Johnson syndrome and toxic epidermal necrolysis. These severe exfoliative dermatitides can be life-threatening. Drug-induced hypersensitivity syndrome (DRIS) and drug rash with eosinophilia and systemic symptoms (DRESS) are other severe forms of drug hypersensitivity marked by eosinophilia, rash, fever, and multiorgan system failure. Patients with certain viral infections, such as Epstein-Barr virus or cytomegalovirus, experience an increased incidence of some type IV drug reactions.

Not all drug allergies are mediated by the immune system. Nonimmune anaphylaxis (formerly called "anaphylactoid" reactions) occurs when mediators are released from mast cells and basophils as a result of direct interaction with the offending drug rather than immune system activation.

Anaphylaxis

Anaphylaxis is a life-threatening condition marked by cardiovascular collapse, interstitial edema, and bronchospasm. Anaphylaxis may occur by immune-mediated or nonimmune-mediated mechanisms. The most common immune-mediated cause of anaphylaxis results when previous exposure to antigens in drugs or foods evokes production of antigen-specific IgE antibodies. Subsequent exposure to the same or a chemically similar antigen results in antigen-antibody interactions that initiate marked degranulation of mast cells and basophils. Approximately 60% of anaphylactic reactions are mediated by IgE antibodies. Less commonly, IgG or IgM antibody reactions are to blame. Nonimmune-mediated anaphylaxis results from direct release of histamine and other mediators from mast cells and basophils.

Patients with a history of allergy (extrinsic asthma, allergy to tropical fruits or drugs) have an increased incidence of anaphylaxis, possibly related to a genetic predisposition to form

TABLE 26.3 Vasoactive Mediators Released During Anaphylaxis

Mediator	Physiologic Effect
Histamine	Increased capillary permeability Peripheral vasodilation Bronchoconstriction Urticaria
Leukotrienes	Increased capillary permeability Bronchoconstriction Negative inotropy Coronary artery vasoconstriction
Prostaglandins	Bronchoconstriction
Eosinophil chemotactic factor	Attraction of eosinophils
Neutrophil chemotactic factor	Attraction of neutrophils
Platelet-activating factor	Platelet aggregation Release of vasoactive amines

increased amounts of IgE antibodies. Patients allergic to penicillin have a three- to fourfold greater risk of experiencing an allergic reaction to any drug.

Initial manifestations of anaphylaxis usually occur within 5 to 10 minutes of exposure to the antigen. In about 10% to 20% of cases, symptoms return an hour or so after initial symptoms appear. Vasoactive mediators released by degranulation of mast cells and basophils are responsible for the clinical manifestations of anaphylaxis (Table 26.3). Urticaria and pruritus are common. Primary vascular collapse occurs in approximately 25% of cases of fatal anaphylaxis. Laryngeal edema, bronchospasm, and arterial hypoxemia may accompany anaphylaxis. Extravasation of up to 50% of intravascular fluid into the extracellular space reflects the extent of microvascular permeability that can accompany anaphylaxis. Indeed, hypovolemia is a likely cause of hypotension in these patients, although leukotriene-mediated negative inotropism may also be a factor.

The estimated incidence of all immune- and nonimmune-mediated cases of anaphylaxis during anesthesia is purported to be between 1 in 3500 and 1 in 20,000 anesthetics. The wide variability reflects the difficulty in determining the denominator (total number of anesthetic cases) as well as inconsistencies in event reporting. Estimated mortality from perioperative anaphylaxis has previously been quoted to be as high as 9%, but more recent data suggest the actual mortality may be significantly lower (<1%). Risk factors include asthma, greater duration of anesthesia, female sex (especially for neuromuscular blocking drugs and hypnotic induction drugs), multiple past surgeries or procedures (especially for latex and ethylene dioxide), and the presence of other allergic conditions or systemic mastocytosis.

Diagnosis

The diagnosis of anaphylaxis is suggested by the dramatic nature of the clinical manifestations in close temporal relationship to exposure to a particular antigen. Cardiovascular, respiratory, and cutaneous manifestations are most common. Typical signs include tachycardia, bronchospasm, and laryngeal edema. Recognition of an allergic reaction that occurs during anesthesia may be compromised by inability of the patient to communicate early symptoms such as urticaria. Coverage of the patient by surgical drapes may obscure recognition of cutaneous signs. Consequently, cardiovascular collapse may be the first detectable signal of the event.

Immunologic and biochemical evidence of anaphylaxis is provided by an increased plasma tryptase concentration within 1 to 2 hours of the suspected event. Tryptase, a neutral protease stored in mast cells, is liberated into the systemic circulation during immune-mediated but not nonimmune-mediated reactions. Its presence verifies that mast cell activation and mediator release have occurred, and thus it serves to distinguish immunologic from chemical reactions. Although plasma histamine concentration peaks immediately after an anaphylactic episode, it returns to baseline within 30 to 60 minutes of an anaphylactic reaction, so unless measured at the onset of symptoms a change in plasma histamine concentration may not be observed.

In cases of IgE-mediated anaphylaxis, identification of the offending agent can be established by a positive skin prick or intradermal test (wheal and flare response), which confirms the presence of specific IgE antibodies. Skin testing should not be performed within 6 weeks of an anaphylactic reaction because mast cell and basophil mediator depletion may result in a false-negative result. Because of the risk of inducing a systemic reaction, testing must be done with a dilute, preservative-free solution of suspected antigen and only by trained personnel with appropriate resuscitative equipment available. In vitro immunoassays for allergen-specific IgE are commercially available for some agents. This type of testing is most commonly used in the evaluation of potential reactions to neuromuscular blockers, latex, penicillin, and other β-lactam antibiotics. Skin testing remains the more sensitive and preferred method of testing in most cases.

Treatment

The immediate goals of anaphylaxis treatment are reversal of hypotension and hypoxemia, replacement of intravascular volume, and inhibition of further cellular degranulation and release of vasoactive mediators (Table 26.4). The patient should be placed supine with lower extremities elevated. Intubation should be performed, if there is stridor, respiratory arrest, or evidence of edema of the tongue or oropharyngeal tissues. Two large-bore intravenous catheters should be inserted if not already present. Several liters of crystalloid and/or colloid solution must be infused to restore intravascular fluid volume and blood pressure. Early intervention with epinephrine is critical for reversing the life-threatening events characteristic of anaphylaxis. Epinephrine, by increasing intracellular concentrations of cyclic adenosine monophosphate (cAMP), restores membrane permeability and decreases the release of vasoactive mediators. The β-agonist effects of epinephrine relax bronchial smooth muscle and reverse bronchospasm. The preferred method of epinephrine administration in the setting of anaphylaxis is intramuscular (IM) because the onset of action is faster than by subcutaneous injection, and the frequency of adverse cardiovascular reactions and errors in dosing is less

TABLE 26.4 Management of Anaphylactic Reactions During Anesthesia

Primary Treatment

General Measures

Inform the surgeon
Request immediate assistance
Cease administration of all drugs, colloids, blood products, and latex (if suspected)
Maintain airway with 100% oxygen and intubate if signs of impending airway obstruction are present
Elevate the legs, if practical

Epinephrine

Titrate dose according to symptom severity and clinical response
Adults: 0.3–0.5 mg IM, preferably in the mid-outer thigh; can repeat every 5–15 min, as needed; IV infusion starting at 0.05–1 μg/kg/min, titrated to effect
Children: 0.01 mg/kg IM, preferably in the mid-outer thigh; maximum dose 0.5 mg; can repeat every 5–15 min; IV infusion starting at 0.05–1 μg/kg/min, titrated to effect

Fluid therapy

Crystalloid: 10–25 mL/kg IV over 20 min, more as needed

Anaphylaxis resistant to epinephrine

Glucagon: 1–5 mg IV, followed by 2–10 μg/min infusion
Norepinephrine: 0.05–0.1 μg/kg/min IV
Vasopressin: 2–10 units IV followed by continuous infusion 0.03 unit/min
Methylene blue: 1–2 mg/kg IV one-time dose

Secondary Treatment

Bronchodilator

β_2 agonist (inhaled or IV) for symptomatic treatment of bronchospasm

Antihistamines

H_1 antagonist: diphenhydramine 15–50 mg IV (adults) or 1–2 mg/kg IV (children)
H_2 antagonist: ranitidine 50 mg IV (adults) or 1 mg/kg IV (children)

Corticosteroids

Adults: hydrocortisone 250 mg IV or methylprednisolone 80–125 mg IV
Children: hydrocortisone 50–100 mg IV or methylprednisolone 1 mg/kg IV (max 125 mg)

Aftercare

Patient may relapse, admit for observation
Obtain blood samples for diagnostic testing (e.g., serum or plasma total tryptase, plasma histamine)
Arrange allergy testing at 6–8 weeks postoperatively

IM, Intramuscular; *IV*, intravenous.
Data from Mertes PM, Tajima K, Regnier-Kimmoun MA, et al. Perioperative anaphylaxis. *Med Clin North Am.* 2010;94(4):780, table 6.

than with intravascular (IV) administration. The recommended IM epinephrine dose is 0.01 mg/kg (maximum dose of 0.5 mg) injected into the vastus lateralis muscle. IM doses of epinephrine may be repeated every 5 to 15 minutes. If given IV, epinephrine should be administered slowly in doses of 0.05 to 0.1 mg. An epinephrine infusion should be initiated in any patient who does not respond to bolus doses. The infusion is typically started at 0.1 μg/kg/min and titrated to blood pressure. In cases where cardiovascular collapse is unresponsive to epinephrine, the use of alternative vasopressors such as vasopressin, glucagon, and methylene blue should be considered. Extracorporeal membrane oxygenation (ECMO) has also been used to resuscitate patients with medication-refractory anaphylaxis.

Antihistamines such as diphenhydramine and ranitidine compete with membrane receptor sites normally occupied by histamine and may decrease some manifestations of anaphylaxis such as pruritus, hives, and bronchospasm. However, antihistamines are not effective in treating anaphylaxis once vasoactive mediators have been released and do not relieve airway edema or hypotension. β_2 agonists such as albuterol delivered by metered-dose inhaler or nebulization are useful for the treatment of bronchospasm associated with anaphylaxis.

Corticosteroids are often administered to patients experiencing life-threatening anaphylaxis, although randomized trials have not confirmed their effectiveness. The favorable impact subjectively observed with corticosteroid therapy may reflect enhancement of the β-agonist effects of other drugs and inhibition of the release of arachidonic acid, which is responsible for the production of leukotrienes and prostaglandins. Corticosteroids may be uniquely helpful in patients experiencing life-threatening allergic reactions due to activation of the complement system.

Drug Allergy

Background

A drug allergy is an adverse drug reaction caused by an immunologic response. Allergic drug reactions must be distinguished from drug intolerance, idiosyncratic reactions, and drug toxicity. The occurrence of undesirable pharmacologic effects at a low dose of drug reflects intolerance, whereas idiosyncratic reactions are undesirable responses to a drug independent of the dose administered. Evidence of histamine release along veins into which drugs are injected reflects localized and nonimmunologic release of histamine insufficient to evoke systemic symptoms. Patients manifesting this localized response should not be diagnosed as allergic to a drug.

Allergic Drug Reactions During the Perioperative Period

The most common identifiable causes of perioperative drug allergy are antibiotics and neuromuscular-blocking agents (NMBAs). The etiology of perioperative drug allergy differs by geographic location; in the United States the most common cause is antibiotics, while in Europe the most common cause is NMBAs. Most drug-induced allergic reactions manifest within 5 to 10 minutes of exposure. An important exception is the allergic response to latex, which is typically delayed for as long as 30 minutes. When signs of allergy appear during maintenance of anesthesia, attention should be directed to the possibility of allergy to latex, volume expanders, antiseptics, or dyes (Table 26.5).

Antibiotics. Antibiotics are a leading cause of anaphylaxis in the perioperative period, accounting for approximately 20% to 50% of all episodes. Penicillin allergy is most common, and in the general population, penicillin accounts for most fatal anaphylactic drug reactions. Approximately 10% of patients report

TABLE 26-5 Perioperative Allergic Drug Reactions

Drug	Estimated Percent of Perioperative Allergic Reactions	Comments
Muscle relaxants	15–70%	Most common cause of perioperative allergic reactions in Europe Frequent cross sensitization between drugs, mainly due to quaternary and tertiary ammonium ions
Antibiotics: β-lactam drugs, quinolones, sulfonamides, vancomycin	20–50%	Most common cause of perioperative allergic reactions in the United States <2% cross reactivity between penicillins and cephalosporins
Latex	<15%	Commonly occurs as a delayed clinical reaction Decreasing in prevalence due to increased use of latex-free products
Chlorhexidine	5–10%	Sensitization may occur from household products such as mouthwash, toothpaste, and disinfectant solutions
Hypnotics: barbiturates, propofol	<3%	
Synthetic colloids: dextran, hydroxyethyl starch	<3%	
Opioids: morphine, codeine, fentanyl	<3%	
Radiocontrast media	<2%	
Protamine, aprotinin	<2%	
Blood and blood products	<2%	
Local anesthetics	<2%	More commonly caused by ester vs amide local anesthetics

Data from Galvão VR, Giavina-Bianchi P, Castells M. Perioperative anaphylaxis. *Curr Allergy Asthma Rep.* 2014;14(8):452, table 1.

a penicillin allergy; however, it has been estimated that up to 90% of these patients are in fact able to tolerate penicillin. This is in part due to initial misattribution of clinical signs to a penicillin reaction rather than to the underlying medical illness being treated. In addition, IgE antibodies to penicillin wane over time; therefore many patients diagnosed as penicillin-allergic in childhood are able to tolerate penicillin as adults. Elective skin testing should be considered for any patient with a convincing history of Ig-mediated penicillin allergy to avoid inappropriate avoidance of β-lactam antibiotics and unnecessary use of more expensive and broad-spectrum antibiotics. The negative predictive value of penicillin skin testing is high (i.e., a negative skin test to penicillin reliably indicates that the patient is not allergic to penicillin). Patients with a positive skin test are candidates for drug desensitization. The structural similarity between penicillin and cephalosporins (both contain β-lactam rings) suggests the possibility of cross sensitivity. However, the incidence of life-threatening allergic reactions following administration of cephalosporins is low (0.05%). Historically the incidence of allergic reaction to cephalosporins in patients with a history of penicillin allergy was reported to be in the range of 7% to 8%. More recent research suggests a much lower rate of cross reactivity (<2%). Cross reactivity is highest in patients reporting an allergy to amoxicillin who are given first-generation cephalosporins or cefamandole; it is lower if later generation cephalosporins are administered. Carbapenems also share a common β-lactam ring with penicillins and hence carry the potential for allergic cross reactivity. However, less than 1% of penicillin-allergic patients will develop an allergic reaction to a carbapenem.

Sulfonamide antibiotics are the second most commonly reported antibiotic allergy. These reactions manifest most often as delayed cutaneous rashes, and sulfonamides are the most common cause of Stevens-Johnson syndrome. In HIV-positive patients, the incidence of skin rash to sulfonamides is approximately 10 times that of HIV-negative patients. Because trimethoprim-sulfamethoxazole is the drug of choice for the treatment and prophylaxis of *Pneumocystis carinii* pneumonia in HIV-positive patients, induction of drug tolerance is advised. This is accomplished via the administration of escalating challenge doses to the allergic patient.

Most purported cases of vancomycin allergy are non-IgE-mediated reactions, involving direct histamine release from mast cells and basophils and are directly related to the rate of drug infusion. In most cases these patients are able to tolerate repeat administration utilizing slower infusion rates and antihistamine premedication. However, rare IgE-mediated allergy has been reported on repeat exposure to this drug.

NMDAs are responsible for 15% to 70% of drug-induced allergic reactions during the perioperative period. Among muscle relaxants, succinylcholine is the drug most commonly implicated. Cross-sensitivity among muscle relaxants emphasizes the structural similarities among these agents. Approximately half of patients who experience an allergic reaction to one muscle relaxant are also allergic to other muscle relaxants. IgE antibodies develop to quaternary or tertiary ammonium ions. Many over-the-counter drugs and cosmetics contain these ammonium ions and may sensitize patients. This is perhaps why up to 75% of reactions to NMDAs occur on first exposure. This may also explain why allergy to NMDAs is more common in women than men. Neostigmine and morphine contain ammonium ions that are also capable of cross-reacting with antibodies to NMDAs. Recently, some controversy has arisen concerning a potential increased prevalence of allergic reactions to rocuronium. However, this apparent increase may be due to other factors, including biased reporting. Antibodies that develop

against NMDAs remain present for decades. Therefore a patient with a history of anaphylaxis to any NMDA should be skin tested preoperatively for all drugs that are likely to be used in future anesthetics; ideally an alternative agent to which the patient has been skin tested and found to be negative should be utilized. Avoidance is preferred if an alternative means of providing anesthesia is available. Desensitization is theoretically possible but not practical given that it would require prolonged exposure to a paralytic agent.

Nonimmune reactions to NMDAs include direct mast cell degranulation that causes release of histamine and other mediators. Benzylisoquinolinium compounds such as d-tubocurarine, metocurine, atracurium, and mivacurium are more likely to cause direct mast cell degranulation than aminosteroid compounds such as pancuronium, vecuronium, and rocuronium. Skin testing has no utility in the investigation of nonimmune-mediated allergic reactions. Reactions that are not IgE mediated may be reduced in frequency or intensity by pretreatment with antihistamines and glucocorticoids.

Sugammadex. Sugammadex is a charged cyclodextrin that encapsulates and inactivates steroidal NMDAs. Since its introduction in 2008 it has been estimated that allergic and anaphylactic reactions occur in 1 in 3500 to 1 in 64,000 exposures. It is unknown whether allergic reactions to sugammadex are IgE- or non-IgE-mediated events.

It has been suggested that administration of sugammadex might be effective in the treatment of rocuronium-induced anaphylaxis. The proposed mechanism is that sugammadex encapsulates rocuronium and may thereby limit further mediator release from mast cells and basophils. However, clinical studies have not found a definitive benefit to sugammadex administration in the treatment of anaphylaxis.

Induction drugs. Approximately 2% of perioperative anaphylactic events are caused by hypnotic induction agents and more commonly by barbiturates than nonbarbiturates. Most reported cases of barbiturate allergy have occurred in patients with a history of previous uneventful exposure to a barbiturate. Cross reactivity among barbiturates is possible, but there is no evidence of cross reactivity between the barbiturate and nonbarbiturate agents. In the past, propofol was solubilized in a castor oil preparation that was associated with non-IgE-mediated anaphylactic reasons. Propofol is now prepared in a soybean oil emulsion with egg byproducts. Allergic reactions to this preparation of propofol are extremely rare, even in patients with known egg or soybean allergies. Allergic reactions to midazolam, etomidate, or ketamine are extremely rare.

Local anesthetics. True allergy to local anesthetics is rare, despite the common labeling of patients as allergic to drugs in this class. It is estimated that only about 1% of purported allergic reactions to local anesthetics are in fact truly allergic; the remainder represent adverse but known responses to inadvertent intravascular injection (hypotension and seizure) or systemic absorption of epinephrine added to local anesthetic (hypertension and tachycardia). Careful history and review of past medical records are most useful in discerning the true mechanism responsible for the event. Urticaria, laryngeal edema, and bronchoconstriction suggest a true allergic response.

Ester-type local anesthetics more commonly cause allergic reactions compared to amide-type anesthetics. Ester-type local anesthetics produce metabolites to compounds related to para-aminobenzoic acid, which is a highly antigenic compound. Preservatives used in local anesthetic solutions such as methylparaben, propylparaben, and metabisulfite also produce allergic reactions. As a result, anaphylaxis actually may be due to stimulation of antibody production to the preservative rather than to the local anesthetic itself.

It is not uncommon to be presented with the question of whether it is safe to administer a local anesthetic to a patient with a purported history of allergy to this class of drugs. It is generally agreed that cross sensitivity does not exist between ester- and amide-type compounds. The use of only preservative-free local anesthetic solutions is recommended, since preservatives may incite allergic reactions. It is reasonable to recommend intradermal testing with preservative-free local anesthetic in the occasional patient with a convincing allergic history in whom failure to document a safe local anesthetic drug would prevent the use of local or regional anesthesia when clinically indicated.

Opioids. Allergic reactions to opioids are very rare, perhaps reflecting the similarity of these drugs to naturally occurring endorphins. Certain opioids, including morphine, codeine, and meperidine, may directly evoke the release of histamine from mast cells and basophils, thus mimicking an allergic response. These reactions are usually limited to cutaneous manifestations such as pruritus and urticaria, consistent with the fact that opioid receptors are found on dermal mast cells but not on mast cells from any other organs. Fentanyl is unique among narcotics in that it lacks the ability to stimulate mast cell degranulation, making it a good option for patients with cutaneous reactions to other narcotics.

NSAIDs and aspirin. Pseudoallergic reactions after administration of NSAIDs and aspirin are well documented. Patients with a history of asthma, hyperplastic sinusitis, and nasal polyps are at increased risk of experiencing these reactions. Common symptoms include rhinorrhea and bronchospasm; airway compromise and severe angioedema may also occur. For the most part, these reactions are attributable to inhibition of the cyclooxygenase-1 (COX-1) enzyme, which promotes the synthesis of leukotrienes and the subsequent release of mediators from basophils and mast cells; this is substantiated by the fact the allergic reactions are far less severe when selective COX-2 inhibitors are employed.

Volatile anesthetics. Clinical manifestations of halothane-induced hepatitis suggest a drug-induced allergic reaction. These include eosinophilia, fever, rash, and previous exposure to halothane. The plasma of patients with a clinical diagnosis of halothane hepatitis may contain antibodies that react with halothane-induced liver antigens (neoantigens). These neoantigens are formed by the covalent interaction of reactive oxidative trifluoroacetyl halide metabolites with hepatic microsomal proteins. Acetylation of liver proteins changes them from self to nonself, resulting in the formation of antibodies against these now foreign proteins. It is postulated that subsequent antigen-antibody interactions are responsible for the liver injury associated with

halothane hepatitis. Similar oxidative halide metabolites are produced after exposure to enflurane, isoflurane, and desflurane, indicating the possibility of cross sensitivity to volatile anesthetics in susceptible patients. Based on the degree of metabolism of these volatile anesthetics, it is predictable that the incidence of anesthetic-induced allergic hepatitis would be greatest after halothane, intermediate with enflurane, minimal with isoflurane, and remote with desflurane. Unlike the other volatile agents, sevoflurane does not produce these oxidative halide metabolites.

Radiocontrast media. Contrast media injected intravenously for radiographic studies evoke allergic reactions in approximately 3% of patients. The risk of an allergic reaction is increased in patients with a history of asthma or allergies to other drugs or foods. However, the pathogenesis of allergy to contrast material is unrelated to that of seafood allergy, which is attributed to high concentrations of iodine. Most reactions to contrast material appear to be nonimmune mediated. In patients with a history of contrast allergy, pretreatment with corticosteroids and histamine antagonists is often advised. A common regimen is oral prednisone 50 mg administered at hours 13, 7, and 1 before exposure and diphenhydramine 50 mg 1 hour prior to contrast administration. Allergic reaction is most common with the use of ionic contrast agents; use of nonionic agents substantially reduces the incidence of allergic reaction.

Though rare, severe progressive nephrogenic fibrosis has been reported in patients exposed to gadolinium-based contrast agents. An immunologic reaction to gadolinium chelates appears to be involved; delayed gadolinium excretion due to preexisting renal failure is an important predisposing factor.

Latex. Latex is a saplike substance produced by the commercial rubber tree *Hevea brasiliensis*. Several different *Hevea* proteins may cause an IgE-mediated antibody response that can lead to cardiovascular collapse during anesthesia and surgery. A feature that distinguishes latex-induced allergic reactions from other drug-induced allergic reactions is its delayed onset, typically longer than 30 minutes after exposure to the latex. This may be the result of the time needed for the responsible antigen to be eluted from rubber gloves and absorbed across mucous membranes into the systemic circulation in amounts sufficient to cause an allergic reaction. Contact with latex at mucosal surfaces is the most significant route of latex exposure. However, inhalation of latex antigens is an alternative route. Cornstarch powder in gloves is not immunogenic but can act as an airborne vehicle for latex antigens.

Sensitized patients develop IgE antibodies directed specifically against latex antigens. Skin testing can confirm latex hypersensitivity, but anaphylaxis has occurred during skin testing, so this test must be performed with great caution. A radioallergosorbent test and an enzyme-linked immunosorbent assay are available for the in vitro detection of latex-specific IgE antibodies. These tests are virtually equal in sensitivity and specificity and avoid the risk of anaphylaxis associated with skin testing.

Questions about itching, conjunctivitis, rhinitis, rash, or wheezing after inflating balloons or wearing latex gloves or following dental or gynecologic examinations involving latex gloves may be helpful in identifying sensitized patients. Operating room personnel and patients with spina bifida have an increased incidence of latex allergy that is thought to reflect frequent exposure to latex devices such as bladder catheters and protective outerwear. The incidence of latex sensitivity in anesthesiologists may exceed 15%, but many of these cases are asymptomatic. Latex sensitivity most often manifests as contact dermatitis or bronchospasm due to inhalation of latex allergens. The frequency of latex allergy peaked in the 1990s and has declined since then. Factors responsible for this trend may include the widespread adoption of universal precautions in the 1990s, with latex gloves worn much more often than before. In addition, the tapping of younger rubber trees and the use of stimulant chemicals to increase latex production probably increased the amount of allergenic protein in the raw material and ultimately in the finished goods of production.

Patients at high risk of latex sensitivity (those with spina bifida; multiple previous operations; history of certain food allergies, including banana, kiwi, avocado, chestnut, papaya, white potato, and tomato; and healthcare workers) should be questioned for symptoms related to exposure to natural rubber during their daily routines or previous surgical procedures. Intraoperative management of these patients is characterized by strict maintenance of a latex-free environment, including the use of nonlatex gloves (styrene, neoprene) by all personnel in contact with the patient. Pharmaceutical vials or injection ports are a rare but potential source of latex exposure. Pharmacy staff should be made aware of patients with known latex allergies to mitigate potential allergen exposure (e.g., use of glass ampules where possible).

Protamine. Anaphylactic reactions following administration of protamine are more likely to occur in patients who are allergic to seafood, reflecting the fact that protamine is derived from salmon sperm. Diabetics treated with protamine-containing insulin preparations such as neutral protamine hagedorn (NPH) are also at increased risk. After vasectomy, men may be at increased risk of allergic reactions to protamine, since they develop circulating antibodies to spermatozoa. Protamine is also capable of causing direct histamine release and activating the complement pathway to produce thromboxane, which causes bronchoconstriction and pulmonary hypertension. Patients known to be allergic to protamine present a therapeutic challenge when neutralization of heparin is required because no effective alternative drug is commonly available.

Blood, blood products, and synthetic volume expanders. Minor urticarial allergic reactions to properly cross-matched blood products may occur in 1% to 3% of patients. The cause is unknown but may be due to soluble antigens in the donor unit to which the recipient has been previously sensitized. Anaphylactic reactions are rare, occurring in approximately 1 in 20,000 to 50,000 transfusions. These may result from antibodies against IgA, HLA, or complement proteins.

The leading cause of transfusion-related morbidity and mortality is transfusion-related acute lung injury (TRALI), which occurs in approximately 1 in 5000 transfused blood products.

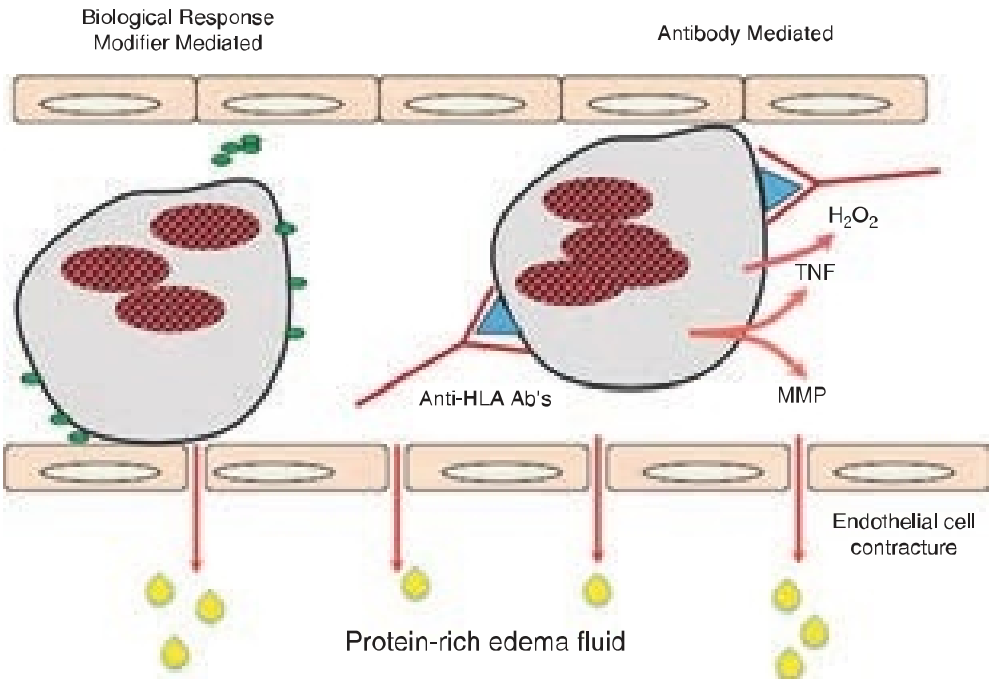

Fig. 26.3 Pathophysiology of transfusion-related acute lung injury (TRALI). The pathogenesis of TRALI appears to be activation of neutrophils on the pulmonary vascular endothelium as a result of donor leukocyte antibodies, particularly anti–human leukocyte antigen (anti-HLA) and antineutrophil antibodies. This results in leakage of protein-rich fluid, which causes pulmonary edema and amplification of the inflammatory cascade. *Ab's,* Antibodies; *MMP,* matrix metalloproteinase; *TNF,* tumor necrosis factor. (From Gilliss BM, Looney MR, Gropper MA. Reducing noninfectious risks of blood transfusion. *Anesthesiology.* 2011;115:635-649, fig. 2.)

Diagnostic criteria for TRALI include hypoxia and bilateral pulmonary edema that occur within 6 hours of transfusion and in the absence of intravascular fluid overload or heart failure. The pathogenesis of TRALI appears to be activation of neutrophils on the pulmonary endothelium as a result of donor leukocyte antibodies, particularly anti-HLA and antineutrophil antibodies (Fig. 26.3). These antibodies are contained in the plasma component of transfused blood products; therefore TRALI is most commonly seen after transfusion of plasma-rich components such as fresh frozen plasma and platelets. Treatment is supportive; mechanical ventilation, using parameters recommended for the treatment of acute respiratory distress syndrome, is advised. In critically ill patients, a mortality rate of 35% to 58% has been reported, though other patients recover within a few days. Neither steroids nor diuresis is beneficial.

Hemolytic transfusion reactions occur in 1 in 10,000 to 70,000 blood component transfusions. These appear to be mediated by immunoglobulins, particularly IgM and IgG. Hemolytic reactions can be classified as acute or delayed based on how soon after transfusion they occur. Acute reactions occur within 24 hours after the transfusion, while delayed reactions occur more than 1 day but usually 1 or 2 weeks following transfusion. Classic symptoms include fever, hypotension, hemoglobinuria, and signs of disseminated intravascular coagulation (DIC).

The estimated incidence of allergic reaction to plasma volume expanders is between 0.03% and 0.22%. Synthetic colloid solutions of high-molecular-weight polysaccharides (dextran, hydroxyethyl starch) have been implicated in immune- and nonimmune-mediated reactions, with manifestations ranging from rash and modest hypotension to bronchospasm and shock. Dextran may also activate the complement system, producing signs of an allergic reaction. IgE-mediated responses to gelatins, especially urea-linked varieties, have also been reported.

Other agents. Several other drugs have been implicated in cases of perioperative drug allergy. These include the serine protease inhibitor aprotinin, formerly used in cardiac surgery to reduce blood loss, antiseptic solutions such as chlorhexidine, dyes, heparin, and insulin. This underscores the importance of including drug allergy as part of the differential diagnosis in any occurrence of cardiovascular collapse that occurs during the perioperative period and considering any drug to which the patient has been exposed as the possible offender.

Eosinophilia

Eosinophilia is defined as a sustained absolute eosinophil count greater than 500/μL, and hypereosinophilia is defined as an eosinophil count of 1500/uL or more. Moderate eosinophilia is commonly seen in a wide spectrum of disorders, including parasitic infestations, systemic allergic disorders, collagen vascular diseases, various forms of dermatitis, drug reactions, and tumors. Hodgkin disease and both B- and T-cell non-Hodgkin lymphomas can present with eosinophilia. Even when there is no obvious sign of an underlying lymphoma, up to 25% of patients with apparent idiopathic eosinophilia will have an expanded clone of aberrant T cells which produce high levels of IL5.

Hypereosinophilic syndromes occur with an eosinophil count greater than 1500/μL and associated tissue damage

secondary to release of basic protein by the eosinophil. Irreversible endomyocardial fibrosis producing a restrictive cardiomyopathy is common in patients who maintain eosinophil counts greater than 5000/μL. Pulmonary fibrosis may also occur. In patients with eosinophilic leukemia or idiopathic hypereosinophilic syndrome, eosinophil counts can reach 20,000 to 100,000/μL. Widespread organ dysfunction and rapidly progressive heart disease are associated with these conditions. These patients need aggressive treatment. Leukapheresis can be used to acutely lower eosinophil counts. Steroids are effective in most cases. In steroid-unresponsive patients, alternative therapies include hydroxyurea, vincristine, and cyclophosphamide.

MISDIRECTED ADAPTIVE IMMUNITY

Autoimmune Disorders

The challenge of adaptive immunity is the need for immune cells to be capable of responding efficiently to a wide variety of foreign antigens yet still be able to recognize and tolerate self antigens. There is evidence that major immunologic stimuli, such as certain infections, can activate self-reactive lymphocytes. In general, these primed self-reactive lymphocytes tend to undergo apoptotic elimination once the immunologic challenge has been controlled. Indeed, transient autoimmunity appears to be a relatively common byproduct of major immune system activation. Other factors that appear to be involved in triggering autoimmunity include a response to microorganisms present in the microbiome (the group of nonpathogenic microorganisms that resides in or on the body), alterations in antigen presentation, and defects in the clearance of products of apoptosis. The specific defects that cause autoimmunity to persist and develop into a chronic, self-destructive immune disorder are not well understood. Genetic predisposition and gender may play a role. Table 26.6 lists some diseases with a known autoimmune basis.

The anesthetic implications of autoimmune disorders can be divided into three categories. The first includes the anesthetic considerations for certain vulnerable organs specific to the particular immune disorder. Examples of this include cervical instability with rheumatoid arthritis, renal injury with systemic lupus erythematosus, and liver failure with chronic autoimmune hepatitis. The second category is related to the consequences of therapy used to treat the autoimmune disorder. The potential for addisonian crisis in patients treated with long-term corticosteroids is well recognized. Newer therapies for autoimmune disorders inhibit specific facets of the immune response, placing patients who take these medications at increased risk of perioperative infection. The third category, especially in patients with long-standing autoimmune disorders, is the risk of accelerated atherosclerosis and associated cardiovascular complications such as heart disease and stroke. Some studies suggest that the risk of cardiovascular morbidity and mortality is increased by as much as 50-fold in the presence of an autoimmune disease. Some of this added risk may be due to the therapies used to treat the autoimmune disease. For example, chronic steroid therapy is associated with hypertension and diabetes mellitus, both of which are powerful risk factors for cardiovascular disease. Therefore patients with long-standing autoimmune conditions warrant thorough cardiovascular evaluation and consideration of the increased risk of perioperative cardiovascular complications.

TABLE 26.6 Examples of Autoimmune Diseases

Rheumatic	
	Rheumatoid arthritis
	Scleroderma
	Sjörgen's syndrome
	Systemic lupus erythematosus
Gastrointestinal	
	Chronic active hepatitis
	Crohn's disease
	Primary biliary cirrhosis
	Ulcerative colitis
Endocrine	
	Graves' disease
	Hashimoto's thyroiditis
	Type I diabetes mellitus
Neurologic	
	Multiple sclerosis
	Myasthenia gravis
Hematologic	
	Autoimmune hemolytic anemia
	Idiopathic thrombocytopenia purpura
	Pernicious anemia
Renal	
	Goodpasture syndrome
Multi-organ System	
	Ankylosing spondylitis
	Polymyositis
	Psoriasis
	Sarcoidosis
	Vasculitis

ANESTHESIA AND IMMUNOCOMPETENCE

Many perioperative factors affect immunocompetence and therefore may alter the incidence of perioperative infection or the body's response to cancer.

Transfusion-Related Immunomodulation

In recent years it has come to be appreciated that transfusion of allogenic blood products has a measurable impact on immune function. Such transfusion-associated immunomodulatory (TRIM) effects include increased susceptibility to infection and promotion of tumor growth. Conversely, a TRIM effect is likely to explain improved renal allograft survival in transplant patients. Specific TRIM effects include decreased NK-cell and phagocytic function, impaired antigen presentation, and suppression of lymphocyte production. The mechanism underlying

TRIM effects remains unclear but may be mediated by donor leukocytes present in transfused blood products and soluble HLA class I peptides. HLA incompatibility between donor leukocytes and the recipient induces a state of microchimerism that prompts the release of IL4, IL10, and other inflammatory mediators that impair cell-mediated immunity and cytotoxicity. An extreme manifestation of microchimerism is the development of transfusion-associated graft versus host disease (TAGVD), a rare but often fatal condition in which immunocompetent donor (graft) cells attack the recipient's cells, leading to pancytopenia and liver failure. Leukoreduction techniques in prestored blood appear to mitigate some but not all TRIM effects. Other soluble mediators in stored blood such as histamine and other proinflammatory cytokines that are not removed through leukoreduction may account for the incomplete effect of leukoreduction.

Resistance to Infection

By far the most important effector of immune function in the perioperative period is the neuroendocrine stress response initiated through activation of the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis. Surgical stress induces release of catecholamines, adrenocorticotropin hormone (ACTH), and cortisol. Monocytes, macrophages, and T cells possess β_2-adrenergic and glucocorticoid receptors. Activation of these receptors results in net inhibition of Th1 cytokine production and promotion of Th2 antiinflammatory cytokine release. Monocyte and macrophage activation lead to the release of cytokines such as IL1, IL6, and tumor necrosis factor α, which further stimulate the HPA axis. The benefit of this immunosuppression is to minimize the inflammatory response caused by surgical trauma. The downside of this immunosuppression is increased vulnerability to infection and tumor proliferation.

Numerous other perioperative factors weaken the immune system. Acute pain suppresses NK-cell activity probably as a result of HPA axis and ANS activation. Hypothermia exacerbates the neuroendocrine stress response and induces thermoregulatory vasoconstriction. Tissue hypoxia impairs oxidative killing by neutrophils and prolongs wound healing. Hypothermia has also been shown to suppress NK-cell activity and lymphocyte function. Elevated plasma cortisol and catecholamines during surgery result in hyperglycemia, which can provide a medium for bacterial growth. Hyperglycemia itself also has deleterious effects on the immune system. Hyperglycemia impedes lymphocyte migration, reduces immune cell proliferation by interfering with critical enzymatic functions, and impairs neutrophil phagocytosis.

Resistance to Cancer

It is well established that immunocompetence is essential for a host to resist cancer. For example, recipients of solid organ transplants who have a history of cancer experience a higher rate of cancer recurrence following the initiation of immunosuppressive therapy. Surgical excision remains the treatment of choice for most locally contained solid organ cancers, but there is concern that exposure to surgery and anesthesia may actually promote tumor progression.

Several mechanisms are likely at play. Surgical disruption of the tumor may release tumor cells into the circulation, providing the seeds for micrometastases. The presence of a primary tumor may itself inhibit angiogenesis; therefore tumor removal may paradoxically favor the survival of minimal residual disease. Release of growth factors and suppression of antiangiogenic factors may also contribute. In addition, tissue injury depresses cell-mediated immunity, including the function of cytotoxic T cells and NK cells. Allogenic RBC transfusion in the perioperative period may also play a role in increasing the risk of tumor recurrence. Laboratory evidence of TRIM has demonstrated a reduction in Th and NK-cell counts and reduction in the Th1 cytokines IL2 and interferon in the context of blood transfusions.

Considerable in vitro and in vivo evidence from animal studies suggests that anesthetics and analgesics also have an impact on the immune response (Table 26.7). The magnitude of this effect is probably considerably less than that of the surgical stress itself, but an additive effect may be important. Ketamine, thiopental, and all of the volatile anesthetics appear to reduce NK-cell activity and/or number. Volatile anesthetics impair neutrophil function by inhibiting the respiratory oxidative burst mechanism and reducing lymphocyte proliferation. Nitrous oxide impairs DNA and nucleotide synthesis and has been observed to depress hematopoietic and mononuclear cell synthesis and depress neutrophil chemotaxis; however, nitrous oxide has not been shown to have any effect on cancer recurrence. Propofol bears chemical resemblance to the antioxidant α-tocopherol and may possess antiinflammatory and antioxidative properties. In contrast to other intravenous anesthetics, propofol does not appear to affect NK cells and may increase cytotoxic lymphocyte activity, exerting a protective effect against cancer cell proliferation. In fact, propofol conjugates have been explored in the treatment of breast cancer, as they have been shown to inhibit cellular adhesion and promote apoptosis of breast cancer cells.

The immunosuppressive effects of opiates have been known for decades. Opioid receptors in the HPA axis promote the

TABLE 26.7 Effects of Anesthetic Drugs on Immune System Function

Drug	Effect
Thiopental	Reduces NK cell activity and number in animal models
Propofol	Reduces NK cell number in animal models
Volatile agents	Inhibits stimulation of NK cell cytotoxicity in animal models
Nitrous oxide	Associated with acceleration in development of lung and liver metastases in animal models
Local anesthetic drugs	Inhibits tumor cell proliferation
Morphine	Inhibits cellular and NK cell immunity in animal models
Fentanyl	Inhibits NK cell activity in humans
Tramadol	Stimulates NK cell activity in animal and human models
Cox-2 inhibitors	Displays anti-angiogenic effects in animal models

NK – natural killer lymphocytes

Modified from Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Brit J Anaesth 2010;105(2):109, table 2

production of ACTH and cortisol release. Sympathetic nervous system activation and catecholamine release further suppress NK-cell, lymphocyte, neutrophil, and macrophage functions. Immune cells possess a specific subset of μ receptors, the activation of which leads to increased intracellular calcium gradients and activation of nitric oxide (NO) synthase. Elevated NO concentrations appear to mediate many of the anti-inflammatory effects of naturally occurring opioids. Morphine also impairs antibody formation and the synthesis of proinflammatory cytokines. As expected, many of the immunomodulatory effects of opioids can be blocked by administration of the μ receptor antagonist naloxone. There is some evidence to suggest that synthetic opioids such as fentanyl and remifentanil have less of an impact on immune function, possibly related to differential activation of specific opioids receptors.

Nonopioid analgesics seem to have less effect on immune function then opiates. In fact, there is some evidence to suggest that tramadol, which has noradrenergic and serotoninergic activity in addition to μ-receptor affinity, may promote NK-cell activity. NSAIDs that inhibit the cyclooxygenase enzyme have been shown in an animal model to possess antitumor and antiangiogenic properties. COX-2 inhibitors such as etodolac and celecoxib may attenuate the deleterious effects of opioid-induced tumor growth.

A few retrospective studies have suggested a benefit to regional anesthesia in reducing the risk of tumor recurrence after oncologic surgery. Several mechanisms may account for this observation. Regional anesthesia attenuates the neuroendocrine surgical stress response by blocking afferent transmission to the HPA axis. In addition, patients who receive regional anesthesia or regional analgesia have reduced requirements for drugs with known immunosuppressive effects, such as general anesthetics and opioids. Local anesthetic agents may also possess intrinsic antitumor properties. Both lidocaine and ropivacaine have been shown to possess antiproliferative effects on tumor cells. Not all research has supported the benefit of regional anesthesia over general anesthesia for cancer prognosis. The impact may differ depending on tumor type. Therefore, despite these promising findings, more research is needed before definitive conclusions can be drawn about the optimal anesthetic choice in a cancer patient.

KEY POINTS

- The immune system is divided into innate and adaptive or acquired pathways.
- Innate immunity mounts the initial response to any infection, recognizes targets that are common to many pathogens, and has no specific memory. Its cellular components are neutrophils, macrophages, monocytes, and NK cells, and its main noncellular elements are the complement proteins.
- Adaptive immunity has a more delayed onset of action and may take days to activate when challenged by an unfamiliar antigen. However, adaptive immunity is capable of developing memory and is more rapidly induced by antigen when memory is present. Adaptive immunity consists of a humoral component mediated by B lymphocytes that produce antibodies and a cellular component dominated by T lymphocytes.
- Angioedema may be hereditary or acquired and is characterized by episodic edema due to increased vascular permeability. The condition commonly involves swelling of the face and mucous membranes and may lead to airway compromise. The most common hereditary form results from an autosomal dominant deficiency of C1 esterase inhibitor, which results in a buildup of the vasoactive compound bradykinin. Treatment of acute attacks involves administration of C1 inhibitor concentrate to replace the deficient enzyme.
- Anaphylaxis is a life-threatening condition caused by massive release of vasoactive mediators via degranulation of mast cells and basophils through either immune- or nonimmune-mediated mechanisms. Treatment requires reversal of hypotension via replacement of intravascular fluid volume and inhibition of further release of vasoactive mediators. Early intervention with epinephrine is critical. Epinephrine increases intracellular cyclic AMP, thereby reducing vasoactive mediator release. It also relaxes bronchial smooth muscle and relieves bronchospasm.
- NMBAs and antibiotics are responsible for most drug-induced allergic reactions in the perioperative period. Reaction may occur on first exposure or following previous uneventful exposure, presumably due to sensitization from other environmental agents. Sugammadex is among the newest drugs implicated in perioperative anaphylaxis. The estimated incidence of anaphylaxis after sugammadex administration is 1 in 3500 to 1 in 64,000.
- Almost all allergic reactions occur within 5 to 10 minutes of exposure to an antigen. An important exception to this rule is the allergic response to latex, which typically occurs at least 30 minutes after exposure. Preoperative referral for skin testing is appropriate for patients with a strong clinical history of previous latex allergic reaction. Patients with a higher than average risk of latex allergy include those with a history of spina bifida, multiple prior surgeries, or fruit allergy. The frequency of latex allergy has declined significantly with the increasing use of latex-free products.
- Autoimmune disorders result in immune-mediated end-organ dysfunction due to inappropriate activation of antibody against self antigens. Each disorder is accompanied by a distinct set of multisystem features. Patients with autoimmune disorders also have an increased risk of cardiovascular disease. Therefore careful preoperative evaluation is imperative to prevent excess perioperative morbidity and mortality. Many of these patients are treated with exogenous glucocorticoids and may require stress-dose steroids prior to major surgery to prevent addisonian crisis.
- Many factors related to surgery and anesthesia impair immune function, which may precipitate infection and cancer progression in susceptible patients. The main factor is the neuroendocrine response to surgical stress, which includes release of catecholamines and glucocorticoids that impair both the innate and adaptive immune responses. Anesthetic agents, including volatile anesthetics and opioids, also impair immune function. Regional and neuraxial anesthesia with local anesthetics may help preserve immune function.

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Cancer

Natalie F. Holt

OUTLINE

INTRODUCTION

Cancer is the second leading cause of death in the United States, exceeded only by heart disease. The lifetime risk of developing cancer is estimated to be one in three for both men and women. The lifetime risk of dying from cancer is one in five. About 90% of patients with cancer require surgery for reasons both related and unrelated to the cancer diagnosis. Furthermore, approximately two-thirds of people diagnosed with cancer survive for at least 5 years, meaning that a growing number of patients will come to surgery in the context of or after cancer treatment.

The anesthetic implications of cancer stem not only from the cancer itself but also from the therapies employed for its treatment. In addition, since the median age at diagnosis is 66 years, patients with cancer often have comorbid conditions that affect their perioperative course.

MECHANISM

Cancer results from an accumulation of genetic mutations, which causes dysregulation of cellular proliferation. Genes are involved in carcinogenesis by virtue of inherited traits that predispose to cancer (e.g., altered metabolism of potentially carcinogenic compounds), mutation of a normal gene into an oncogene that promotes the conversion of normal cells into cancer cells, or inactivation of a tumor suppressor gene thus triggering malignant transformation. A critical gene related to cancer in humans is the tumor suppressor *p53*. This gene is not only essential for cell viability but critical for monitoring damage to deoxyribonucleic acid (DNA). Inactivation of *p53* is an early step in the development of many types of cancer. Stimulation of oncogene formation by carcinogens is a major contributor to cancer development. It has been estimated that nine modifiable factors cause 35% of cancer deaths worldwide: smoking, alcohol, diets low in fruits and vegetables, obesity, inactivity, unsafe sex, urban air pollution, use of solid fuels, and contaminated injections in healthcare settings. About 20% of cancer deaths worldwide are attributable to tobacco.

The fundamental event that causes cells to become malignant is an alteration in their DNA structure. These mutations occur in cells of target tissues, with these cells then becoming ancestors of the entire future tumor cell population. Evolution to more undifferentiated cells reflects high mutation rates and contributes to the development of tumors that are resistant to therapy.

Cancer cells must evade the host's immune surveillance system, which is designed to seek out and destroy tumor cells. Most mutant cancer cells stimulate the host's immune system to form antibodies. This protective role of the immune system is apparent in those with acquired immunodeficiency syndrome (AIDS) and recipients of organ transplants who are maintained on long-term immunosuppressive drugs. These individuals have an increased incidence of cancer.

DIAGNOSIS

Most cancers produce solid tumors. Cancer often becomes clinically evident when tumor bulk compromises vital organ function. The initial diagnosis is often made by aspiration cytology or biopsy. Monoclonal antibodies that recognize antigens for specific cancers may aid in the diagnosis of cancer. A commonly used staging system for solid tumors is the TNM system based on tumor size (T), lymph node involvement (N), and distant metastases (M). This system groups patients into stages ranging from best (stage I) to poorest (stage IV) prognosis. Tumor invasiveness is related to the release of various tumor mediators that modify the surrounding microenvironment in such a way as to permit cancer cells to spread along the lines of least resistance. Lymphatics lack a basement membrane so local spread of cancer is influenced by the anatomy of the regional lymphatics. For example, regional lymph node involvement occurs late in squamous cell cancer of the vocal cords because these structures have few lymphatics, whereas regional lymph node involvement is an early manifestation of supraglottic cancer because this region is rich in lymphatics. Imaging techniques, including computed tomography (CT) and magnetic resonance imaging (MRI), are used for further delineation of tumor presence and spread.

TREATMENT

Most cancers are treated by a multimodal approach involving surgery, radiation therapy, and/or chemotherapies that vary by tumor type and stage. The development of more effective treatments has dramatically improved cancer survival. However, use of these more powerful therapies is associated with toxicities and side effects that have the potential to affect nearly every organ system. Some of these effects are transient; others produce permanent sequelae. All of them have important potential consequences in the perioperative care of cancer patients.

Traditional Chemotherapy

Traditional chemotherapy involves the use of cytotoxic agents that target rapidly dividing cells and interfere with replication. They are divided into classes based on mechanism of action: alkylating agents, antimetabolites, antibiotics, microtubule assembly inhibitors, hormonal agents, and various miscellaneous or mixed-mechanism drugs. Alkylating agents form reactive molecules that cause DNA cross-linking problems such as abnormal base pairing and strand breaks that interfere primarily with DNA but also ribonucleic acid (RNA) and protein synthesis and replication. Antimetabolites are structural analogs of folic acid, purines, or pyrimidines that block enzymes necessary for nucleic acid and protein synthesis. Antitumor antibiotics form complexes with DNA or RNA that inhibit their subsequent synthesis. Microtubule assembly inhibitors include the vinca alkaloids and taxanes, both of which act on the mitotic process by interfering with microtubule assembly or disassembly.

The growth of certain tumor types, notably breast and prostate, is responsive to hormonal agents. Hormones are not cytotoxic so they often stimulate tumor regression but do not cause cell death. Several other drugs have been shown to have anticancer properties. The epipodophyllotoxins act by inhibiting the topoisomerase II enzyme, which causes DNA strand breaks that lead to apoptotic cell death. The topoisomerase I inhibitors work by a similar mechanism but on a different enzyme.

Targeted Chemotherapy

Targeted therapy involves a new set of chemotherapeutics directed against specific processes involved in tumor cell proliferation and migration. The first targeted therapy was that developed for estrogen receptors present with certain types of breast cancers. Binding of estrogen to estrogen receptors is an important step in the growth of these tumor cells, and estrogen receptor blockade turned out to be an effective way to mitigate tumor spread.

Other targeted therapies have been developed against a number of cell processes, including secretion of growth

factors that facilitate gene expression, angiogenesis (creation of new blood vessels), cell migration, and tumor growth. These include endothelial growth factor (EGF), vascular endothelial growth factor (VEGF), and matrix metalloproteinases. These growth factors are involved in growth and differentiation of normal cells, but they are usually overexpressed or mutated on cancer cells. Binding of growth factors to receptors on the cell membrane induces a cascade of signal transduction events that often involve activation of the enzyme tyrosine kinase. Absence of these signals may lead to apoptosis. Drugs have now been developed that block these growth factors, their receptors, or their associated tyrosine kinases. Included among the targeted therapies are monoclonal antibodies that act on extracellular receptors such as EGF and VEGF, as well as small molecules that penetrate cell membranes and block intracellular signaling pathways. Cancer cells have the ability to mutate and develop resistance to targeted therapies so targeted therapies are often used in conjunction with other drugs.

Radiation

Radiation induces cell death by causing damage to DNA. The sensitivity of a cell to radiation injury is influenced by its phase in the cell cycle and its ability to repair DNA damage. X-rays and γ-rays are the forms of ionizing radiation most commonly used to treat cancer. Radiation timing and delivery is adjusted to maximize therapeutic benefit and minimize damage to surrounding tissue. Radiation can be administered through external beam technology or implanted into a target organ (e.g., radiation "seeds" for prostate cancer). Technologic advances such as three-dimensional imaging and conformal radiotherapy, which allow radiation energy to be conformed to tumor shape, have helped minimize damage to surrounding tissue. Radiation may also be delivered systemically through the use of radionuclides administered intravenously and targeted to a tumor site. For example, isotopes of iodide salts have an important role in the treatment of thyroid neoplasms. Organs have variable resistance to the effects of radiation. The testes, ovaries, and bone marrow are among the most sensitive, while bone is among the most resistant.

Side Effects of Cancer Treatment

Bone marrow suppression, cardiovascular, and pulmonary toxicity, as well as central and peripheral nervous system damage, are among the most serious side effects of cancer treatment. However, dysfunction of nearly every organ system has been described. The following sections present a system-specific review of toxicities related to cancer treatment. Tables 27.1 and 27.2 summarize the side effects of selected chemotherapies and radiation treatment.

TABLE 27.1 Toxicities of Commonly Used Chemotherapies

Agent	Effects
Adriamycin	Cardiac toxicity, myelosuppression
Arsenic	Leukocytosis, pleural effusion, QT interval prolongation
Asparaginase	Coagulopathy, hemorrhagic pancreatitis, hepatic dysfunction, thromboembolism
Bevacizumab	Bleeding, congestive heart failure, gastrointestinal perforation, hypertension, impaired wound healing, pulmonary hemorrhage, thromboembolism
Bleomycin	Pulmonary hypertension, pulmonary toxicity
Busulfan	Cardiac toxicity, myelosuppression, pulmonary toxicity
Carmustine	Myelosuppression, pulmonary toxicity
Chlorambucil	Myelosuppression, pulmonary toxicity, SIADH
Cisplatin	Dysrhythmias, magnesium wasting, mucositis, ototoxicity, SIADH, peripheral neuropathy, renal tubular necrosis, thromboembolism
Cyclophosphamide	Encephalopathy/delirium, hemorrhagic cystitis, myelosuppression, SIADH, pericardial effusion, pericarditis, pulmonary fibrosis
Erlotinib	Deep venous thrombosis, pulmonary toxicity
Etoposide	Cardiac toxicity, myelosuppression, pulmonary toxicity
Fluorouracil	Acute cerebellar ataxia, cardiac toxicity, gastritis, myelosuppression
Ifosfamide	Cardiac toxicity, hemorrhagic cystitis, renal insufficiency, SIADH
Methotrexate	Encephalopathy, hepatic dysfunction, mucositis, platelet dysfunction, pulmonary toxicity, renal failure, myelosuppression
Mitomycin	Myelosuppression, pulmonary toxicity
Mitoxantrone	Cardiac toxicity, myelosuppression
Paclitaxel	Ataxia, autonomic dysfunction, myelosuppression, peripheral neuropathy, arthralgias
Sorafenib	Cardiac ischemia, hypertension, impaired wound healing, thromboembolism
Sunitinib	Adrenal insufficiency, cardiac ischemia, hypertension, thromboembolism
Tamoxifen	Thromboembolism
Thalidomide	Bradycardia, neurotoxicity, thromboembolism
Tretinoin	Myelosuppression, retinoic acid syndrome
Vinblastine	Cardiac toxicity, hypertension, myelosuppression, pulmonary toxicity, SIADH
Vincristine	Autonomic dysfunction, cardiac toxicity, peripheral neuropathy, SIADH, pulmonary toxicity

SIADH, Syndrome of inappropriate antidiuretic hormone secretion.

TABLE 27.2 Common Side Effects of Radiation Therapy

System	Acute	Chronic
Skin	Erythema, rash, hair loss	Fibrosis, sclerosis, telangiectasias
Gastrointestinal	Malnutrition, mucositis, nausea, vomiting	Adhesions, fistulae, strictures
Cardiac		Conduction defects, pericardial effusion, pericardial fibrosis, pericarditis
Respiratory		Airway fibrosis, pneumonitis, pulmonary fibrosis, tracheal stenosis
Renal	Glomerulonephritis	Glomerulosclerosis
Hepatic	Sinusoidal obstruction syndrome	
Endocrine		Hypothyroidism, panhypopituitarism
Hematologic	Bone marrow suppression	Coagulation necrosis

Cardiovascular System

Anthracyclines such as doxorubicin (adriamycin) and idarubicin are the chemotherapeutic drugs most often associated with cardiotoxicity. These drugs are commonly used to treat cancers such as leukemias and lymphomas. Anthracyclines impair myocyte function via the formation of free radicals, which interfere with mitochondrial activation and cause lipid peroxidation. Cardiotoxicity may be acute or chronic. Acute toxicity begins early on in treatment with the development of dysrhythmias, QT prolongation, and cardiomyopathy and then reverses with discontinuation of therapy. Chronic toxicity (left ventricular dysfunction and cardiomyopathy) can occur in an early-onset form usually within 1 year of treatment or a late-onset form that can occur several years or decades after completion of therapy. Risks factors for cardiotoxicity include a large cumulative dose of drug (for doxorubicin, ⁻1500 mg/m^2), a history of high-dose bolus administration, a history of concomitant radiation, or use of other cardiotoxic agents. The cardiotoxicity of doxorubicin may be decreased by the use of free radical scavengers such as dexrazoxane or liposomal preparations.

Mitoxantrone, which is structurally similar to the anthracyclines, has also been associated with cardiomyopathy, as have other drugs, including cyclophosphamide, clofarabine, interferon, and certain of the tyrosine kinase inhibitors. Trastuzumab is a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2). It and other HER2 antibodies have also been implicated as causing left ventricular heart failure in a small subset of patients.

Baseline echocardiography is recommended for all patients prior to initiation of chemotherapy with a known risk of cardiotoxicity. Periodic echocardiography is advised in patients, although the optimal surveillance strategy has yet to be established.

Pericarditis, angina, coronary artery vasospasm, ischemic electrocardiogram (ECG) changes, and conduction defects are other cardiac complications related to cancer chemotherapy. Fluorouracil and capecitabine cause the highest incidence of chemotherapy-related ischemia. Estimates vary widely from 1% to 68% for fluorouracil and 3% to 9% for capecitabine. Other drugs that may cause myocardial ischemia are the vinca alkaloids, interferon, and etoposide.

Arrhythmias may also result from chemotherapies. Paclitaxel and thalidomide can cause severe bradycardia requiring pacemaker implantation. Arsenic, lapatinib, and nilotinib frequently cause QT prolongation. Platinum-based drugs such as cisplatin have precipitated conduction abnormalities related to electrolyte imbalance.

Hypertension has emerged as a relatively common side effect of treatment with newer targeted chemotherapies such as bevacizumab, trastuzumab, sorafenib, and sunitinib, occurring in as many as 35% to 45% of patients. The pathophysiology of the cardiac damage related to the use of these drugs is probably directly related to inhibition of EGF and VEGF. Although important to tumor cell proliferation, these growth factors also play a role in normal myocyte growth, repair, and adaptation to pressure loads. On the other hand, hypotension is relatively common with administration of monoclonal antibodies due to a massive release of cytokines.

Patients with cancer are considered to be in a hypercoagulable state independent of treatment; however, certain chemotherapeutics further increase this risk. These include bevacizumab, estramustine, thalidomide, and tamoxifen.

Patients who receive radiation to the mediastinum are at risk for developing myocardial fibrosis, pericarditis, valvular fibrosis, conduction abnormalities, and accelerated development of coronary artery disease. Incidence is related to cumulative radiation exposure as well as concomitant administration of cardiotoxic chemotherapies.

Respiratory System

Pulmonary toxicity is a well-recognized complication of bleomycin therapy. Other agents associated with pulmonary damage include busulfan, cyclophosphamide, methotrexate, lomustine, carmustine, mitomycin, busulfan, and the vinca alkaloids. The mechanism of injury differs for each drug. In the case of bleomycin, free radical formation seems to be a factor. EGF receptor blockade is the postulated mechanism reported with erlotinib and gefitinib, both of which are EGF receptor blockers. Type II pneumocytes possess EGF receptors that play a role in alveolar repair.

Pneumonitis or bronchiolitis obliterans with organizing pneumonia (BOOP) occurs in up to 10% of patients treated with bleomycin, depending on dose. Pulmonary fibrosis can develop decades after treatment. Risk factors include preexisting lung disease, smoking, and radiation exposure. Baseline and serial pulmonary function testing and chest x-rays are often performed. It has widely been taught that intraoperative exposure to high concentrations of oxygen may exacerbate preexisting bleomycin-induced lung injury and contribute to postoperative ventilatory failure. While newer evidence suggests this may not be the case, current recommendations are still to minimize the inspired oxygen concentration to that required to

maintain oxygen saturation between 90% and 92%. Pretreatment with corticosteroids has been suggested as a means to minimize perioperative pulmonary complications.

Many other chemotherapies have been associated with pulmonary toxicity. These include mitomycin C, epirubicin, busulfan, methotrexate, fludarabine, carmustine, and all-trans retinoic acid.

Interstitial pneumonitis and pulmonary fibrosis are complications of radiation to the thorax or total body irradiation. Symptoms typically begin within the first 2 to 3 months of treatment and generally regress within 12 months of treatment completion. However, subclinical abnormalities on pulmonary function testing reportedly occur in up to 50% of patients exposed to radiation for treatment of childhood cancers. Radiation recall pneumonitis is a recognized clinical syndrome in which patients with prior radiation exposure manifest symptomatic pneumonitis after exposure to a second pulmonary toxin.

Renal System

Many of the chemotherapeutic agents can be nephrotoxic; among the most commonly cited are the platinum-based chemotherapeutics such as cisplatin, high-dose methotrexate, and ifosfamide. Renal insufficiency and hypomagnesemia are the typical presenting signs of cisplatin-related nephrotoxicity. Ifosfamide usually causes proximal tubule dysfunction marked by proteinuria and glucosuria. Leucovorin, a folic acid precursor, can be helpful in treating methotrexate-related renal failure. Renal insufficiency usually resolves with cessation of treatment and supportive therapy. Prehydration and avoidance of other nephrotoxins limit the risk of renal toxicity. Pretreatment with the organic thiophosphate amifostine is sometimes used for the prevention of cisplatin-induced nephrotoxicity.

Cyclophosphamide is often associated with the syndrome of inappropriate antidiuretic hormone (SIADH) via a direct effect on renal tubules, but this condition is usually benign. The most serious side effect of cyclophosphamide is hemorrhagic cystitis, which can cause hematuria severe enough to produce obstructive uropathy.

Induction chemotherapy or high-dose radiation can induce tumor cell lysis that causes the release of large amounts of uric acid, phosphate, and potassium. Hyperuricemia can cause uric acid crystals to precipitate in renal tubules, leading to acute renal failure. Calcium phosphate deposition may exacerbate the condition. Radiation exposure can cause glomerulonephritis or glomerulosclerosis with permanent injury marked by chronic renal insufficiency and systemic hypertension.

Hepatic System

Antimetabolites such as methotrexate, as well as asparaginase, arabinoside, plicamycin, and streptozocin, have been associated with acute liver dysfunction. However, chronic liver disease is uncommon. Radiation-induced liver injury is also typically dose dependent and reversible.

The most severe form of liver dysfunction in cancer patients is sinusoidal obstruction syndrome. This usually occurs in patients receiving total body irradiation in preparation for hematopoietic stem cell transplantation (HSCT); however, several chemotherapies have also been associated with this syndrome, including busulfan, cyclophosphamide, vincristine, and dactinomycin. Mortality ranges from 19% to 50%.

Airway and Oral Cavity

Mucositis is a painful inflammation and ulceration of the mucous membranes of the digestive tract. Oral lesions begin as mucosal whitening followed by the development of erythema and tissue friability. Oral mucositis is a relatively common side effect of high-dose chemotherapy and radiation to the head and neck. Chemotherapies associated with mucositis include the anthracyclines, taxanes, and platinum-based compounds, as well as antimetabolites such as methotrexate and fluorouracil. Mucositis associated with chemotherapies often begins during the first week of treatment and typically resolves after treatment is terminated. Mucositis associated with radiation therapy usually has a more delayed onset. Patients with mucositis are at risk of infection from spread of oral bacteria. Narcotics are frequently required to achieve adequate analgesia. In its most severe form, pseudomembrane formation, edema, and bleeding may cause airway compromise or risk of aspiration.

Radiation to the head and neck can result in permanent tissue fibrosis, which may limit mouth opening and neck and tongue mobility. Airway fibrosis and tracheal stenosis may result in difficult ventilation and intubation that is not evident on physical exam.

Gastrointestinal System

Almost all chemotherapy and radiation produce gastrointestinal side effects. Nausea, vomiting, diarrhea, and enteritis are common. Diarrhea is frequent with fluorouracil, melphalan, anthracyclines, and the topoisomerase inhibitors. In the short term, these symptoms can produce dehydration, electrolyte abnormalities, and malnutrition, but they are usually transient. Radiation, however, may produce permanent sequelae such as adhesions and stenotic lesions anywhere along the gastrointestinal tract. Hemorrhagic pancreatitis is a unique complication associated with asparaginase.

Endocrine System

Hyperglycemia is a common side effect of glucocorticoid therapy, as is suppression of the hypothalamic-pituitary-adrenal axis, which may become evident during stress or surgery. Adrenal suppression is reversible but may it take up to a year for adrenal function to return to normal. SIADH can be seen with cyclophosphamide, ifosfamide, cisplatin, and melphalan, although symptomatic hyponatremia is uncommon.

Total body irradiation in the context of HSCT or radiation for head and neck cancers can cause panhypopituitarism and/or hypothyroidism, which typically becomes symptomatic during the first few years following treatment. Patients with a history of radiation exposure to the neck are also at increased risk of thyroid cancer.

Hematologic System

Myelosuppression is the most frequent side effect associated with chemotherapy. In most cases, this effect is transient, and

blood cell counts return to normal within a week following therapy.

Bleeding is relatively common in patients on chemotherapy and may be the result of thrombocytopenia and/or platelet dysfunction. Depletion of vitamin K–dependent coagulation factors contributes to this problem. Bleeding has also been associated with the angiogenesis inhibitor bevacizumab as well as several of the tyrosine kinase inhibitors, particularly when used in conjunction with other drugs. For this reason it has been recommended that bevacizumab therapy be withheld prior to major surgery.

Tumors release procoagulants such as tissue factor that create a hypercoagulable state. Some chemotherapies can exacerbate this condition. Thalidomide and the related drug lenalidomide pose an especially high risk of venous thromboembolism, particularly when used in combination with glucocorticoids and doxorubicin. Other drugs associated with an increased risk of thromboembolism include cisplatin and tamoxifen.

Radiation-induced coagulation disorders occur as a delayed effect and involve coagulation necrosis of vascular endothelium. Postradiation bleeding in the rectum, vagina, bladder, lung, and brain have been reported.

Nervous System

Chemotherapy can cause a number of neurotoxic side effects, including peripheral neuropathy and encephalopathy. Virtually all patients treated with vincristine develop paresthesias in their hands and feet. Autonomic neuropathy may accompany the paresthesias. These changes are usually reversible. Cisplatin causes dose-dependent large-fiber neuropathy by damaging dorsal root ganglia. Loss of proprioception may be sufficiently severe to interfere with ambulation. Performance of regional anesthesia in patients being treated with cisplatin chemotherapy must be counterbalanced by the realization that subclinical neurotoxicity is present in a large percentage of these patients, and cisplatin neurotoxicity may extend several months beyond discontinuation of treatment. Paclitaxel causes dose-dependent ataxia that may be accompanied by paresthesias in the hands and feet and proximal skeletal muscle weakness. Corticosteroids (prednisone or its equivalent at ¯40 mg/day) may cause a myopathy characterized by weakness of the neck flexors and proximal weakness of the extremities. The first sign of corticosteroid-induced neuromuscular toxicity is difficulty rising from the sitting position. Respiratory muscles may also be affected. Corticosteroid-induced myopathy usually resolves when the drug is discontinued.

Cancer chemotherapeutic drugs can cause encephalopathy, delirium, and/or cerebellar ataxia. Examples include high-dose cyclophosphamide, methotrexate, and ifosfamide. Prolonged administration of methotrexate, especially in conjunction with radiation therapy, can lead to progressive irreversible dementia.

Tumor Lysis Syndrome

Tumor lysis syndrome is caused by sudden destruction of tumor cells by chemotherapy or radiation, leading to the release of large amounts of uric acid, potassium, and phosphate. This syndrome occurs most often after induction treatment of hematologic neoplasms, such as acute lymphoblastic leukemia. Acute renal failure can occur because of uric acid crystal formation and/or calcium phosphate deposition in the kidney. Hyperkalemia and cardiac dysrhythmias are more likely in the presence of renal dysfunction. Hyperphosphatemia can lead to secondary hypocalcemia, which increases the risk of cardiac dysrhythmias from hypokalemia and can cause neuromuscular symptoms such as tetany.

CANCER IMMUNOLOGY

Diagnosis

The use of monoclonal antibodies to detect proteins encoded by oncogenes or other types of tumor-associated antigens (TAs) is a common method for identifying cancer. TAs (⊥fetoprotein, prostate-specific antigen, carcinoembryonic antigen) are present on cancer cells and normal cells, but concentrations are higher in tumor cells. Monoclonal antibodies to various TAs can be labeled with radioisotopes and injected to monitor the spread of cancer. Because TAs are present on normal tissues, measurement of these antigens may be less useful for the diagnosis of cancer than for monitoring patients with known malignancies.

Immunomodulators

Tumor cells are antigenically different from normal cells, and evidence now confirms that the body is able to mount an immune response against TAs in a process similar to that which causes allograft rejection. However, because TAs also exist on normal cells, they are only weakly antigenic. Adjuvants are compounds that potentiate the immune response. Examples include the bacillus Calmette-Guérin (BCG) bacteria and naturally occurring interferons such as interleukin-2 (IL2), interferon-⊥ (INF-⊥), and granulocyte-macrophage colony-stimulating factor (GM-CSF). These agents are used to augment the host's intrinsic anticancer capabilities.

Cancer Vaccines

Appreciation of the role of TAs in eliciting an immune response is now driving the development of cancer vaccines. Two types of cancer vaccines exist: preventive and therapeutic. The preventive vaccines target infectious agents know to contribute to cancer formation. Two preventive vaccines are currently marketed, one against human papillomavirus (HPV) types 6, 11, 16, and 18 and another against hepatitis B virus (HBV). HPV types 16 and 18 are responsible for approximately 70% of cervical cancers and are a causal factor in some cancers of the vagina, vulva, anus, penis, and oropharynx. Chronic HBV infection is a major risk factor for the development of hepatocellular carcinoma. HBV vaccination is now recommended in childhood as part of a strategy to reduce not only the risk of HBV infection but also the incidence of hepatocellular cancer.

The premise behind therapeutic cancer vaccines is that injection of tumor antigen can be used to stimulate an immune system response against tumor cells. In 2010, the US Food and Drug Administration approved the first therapeutic cancer

vaccine, sipuleucel-T (Provenge), for the treatment of some cases of metastatic prostate cancer. This is an autologous vaccine produced by isolating antigen-presenting cells from the patient's own immune system, then culturing this protein with a protein consisting of prostatic acid phosphatase linked to granulocyte-macrophage-colony-stimulating factor (GM-CSF). Treatment elicits an immune response that has shown efficacy in reducing tumor progression. Vaccines are in development for a number of other cancers. Some of these are made from weakened or killed cancer cells that contain TAs, others from immune cells that have been modified to express TAs. Others are being made synthetically. A novel type of cancer vaccine uses naked DNA or RNA that codes for TAs. Injection of the vaccine either directly or via a virus carrier induces massive TA production, which in turn promotes a robust immune response that is intended to halt tumor progression.

PARANEOPLASTIC SYNDROMES

Paraneoplastic syndromes are pathophysiologic disturbances that accompany an estimated 8% of patients with cancer. Sometimes symptoms of a paraneoplastic syndrome manifest before the cancer diagnosis and may actually be the precipitant to cancer detection. Certain of these conditions (superior vena cava obstruction, increased intracranial pressure) may manifest as life-threatening medical emergencies.

Fever and Cachexia

Fever may accompany any type of cancer but is particularly likely with metastases to the liver. Increased body temperature may accompany rapidly proliferating tumors, such as leukemias and lymphomas. Fever may reflect tumor necrosis, inflammation, the release of toxic products by cancer cells, or the production of endogenous pyrogens.

Cancer cachexia is a frequent occurrence in cancer patients. In some cases, cancer appears to increase resting energy expenditure (REE). Cancer cells compete with normal tissues for nutrients and may eventually cause nutritive death of normal cells. Tumor factors such as proteolysis-inducing factor and host responses such as tumor necrosis factor ¬ (TNF-¬), interferon-¬ (IFN-¬), and IL6 also contribute to muscle atrophy and lipolysis. Hyperalimentation is indicated for nutritional support when malnutrition is severe, especially if surgery is planned.

Neurologic Abnormalities

Paraneoplastic neurologic syndromes are the result of antibody-mediated damage to the nervous system. Antibodies produced by the host in response to TAs cross-react with elements of the nervous system, leading to neurologic dysfunction. The vast majority of paraneoplastic neurologic syndromes (80%) manifest *before* the diagnosis of cancer. They can affect both the central and peripheral nervous systems. They are relatively rare—occurring in about 1% of cancer patients—but occur disproportionately in those patients with small cell lung cancer, lymphoma, and myeloma. Examples include limbic encephalitis, paraneoplastic cerebellar degeneration, Lambert-Eaton myasthenia syndrome, and myasthenia gravis. Lambert-Eaton syndrome is caused by antibodies to voltage-gated calcium channel receptors and is commonly associated with small cell lung cancer. Myasthenia gravis is caused by antibodies to the acetylcholine receptor and is often present in patients with thymoma. Potentiation of neuromuscular blocking agents may be observed in these myasthenic disorders.

These paraneoplastic neurologic syndromes often present a diagnostic challenge because symptoms are nonspecific, and the underlying cancer diagnosis is usually unknown. The presence of antibodies in the serum to tumor-associated material (called onconeural antibodies) occurs in some but not all patients. Immunosuppression is the mainstay of treatment of these syndromes. Corticosteroids and immunoglobulin therapies are frequently employed. Plasmapheresis may also be required to reduce the antibody burden. Once diagnosed, screening for an underlying malignancy is indicated.

Endocrine Abnormalities

Paraneoplastic endocrine syndromes arise from hormone or peptide production within tumor cells (Table 27.3). Most occur after the diagnosis of cancer has been established. Treatment of the underlying tumor is the preferred management.

Syndrome of Inappropriate Antidiuretic Hormone

SIADH secretion affects approximately 1% to 2% of cancer patients, with most cases related to small cell lung cancer. Headache and nausea are early symptoms that may progress to confusion, ataxia, lethargy, and seizures. Symptoms depend on the degree and rapidity with which hyponatremia develops. SIADH resolves with treatment of the underlying tumor. Vasopressin

TABLE 27.3 Ectopic Hormone Production

Hormone	Associated Cancer	Manifestations
Adrenocorticotropic hormone	Carcinoid, lung (small cell), thymoma, thyroid (medullary)	Cushing syndrome
Antidiuretic hormone	Duodenum, lung (small cell), lymphoma, pancreas, prostate	Water intoxication
Erythropoietin	Hemangioblastoma, hepatic, renal cell, uterine myofibroma	Polycythemia
Human chorionic gonadotropin	Adrenal, breast, lung (large cell), ovary, testis	Gynecomastia, galactorrhea, precocious puberty
Insulin-like substances	Retroperitoneal tumors	Hypoglycemia
Parathyroid hormone	Lung (small cell), lung (squamous cell), ovary, pancreas, renal	Hyperparathyroidism, hypercalcemia, hypertension, renal dysfunction, left ventricular dysfunction
Thyrotropin	Choriocarcinoma, testicular (embryonal)	Hyperthyroidism, thrombocytopenia
Thyrocalcitonin	Thyroid (medullary)	Hypocalcemia, hypotension, muscle weakness

receptor antagonists and demeclocycline are the pharmacologic therapies available if symptoms are severe.

Hypercalcemia

Cancer is the most common cause of hypercalcemia in hospitalized patients and is considered a poor prognostic indicator. There are several different mechanisms for the hypercalcemia seen in cancer patients. The most common is secretion of a parathyroid hormone (PTH)–related protein by tumor cells that binds to PTH receptors in the bone and kidney. This type occurs commonly with squamous cell cancers of the kidneys, lungs, pancreas, or ovaries. Hypercalcemia can also be caused by local osteolytic activity from bone metastases, especially from breast cancer, multiple myeloma, and some lymphomas. Occasionally, tumors secrete vitamin D.

The rapid onset of hypercalcemia that occurs in patients with cancer may present as lethargy or coma. Polyuria accompanies hypercalcemia and may lead to dehydration. Treatment includes hydration with normal saline. Intravenous bisphosphonates or calcitonin may also be indicated.

Cushing Syndrome

Cushing syndrome is most commonly associated with neuroendocrine tumors of the lung such as small cell lung cancer and carcinoid. It is caused by tumor secretion of either adrenocorticotropic hormone (ACTH) or corticotropin-releasing factor (CRF). Clinical symptoms include hypertension, weight gain, central obesity, and edema. The diagnosis can be confirmed by measuring serum ACTH or CRF concentrations and with a dexamethasone suppression test, which involves administration of dexamethasone followed by measurement of urinary cortisol. Normally administration of dexamethasone causes a marked reduction in urinary cortisol concentration. In patients with paraneoplastic Cushing syndrome there is no reduction in urinary cortisol following dexamethasone administration. Treatment includes agents that block steroid production such as ketoconazole and mitotane. Antihypertensives and diuretics may also be needed for symptom management.

Hypoglycemia

Intermittent hypoglycemic episodes can occur with insulin-producing islet-cell tumors in the pancreas or with nonislet cell tumors outside of the pancreas that secrete insulin-like growth factor 2 (IGF-2). Patients with islet cell tumors demonstrate a high serum insulin level. In contrast, those with nonislet cell tumors that secrete insulin-like materials demonstrate a low serum insulin and an elevated IGF-2.

Several other active hormones can be secreted by tumor cells, the results of which produce predictable clinical signs and symptoms.

Renal Abnormalities

Paraneoplastic glomerulopathies occur in a variety of different forms, including membranous glomerulonephritis, nephrotic syndrome, and amyloidosis. Many involve renal deposition of immunoglobulins or immune complexes containing tumor-associated antigens with host antibodies. Amyloidosis is marked by deposition of a unique protein called amyloid and is most often associated with renal cell carcinoma. Glomerulopathies are relatively common with lymphoma and leukemia.

Dermatologic and Rheumatologic Abnormalities

Paraneoplastic dermatologic and rheumatologic conditions can occur without overt evidence of malignancy, but their appearance should initiate surveillance for an underlying cancer. Acanthosis nigricans is a thickening and hyperpigmentation of the skin. It usually occurs in the axilla or neck and is most commonly related to insulin resistance or other noncancer-related conditions. When found on the palms it is almost always cancer associated—most often an adenocarcinoma. Dermatomyositis is an inflammatory condition that causes proximal muscle weakness as well as characteristic skin changes, including a rash on the eyelids and hands. It can be seen with ovarian, breast, lung, prostate, and colorectal cancers. Hypertrophic osteoarthropathy (commonly known as clubbing) involves subperiosteal bone deposition that causes a characteristic remodeling of the phalangeal shafts. It is classically associated with intrathoracic tumors or metastases to the lungs.

Hematologic Abnormalities

Paraneoplastic hematologic syndromes are rarely symptomatic but usually are present with advanced cancer. Paraneoplastic eosinophilia is related to production of specific interleukins that promote eosinophilic differentiation and is most often seen with leukemia and lymphoma. Eosinophilia can sometimes cause wheezing or occasionally end-organ damage due to eosinophilic infiltration. Granulocytosis usually occurs with solid tumors, particularly large cell lung cancer. Pure red cell aplasia is commonly associated with thymoma but also occurs with leukemia and lymphoma. Underlying malignancy is the diagnosis in about a third of patients with thrombocytosis (platelet count ⊐400,000/mL). This appears to be the result of tumor-released cytokines such as IL6.

LOCAL EFFECTS OF CANCER AND METASTASES

Superior Vena Cava Syndrome/Superior Mediastinal Syndrome

Obstruction of the superior vena cava is caused by spread of cancer into the mediastinum or directly into the caval wall, most often by lung cancer. Engorgement of veins above the level of the heart occurs, particularly the jugular veins and veins in the arms. Edema of the face and upper extremities is usually prominent. Increased intracranial pressure manifests as nausea, seizures, and decreased levels of consciousness and is most likely due to the increase in cerebral venous pressure. Compression of the great vessels may cause syncope.

Superior mediastinal syndrome is the combination of superior vena cava syndrome plus tracheal compression. Hoarseness, dyspnea, and airway obstruction may be present because of tracheal compression. Treatment consists of prompt radiation or chemotherapy for symptomatic relief. Bronchoscopy and/or mediastinoscopy to obtain a tissue diagnosis can be very hazardous, especially in the presence of coexisting airway obstruction and increased pressure in the mediastinal veins.

Spinal Cord Compression

Spinal cord compression results from the presence of metastatic lesions in the epidural space, most often breast, lung, or prostate cancer or lymphoma. Symptoms include pain, skeletal muscle weakness, sensory loss, and autonomic dysfunction. CT and MRI can visualize the limits of compression. Radiation therapy is a useful treatment when neurologic deficits are only partial or in development. Corticosteroids are often administered to minimize the inflammation and edema that can result from radiation directed at tumors in the epidural space. Once total paralysis has developed, the results of surgical laminectomy or of radiation to decompress the spinal cord are poor.

Increased Intracranial Pressure

Metastatic brain tumors, most often from lung and breast cancer, present initially as mental deterioration, focal neurologic deficits, or seizures. Treatment of an acute increase in intracranial pressure caused by a metastatic lesion includes corticosteroids, diuretics, and mannitol. Radiation therapy is the usual palliative treatment, but surgery can be considered for patients with only a single metastatic lesion. Intrathecal administration of chemotherapeutic drugs is usually necessary when the tumor involves the meninges.

CANCER PAIN

Cancer patients may experience acute pain associated with pathologic fractures, tumor invasion, surgery, radiation, and/or chemotherapy. In addition, about 75% of cancer patients develop a chronic pain syndrome. Chronic pain is more commonly the result of cancer progression or therapeutic interventions, including side effects of antineoplastic treatments. A frequent source of pain is related to metastatic spread of the cancer, especially to bone. Nerve compression or infiltration may also cause pain. Patients with cancer who experience frequent and significant pain often exhibit signs of depression and anxiety.

Pathophysiology

Organic causes of cancer pain may be subdivided into nociceptive and neuropathic pain. Nociceptive pain includes somatic and visceral pain and refers to pain due to the peripheral stimulation of nociceptors in somatic or visceral structures. Somatic pain is related to tumor involvement of somatic structures such as bones or skeletal muscles and is often described as aching, stabbing, or throbbing. Visceral pain is related to lesions in a hollow or solid viscus and is described as diffuse, gnawing, or crampy if a hollow viscus is involved and as aching or sharp if a solid viscus is involved. Nociceptive pain is typically responsive to both nonopioid and opioid medication. Neuropathic pain involves peripheral or central afferent neural pathways and is commonly described as burning or lancinating pain. Many chemotherapeutic agents are neurotoxic. Vincristine is one of the most commonly implicated drugs in the development of polyneuropathy. Other agents with a high incidence of polyneuropathy include cisplatin, paclitaxel, oxaliplatin, thalidomide, and bortezomib. Patients experiencing neuropathic pain often respond poorly to opioids.

Trauma associated with surgery for removal of cancerous tissue may also be a cause of chronic pain. Scars and injury of soft tissue and of sensory afferents that innervate the surgical area may contribute to the development of chronic pain.

Drug Therapy

Drug therapy is the cornerstone of cancer pain management because of its efficacy, rapid onset of action, and relatively low cost. Mild to moderate cancer pain is initially treated with nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen. NSAIDs are especially effective for managing bone pain, which is the most common cause of cancer pain. Short-acting opioids are used for the management of moderate to severe pain. Morphine is commonly selected and can be administered orally. Other options include oxycodone, hydromorphone, or oxymorphone. When the oral route of administration is inadequate, alternative routes (intravenous, subcutaneous, epidural, intrathecal, transmucosal, transdermal) are considered. Fentanyl is available in transdermal and transmucosal delivery systems. Tolerance to opioids does occur and may necessitate dose adjustment. Opioid rotation involves periodically switching patients from one opioid to another in equianalgesic doses. Opioid rotation is one approach to managing opioid tolerance. Fear of addiction is a major reason why opioids are underutilized despite the fact that addiction is rare when these drugs are correctly managed.

Serotonin-norepinephrine reuptake inhibitors or tricyclic antidepressant drugs are indicated for patients with depressive symptoms. They may also exhibit analgesic properties; the mechanism is most probably related to enhanced availability of monoamines.

Gabapentin and pregabalin are considered first-line therapies in the management of chronic neuropathic pain. Other options include anticonvulsants such as oxcarbazepine or the cannabinoid receptor agonist dronabinol.

Corticosteroids can decrease pain perception, have a sparing effect on opioid requirements, improve mood, increase appetite, and lead to weight gain. They may also be particularly useful in treating bone pain and visceral pain. Dexamethasone is the preferred agent, owing to its long half-life and minimal mineralocorticoid effects. Osteoclast inhibitors such as bisphosphonates or calcitonin are particularly useful in the treatment of bone pain.

For those patients who have no response to first-line therapies, the α_2-adrenergic agonists clonidine or tizanidine may be useful. Multimodal analgesia with local anesthetics and adjunctive agents such as ketamine may be effective in preventing both acute and chronic pain and reducing analgesic consumption after surgery.

Radiation Therapy

Local external beam radiation therapy is commonly used to treat bone pain from metastases.

Neuraxial Analgesia

Neuraxial analgesia is an effective way to control pain in cancer patients undergoing surgery and may play a role in providing

preemptive analgesia. Neuraxial analgesia with local anesthetics provides immediate pain relief in patients whose pain cannot be relieved with oral or intravenous analgesics and is frequently used for the treatment of cancer pain. Neuraxial analgesia is not performed in patients with local infection, bacteremia, and systemic infection because of the increased risk of epidural abscess. However, in the presence of intractable cancer pain there may be a role for the use of epidural analgesia despite meningeal infection. Morphine may be administered intrathecally or epidurally for management of acute and chronic cancer pain. Spinal opioids may be delivered for weeks to months via a long-term, subcutaneously tunneled, exteriorized catheter or an implanted drug delivery system. The implantable systems can be intrathecal or epidural and typically feature a drug reservoir and the capability for external programming. Patients are typically considered for neuraxial opioid administration when systemic opioid administration has failed as a result of the onset of intolerable adverse side effects or in adequate analgesia. Neuraxial administration of opioids is usually successful, but some patients may require the addition of a dilute concentration of local anesthetic to the infusate to achieve adequate pain control.

Neurolytic Procedures

Neurolytic procedures intended to destroy sensory components of nerves cannot be used without also destroying motor and autonomic nervous system fibers. Important aspects of determining the suitability of a destructive nerve block are the location and quality of the pain, the effectiveness of less destructive treatment modalities, the inherent risks associated with the block, the availability of experienced anesthesiologists to perform the procedures, and the patient's anticipated life expectancy. In general, constant pain is more amenable to destructive nerve block than is intermittent pain. Neurolytic celiac plexus block with alcohol or phenol has been used to treat pain originating from abdominal viscera, especially in the context of pancreatic cancer. The block is associated with significant side effects, but analgesia usually lasts 6 months or longer.

Neuroablative or neurostimulatory procedures for managing cancer pain are reserved for patients unresponsive to other less invasive procedures. Cordotomy involves interruption of the spinothalamic tract in the spinal cord and is considered for treatment of unilateral pain involving the lower extremity, thorax, or upper extremity. Dorsal rhizotomy involves interruption of sensory nerve roots and is used when pain is localized to specific dermatomal levels. Dorsal column stimulators or deep brain stimulators may be used in select patients.

PREOPERATIVE EVALUATION AND MANAGEMENT

Preoperative evaluation of patients with cancer includes consideration of the pathophysiologic effects of the disease and recognition of the potential adverse effects of cancer treatments (Table 27.4). In addition, the patient's underlying medical comorbidities must not be overlooked. Correction of nutrient deficiencies, electrolyte abnormalities, anemia, and coagulopathies may be needed preoperatively. In most cases, laboratory evaluation should include complete blood count, coagulation profile, serum electrolytes, and transaminases. Chest radiograph, echocardiogram, pulmonary function evaluation, and other specialized testing should be used if clinical suspicion warrants. There are no specific rules regarding the preoperative management of chemotherapeutic drugs. However, most of them have the potential to impair wound healing, in particular the growth factor and angiogenesis inhibitors. For this reason it has been suggested that surgery be delayed 4 to 8 weeks following treatment with bevacizumab, owing to its long half-life. Because of their shorter half-lives, other antiangiogenic tyrosine kinase inhibitors (e.g., sunitinib, sorafenib, pazopanib, vandetanib, cabozantinib) may be stopped 1 week prior to surgery.

Potential pulmonary or cardiac toxicity is a consideration in patients being treated with chemotherapeutic drugs known to be associated with these complications. The myocardial depressant effects of anesthesia can unmask cardiac dysfunction related to cardiotoxic chemotherapies such as doxorubicin. Therefore, when major surgery is planned, preoperative echocardiography may be indicated. Since several chemotherapies can cause ECG abnormalities such as QT prolongation, a baseline ECG should be reviewed.

A preoperative history of drug-induced pulmonary fibrosis (dyspnea, nonproductive cough) or congestive heart failure will influence the subsequent conduct of anesthesia. In patients treated with bleomycin, it may be helpful to monitor arterial blood gases in addition to oximetry and to carefully titrate intravascular fluid replacement, keeping in mind that these patients are at risk of developing interstitial pulmonary edema presumably because of impaired lymphatic drainage in the lung. Bleomycin-associated pulmonary injury may be exacerbated by high oxygen concentrations; therefore it is prudent to adjust the delivered oxygen concentration to the minimum that provides adequate oxygen saturation. Nitrous oxide may augment the toxicity of methotrexate, so it is best avoided.

The presence of hepatic or renal dysfunction should influence the choice and dose of anesthetic drugs and muscle relaxants. Although not a consistent observation, the possibility of a prolonged response to succinylcholine is a consideration in patients being treated with alkylating chemotherapeutic drugs such as cyclophosphamide, which is an inhibitor of pseudocholinesterase. The existence of paraneoplastic syndromes such as myasthenia gravis and Lambert-Eaton syndrome may also affect the patient's response to muscle relaxants.

Attention to aseptic technique is important because immunosuppression occurs with most chemotherapeutic agents and is exacerbated by malnutrition. Immunosuppression produced by anesthesia, surgical stress, or blood transfusion during the perioperative period could exert deleterious effects on the patient's subsequent response to their cancer. Adrenal suppression may be present in patients who have been on steroid therapy. Those who have been on more than 20 mg prednisone (or its equivalent) per day for more than 3 weeks are considered most at risk; however, adrenal suppression may occur in patients maintained on as low a dose as 5 mg prednisone daily. Recovery of the hypothalamic-pituitary-adrenal axis may take up to

TABLE 27.4 Preanesthetic Evaluation of the Cancer Patient

System	Risk Factors	Evaluations	Anesthetic Considerations
Cardiovascular	Adriamycin exposure Radiation to the mediastinum Anterior mediastinal mass	Chest x-ray, chest CT scan, echocardiogram	• Left ventricular dysfunction • Dysrhythmias • Engorgement of great vessels
Pulmonary	Bleomycin, busulfan, chlorambucil exposure Radiation to the thorax	Arterial blood gas, chest x-ray, chest CT scan, flow-volume loops, pulmonary function testing	• Obstructive/restrictive disease • Avoid high concentrations of oxygen with history of bleomycin exposure
Renal and hepatic	Induction chemotherapy or radiation Tumor lysis syndrome	Renal and liver function tests, coagulation profile, uric acid	• Dose adjustments based on end-organ damage • Acute renal failure with tumor lysis syndrome
Hematologic	Metastatic disease Most chemotherapies and radiation	Complete blood count, coagulation profile	• Infection risk • Bleeding risk • Thromboembolism prophylaxis
Neurologic	Cisplatin, vincristine, fluorouracil exposure Metastatic disease Paraneoplastic syndromes (myasthenia gravis, Eaton-Lambert syndrome)	Physical exam and documentation of preexisting sensorimotor defects	• Caution with administration of peripheral nerve blocks, neuraxial anesthesia • Elevated ICP, papilledema • Spinal cord compression due to metastases • Phrenic nerve palsy in presence of metastases or superior vena cava syndrome
Gastrointestinal	All chemotherapies and radiation Advanced cancer	Physical exam, serum electrolytes, prealbumin	• Hypovolemia • Electrolyte abnormalities • Metabolic acidosis/alkalosis • Mucositis/oral ulcerations may predispose to bleeding with airway instrumentation • Increased aspiration risk in presence of nausea/vomiting • Increased infection risk, poor wound healing
Endocrine	Steroid exposure Paraneoplastic syndrome/SIADH, hypercalcemia	Preoperative medications, serum electrolytes	• Consider stress-dose steroids due to adrenal insufficiency • Risk of electrolyte abnormalities (hyponatremia, hypercalcemia, hypocalcemia)
Airway	Radiation to head/neck Anterior mediastinal mass	Physical exam, chest x-ray, chest CT scan, flow-volume loops	• Difficult airway precautions • Tracheal compression • Airway collapse with cessation of spontaneous ventilation

CT, Computed tomography; *ICP,* intracranial pressure; *SIADH,* syndrome of inappropriate antidiuretic hormone secretion.
Adapted from Latham GJ, Greenberg RS. Anesthetic considerations for the pediatric oncology patient—part 3: pain, cognitive dysfunction, and preoperative evaluation. *Pediatr Anesthes.* 2010;20(6):486, fig. 2.

1 year. A typical steroid replacement regimen is hydrocortisone 100 mg administered intravenously at induction of anesthesia followed by 100 mg IV every 8 hours for the first 24 hours after major surgery. Lower doses may be used in the context of surgeries of low or intermediate complexity.

Intubation in the presence of oral mucositis may cause bleeding. Patients with cancers of the head, neck, and anterior mediastinum may exhibit airway compromise. Patients with a history of radiation exposure may have airway deformities that are difficult to recognize on physical exam.

Anesthesia Technique and Tumor Progression

Recent evidence suggests that anesthetics and analgesics have immunomodulatory properties (see also Chapter 26). Opioids are widely believed to promote tumor cell proliferation. Several mechanisms are in play, including ¬μ opioid receptor-mediated activation of tumor cell angiogenesis and epidermal growth factor activation. Many opioids also have the ability to blunt natural killer (NK)–cell activity, producing an immunosuppressive effect that supports tumor cell proliferation. On the other hand, in animal models, cyclooxygenase (COX) inhibitors have been shown to reduce the risk of tumor progression. The COX-2 enzyme is overexpressed in a number of tumor types, and COX pathways play a role in tumor proliferation and invasion; therefore inhibition of the COX enzyme is hypothesized to account for this finding.

Local anesthetics inhibit TNF-_ and other immune mediators that tend to enhance tumor cell proliferation. In addition, regional anesthetic techniques tend to blunt the neuroendocrine stress response to surgery, which helps preserve the host's intrinsic anticancer defenses. However, despite some promising studies there is insufficient evidence to conclude that choice of anesthetic technique impacts cancer recurrence. In addition, coagulopathies may increase the risk of utilizing regional anesthetic techniques in some cancer patients. In all cases, when regional anesthesia is employed, baseline peripheral neuropathies related to chemotherapies such as vincristine and cisplatin should be well documented.

Among the hypnotic agents, propofol is thought to exert antitumor effects through enhancement of NK-cell activity and inhibition of COX, while volatile anesthetics have been linked to increased tumor growth. However, none of these findings is conclusive enough to advocate a definitive approach to anesthesia management of the cancer patient.

Adequate pain control has been associated with improved outcomes of cancer surgery. As a result, regardless of the intraoperative anesthetic technique employed, postoperative care must include adequate attention to pain management. Many cancer patients have been treated for pain related to their underlying diagnosis. Therefore narcotic dosing must be adjusted to account for possible drug tolerance. Prophylaxis against infection and thromboembolism as well as optimization of nutrition must be considered.

COMMON CANCERS ENCOUNTERED IN CLINICAL PRACTICE

The most commonly encountered cancers in adults are lung cancer, breast cancer, colon cancer, and prostate cancer. Lung cancer is the second most common malignancy surpassed only by prostate cancer in men and breast cancer in women.

Lung Cancer

Lung cancer is the leading cause of cancer deaths among men and women. It is largely a preventable disease, since about 90% of lung cancer deaths are related to cigarette smoking. Five-year survival varies significantly based on stage at diagnosis: Fifty-six percent of patients with only local disease will survive for at least 5 years, but only 5% of those with distant metastases evident at the time of diagnosis will be alive at 5 years. Due to late diagnosis, more than half of people diagnosed with lung cancer will die within 1 year.

Etiology

The strong association between cigarette smoking and lung cancer is well established. Smoking marijuana produces a greater carbon monoxide and tar burden than smoking a similar quantity of tobacco and thus may pose an additional risk factor for lung cancer in cigarette smokers. The mutagens and carcinogens present in cigarette smoke may cause chromosomal damage and over time may cause malignancy. Other carcinogens that cause lung cancer include ionizing radiation (a byproduct of coal and iron mining), asbestos (increases the incidence of lung cancer in nonsmokers and acts as a synergistic cocarcinogen with tobacco smoke), and naturally occurring radon gas. Adjuvant radiation therapy for breast cancer following mastectomy is also associated with an increased risk of lung cancer.

There is a familial risk of lung cancer that is related to genetic and ecogenetic factors and to exposure to passive smoke. Inhalation of secondhand smoke increases the risk of lung cancer and contributes to the development of childhood respiratory infections and asthma. Cigarette smokers who develop emphysema are at increased risk for the development of lung cancer. Patients who have pulmonary fibrosis are also at increased risk of developing lung cancer, as are those with AIDS.

TABLE 27.5 2015 World Health Organization Classification of Malignant Lung Tumors

Name
Adenocarcinoma
Adenosquamous cell carcinoma
Squamous cell carcinoma
Large cell carcinoma
Sarcomatoid carcinoma
Neuroendocrine carcinoma
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Signs and Symptoms

Patients with lung cancer present with features related to the extent of the disease, including local and regional manifestations, signs and symptoms of metastatic disease, and various paraneoplastic syndromes related indirectly to the cancer. Cough, hemoptysis, wheezing, stridor, dyspnea, or pneumonitis from airway obstruction may be presenting clinical signs. Mediastinal metastases may cause hoarseness (recurrent laryngeal nerve compression), superior vena cava syndrome, cardiac dysrhythmias, or congestive heart failure from pericardial effusion and tamponade. Pleural effusion results in increasing dyspnea and often chest pain. Generalized weakness, fatigue, anorexia, and weight loss are common.

Histologic Subtypes

Clinical manifestations of lung cancer vary with histologic subtype (Table 27.5). Adenocarcinoma is the most common lung cancer subtype, and the incidence is on the rise especially in women.

Adenocarcinomas most often originate in the lung periphery. These tumors commonly present as subpleural nodules and have a tendency to invade the pleura and induce pleural effusions that contain malignant cells. Lung adenocarcinomas may be difficult to differentiate morphologically from malignant mesothelioma or adenocarcinoma that has metastasized from other sites such as breast, gastrointestinal tract, or pancreas.

Squamous cell cancers arise in major bronchi or their primary divisions (central origin) and are usually detected by sputum cytology. These tumors tend to grow slowly and may reach a large size before they are finally detected. Hemoptysis, bronchial obstruction with associated atelectasis, dyspnea, and fever from pneumonia are common presenting signs. Cavitation may be evident on chest radiography.

Large cell carcinomas are usually peripheral in origin and present as large, bulky tumors. Like adenocarcinomas, these tumors metastasize early and preferentially to the central nervous system.

There are several lung cancer tumor types that have neuroendocrine characteristics. These include small cell carcinoma, large cell neuroendocrine carcinoma, typical carcinoid, atypical carcinoid, and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. Small cell carcinomas are the most common subtype of neuroendocrine lung tumors.

Small cell carcinomas are usually of central bronchial origin and have a high frequency of early lymphatic invasion especially to lymph nodes in the mediastinum and metastases to liver, bone, central nervous system, adrenal glands, and pancreas. Prominent mediastinal lymphadenopathy may lead to the erroneous diagnosis of malignant lymphoma. Superior vena cava syndrome may result from mediastinal compression. Small cell tumors have a marked propensity to produce polypeptides and ectopic hormones resulting in metabolic abnormalities. These patients do not usually present before the disease process is widespread.

Diagnosis

Cytologic analysis of sputum is often sufficient for the diagnosis of lung cancer especially when the cancer arises in proximal endobronchial locations where shedding of cells is likely to occur. Peripheral lesions as small as 3 mm can be detected by high-resolution CT. Lung cancer screening has been recommended for patients who are at highest risk, such as cigarette smokers with chronic obstructive lung disease.

Flexible fiberoptic bronchoscopy, in combination with a biopsy, brushings, or washings, is a standard procedure for initial evaluation of lung cancer. Peripheral lung lesions can be diagnosed by percutaneous fine-needle aspiration guided by fluoroscopy, ultrasonography, or CT. Video-assisted thoracoscopic surgery is useful for diagnosing peripheral lung lesions and pleura-based tumors. CT with or without integrated positron emission tomography (PET) is sensitive for detecting pulmonary metastases. Brain MRI and head CT are useful for detecting metastases even in patients without neurologic abnormalities. Mediastinoscopy and video-assisted thoracoscopy provide the opportunity to biopsy lymph nodes and stage the tumor.

Treatment

Treatments for lung cancer include surgery, radiation, and chemotherapy. Preferred therapy depends on cell type, stage, and the patient's underlying health.

Pulmonary function testing is used to evaluate a patient's candidacy for lung resection. Forced expiratory volume in 1 second (FEV_1) and diffusing capacity for carbon monoxide (DLCO) are considered among the most useful predictors of postoperative complications. If FEV_1 is greater than 2 L and DLCO is greater than 80%, patients are at low risk of postoperative respiratory complications. When patients are not clearly in a low-risk category, predicted postoperative pulmonary function can be evaluated. Predicted postoperative pulmonary function takes into consideration preoperative lung function, the amount of lung tissue that will be resected, and the relative contribution of that tissue to overall lung function. Ideally its calculation is based on preoperative pulmonary function tests as well as some quantitative measure of differential lung function, such as ventilation-perfusion scanning. Predicted postoperative FEV_1 can also be estimated using a formula that takes into account the number of lung segments expected to be removed (predicted postoperative FEV_1 − preoperative FEV_1 − [number of segments remaining postoperatively/total number of lung segments]). It has been widely considered that if predicted postoperative FEV_1 is less than 0.8 L, patients are considered poor candidates for pneumonectomy. Other studies have suggested that a DLCO or FEV_1 less than 40% of that predicted based on age, height, and gender of the patients is a poor prognostic indicator. Cardiopulmonary exercise testing with measurement of maximum oxygen consumption is another test that can be used to evaluate high-risk patients.

Surgery has little effect on survival when the disease has spread to mediastinal lymph nodes or when metastases are present. Even among those considered surgically curable, recurrent metastatic disease develops in half of these patients within 5 years. Video-assisted thoracoscopy is the preferred surgical approach, especially for wedge resection and lobectomy. Standard thoracotomy is needed for more complex procedures or pneumonectomy.

Systemic chemotherapy and radiation are the preferred treatments for small cell carcinoma because most patients do not present until disease is extensive. In the rare cases in which diagnosis is made when the tumor size is no more than 5 cm, surgery lobectomy may be considered.

Management of Anesthesia

Management of anesthesia in patients with lung cancer includes preoperative consideration of tumor-induced effects such as malnutrition, pneumonia, pain, and ectopic endocrine effects such as hyponatremia or hypercalcemia. When resection of lung tissue is planned, it is important to evaluate underlying pulmonary and cardiac function.

Hemorrhage and pneumothorax are the most frequently encountered complications of mediastinoscopy. The mediastinoscope can also exert pressure on the right innominate artery, causing loss of the radial pulse and an erroneous diagnosis of cardiac arrest. Likewise, unrecognized compression of the right innominate artery of which the right carotid artery is a branch may manifest as a postoperative neurologic deficit. Bradycardia during mediastinoscopy may be due to stretching of the vagus nerve or tracheal compression by the mediastinoscope. Lung resection requires the ability to perform differential lung ventilation such as with a double lumen tube or bronchial blocker.

Colorectal Cancer

Colorectal cancer is the second leading cause of cancer death in men and the third leading cause of cancer death in women. Almost all colorectal cancers are adenocarcinomas. The disease generally occurs in adults older than 50 years, although in the last two decades the incidence among individuals under age 50 has been steadily increasing.

Etiology

Most colorectal cancers arise from premalignant adenomatous polyps. Although adenomatous polyps are common (present in ¬30% of patients age ¬50 years), less than 1% become malignant. Large polyps, especially those larger than 1.5 cm in diameter, are more likely to contain invasive cancer. It is thought that adenomatous polyps require 5 to 10 years of growth before they develop into a cancer. The evolution of normal colonic mucosa to a benign adenomatous polyp that contains cancer and then

to life-threatening invasive cancer is associated with a series of genetic events that involve the mutational activation of a proto-oncogene and the loss of several genes that normally suppress tumorigenesis.

Although hereditary conditions such as familial adenomatous polyposis as well as inflammatory bowel disease are associated with increased susceptibility to colorectal center, most colorectal cancers occur sporadically and appear to be related to diet. There is a direct correlation between calories, animal fat, and meat protein consumption. Positive family history, alcohol consumption, and cigarette smoking for longer than 35 years are also risk factors.

Diagnosis

The rationale for colorectal cancer screening is that early detection and removal of localized superficial tumors and precancerous lesions in asymptomatic individuals increases the cure rate. Screening programs (digital rectal examination, examination of the stool for occult blood, colonoscopy) appear to be particularly useful for persons who have first-degree relatives with a history of the disease, especially if these relatives developed the colorectal cancer before 55 years of age.

Signs and Symptoms

The presenting signs and symptoms of colorectal cancer reflect the anatomic location of the cancer. A change in bowel habits is the most commonly reported symptom. Because stool is relatively liquid as it passes into the right colon through the ileocecal valve, tumors in the cecum and ascending colon can become large and can markedly narrow the bowel lumen without causing obstructive symptoms. Ascending colon cancers frequently ulcerate, leading to chronic blood loss in the stool. These patients experience symptoms related to anemia.

Stool becomes more concentrated as it passes into the transverse colon. Transverse colon cancers cause abdominal cramping, occasional bowel obstruction, and even perforation. Abdominal radiographs reveal characteristic abnormalities in the colonic gas pattern, reflecting narrowing of the lumen (napkin ring or apple core lesion). Colon cancers developing in the rectosigmoid portion of the large intestine result in tenesmus and thinner stools. Anemia is unusual despite the relatively frequent presence of hematochezia.

Colorectal cancers initially spread to regional lymph nodes and then through the portal venous circulation to the liver, which represents the most common visceral site of metastases. Colorectal cancers rarely spread to lung, bone, or brain in the absence of liver metastases. A preoperative increase in the serum concentration of carcinoembryonic antigen (CEA) suggests that the tumor will recur following surgical resection. CEA is a glycoprotein that is also increased in the presence of other cancers (stomach, pancreas, breast, lung) and nonmalignant conditions (alcoholic liver disease, inflammatory bowel disease, cigarette smoking, pancreatitis).

Treatment

The prognosis for patients with adenocarcinoma of the colorectum depends on the depth of tumor penetration into the bowel wall and the presence or absence of regional lymph node involvement and distant metastases (liver, lung, bone). Radical surgical resection, which includes the blood vessels and lymph nodes draining the involved bowel, offers the best potential for cure. Surgical management of cancers that arise in the distal rectum may necessitate a permanent colostomy (abdominoperineal resection). Because most recurrences occur within 3 to 4 years, the cure rate for colorectal cancer is often estimated by 5-year survival rate.

Radiation therapy is a consideration in patients with rectal tumors, since the risk of recurrence following surgery is significant. Postoperative radiation therapy causes transient diarrhea and cystitis, but permanent damage to the small intestine and bladder is uncommon.

Management of Anesthesia

Management of anesthesia for surgical resection of colorectal cancers may be influenced by anemia and the effects of metastatic lesions in liver, lung, bone, or brain. Chronic large bowel obstruction probably does not increase the risk of aspiration during induction of anesthesia, although abdominal distention could interfere with adequate ventilation and oxygenation. Blood transfusion during surgical resection of colorectal cancers has been alleged to be associated with a decrease in the length of patient survival. This could reflect immunosuppression produced by transfused blood. For this reason, careful review of the risks and benefits of blood transfusions in these patients is prudent.

Prostate Cancer

About 11% of men in the United States will be diagnosed with prostate cancer in their lifetime; however, substantially fewer will die as a result of prostate cancer. Nearly 80% of men diagnosed with prostate cancer have localized disease at the time of diagnosis, and the 5-year survival is nearly 100%. However, for men diagnosed with prostate cancer that has metastasized to other parts of the body, 5-year survival is only about 30%. The reported number of cases of prostate cancer has increased dramatically in recent years, presumably reflecting the widespread use of prostate-specific antigen (PSA) testing. The incidence of prostate cancer is highest in men of African descent and lowest in Asians. Prostate cancer clearly has a genetic factor. Many genetic mutations have been implicated in the development of prostate cancer, most notably the *BRCA2* and *BRCA1* mutations. The possibility that vasectomy may be associated with an increased risk of prostate cancer has not been substantiated. Prostate cancer is almost always an adenocarcinoma.

Diagnosis

The use of PSA-based screening has changed the way prostate cancer is diagnosed. An increased serum PSA concentration may indicate the presence of prostate cancer in asymptomatic men and prompt a digital rectal examination. Detection of a discrete nodule or diffuse induration on digital rectal examination leads to suspicion of prostate cancer, especially in the presence of impotence or symptoms of urinary obstruction (frequency, nocturia, hesitancy, urgency). However, the rectal

examination can evaluate only the posterior and lateral aspects of the prostate. If the rectal examination indicates the possible presence of cancer, transrectal ultrasonography and biopsy are needed regardless of the PSA concentration. There is a much greater likelihood of detecting cancer if the PSA level is higher than 10 ng/mL, regardless of the findings on rectal examination. Infrequently, patients present with symptoms of metastatic disease, such as bone pain and weight loss.

Treatment

Treatment of prostate cancer is guided by several factors, including the anatomic extent of the disease, histologic grade, PSA velocity, and the general medical condition and life expectancy of the patient. The staging system of the American Joint Committee on Cancer/Union for Internal Cancer Control takes into account anatomic extent of disease using the TNM classification as well as histologic grade, which is based on the Gleason score. Focal, well-differentiated prostate cancers are usually cured by transurethral resection. However, progressive disease may develop in up to 16% of these patients within 8 years. For this reason, more aggressive treatment such as radical prostatectomy or radiation may be indicated in subsets of these patients, especially those younger than 65 years of age. If lymph nodes are involved, radical prostatectomy or definitive radiation therapy may be recommended. Radical prostatectomy can be performed via a retropubic or perineal approach. The retropubic approach permits the surgeon to take lymph node samples for frozen section before beginning the prostatectomy. The advent of robotic surgical approaches to prostate resection has substantially decreased the morbidity associated with prostatectomy. Radiation therapy can be delivered either by an external beam or by implantation of radioactive seeds (brachytherapy). The decision to select surgery or radiation is based on the side effects of each treatment and the patient's overall health. Impotence and urinary incontinence are risks of radical prostatectomy. Preservation of the neurovascular bundles on each side of the prostate may decrease the risk of impotence following surgery. Radiation therapy produces impotence less often, but debilitating cystitis or proctitis may develop. Active surveillance, which involves serial monitoring of PSA level and routine digital rectal examinations, is an option for patients with localized prostate cancer with low-risk features.

Hormone therapy is indicated for management of metastatic prostate cancer because these tumors are under the trophic influence of androgens. Androgen deprivation therapy dramatically reduces testosterone levels and causes tumor regression. Androgen deprivation can be obtained by surgical castration, administration of exogenous estrogens such as diethylstilbestrol, use of analogues of gonadotropin-releasing hormone (GNRH) such as leuprolide that inhibit the release of pituitary gonadotropins, use of antiandrogens such as flutamide that block the action of androgens at target tissues, and combination therapy such as an antiandrogen in combination with a GNRH agonist or bilateral orchiectomy. In patients with high-risk disease, combining androgen deprivation therapy with either abiraterone or docetaxel chemotherapy may prolong survival.

When advanced prostate cancers become resistant to hormone therapy, incapacitating bone pain often develops. There are several approaches to the management of prostate cancer–related bone pain. These include external beam radiation, bone-targeted radioisotopes, and bisphosphonates. Certain systemic chemotherapies have been shown to reduce the occurrence of symptomatic skeletal metastases. These include enzalutamide and abiraterone.

Breast Cancer

Women in the United States have a 12% lifetime risk of developing breast cancer. The risk of death from breast cancer is approximately 3%. Most women in whom breast cancer is diagnosed do not die of the disease.

Risk Factors

The principal risk factors for development of breast cancer are increasing age (75% of cases occur in patients age _ 50 years) and family history (a first-degree relative diagnosed with breast cancer before age 50 increases the risk three- to fourfold). Reproductive risk factors that increase the risk of breast cancer include early menarche, late menopause, late first pregnancy, and nulliparity, which are all presumed to prolong exposure of the breasts to estrogen. Two breast cancer susceptibility genes (*BRCA1* and *BRCA2*) are mutations that are inherited as autosomal dominant traits.

Screening

Recommended screening strategies for breast cancer include the triad of breast self-examination, clinical breast examination by a professional, and screening mammography. Clinical breast examination by a professional and regular mammography appear to decrease mortality from breast cancer by approximately one-third in women older than age 50. Annual screening mammography is generally recommended for all women beginning between the ages of 40 and 50 years. A small percentage of breast cancers are not detected by mammography, so alternative screening methods such as ultrasonography and/or MRI may be of value in selected patients.

Prognosis

Axillary lymph node invasion and tumor size are the two most important determinants of outcome in patients with early breast cancer. Other established prognostic factors include the histologic grade of the tumor, hormone receptor expression, and human epidermal growth factor 2 (HER2) expression. The absence of estrogen and progesterone receptor expression is associated with a worse prognosis, as is the overexpression of HER2. Most tumors that express hormone receptors are responsive to endocrine therapy. Tumors that exhibit HER2 overexpression are best treated with a regimen that includes HER2-directed agents.

Treatment

Although radical mastectomy (removal of the involved breast, axillary contents, and underlying chest wall musculature) was the principal treatment for invasive breast cancer in the past,

it is seldom used in current practice. Breast conservation therapy, including lumpectomy with radiation therapy, simple mastectomy, and modified radical mastectomy provide similar survival rates. Because the likelihood of distant micrometastases is highly correlated with the number of lymph nodes containing tumor invasion, axillary lymph node dissection provides prognostic information. Sentinel lymph node mapping involves injection of a radioactive tracer or isosulfan blue dye into the area around the primary breast tumor. The injected substance tracks rapidly to the dominant axillary lymph node (sentinel node). If the sentinel node is tumor free, the remaining lymph nodes are also likely to be tumor free, and further axillary surgery can be avoided. The morbidity associated with breast cancer surgery is now largely related to side effects of lymph node dissection such as lymphedema and restricted arm motion. Obesity, weight gain, and infection in the arm are additional risk factors for the development of lymphedema.

Radiation is an important component of breast conservation therapy, since lumpectomy alone is associated with a high incidence of recurrence. Radiation after a mastectomy is reserved for women with extensive local disease such as skin and chest wall invasion and extensive lymph node involvement.

Systemic Treatment

Many women with early-stage breast cancer already have distant micrometastases at the time of diagnosis. Systemic therapy is intended to prevent or delay recurrence of the disease. Tamoxifen and other chemotherapies as well as ovarian ablation are the most commonly used modes of systemic therapy.

Tamoxifen. Tamoxifen is a mixed estrogen agonist-antagonist often referred to as a selective estrogen receptor modulator (SERM). It acts as an estrogen antagonist on tumor cells but has agonist properties on some other targets. Five years of tamoxifen therapy in patients with estrogen receptor-positive tumors is associated with a significant reduction in the risk of recurrence. Benefits of tamoxifen therapy are similar for node-positive and node-negative patients. However, tamoxifen does not alter outcome in patients with minimal or no estrogen receptor expression on their tumors.

Tamoxifen can cause body temperature disturbances (hot flashes), vaginal discharge, and an increased risk of developing endometrial cancer. Megestrol (progestin) may be administered to decrease the severity of hot flashes associated with tamoxifen treatment. Tamoxifen lowers serum cholesterol and low-density lipoprotein concentrations, but the importance of these effects in reducing the risk of ischemic heart disease is unclear. Tamoxifen preserves bone density in postmenopausal women by its proestrogenic effects and may decrease the incidence of osteoporosis-related fractures of the hip, spine, and radius. There is an increased risk of thromboembolic events, including deep venous thrombosis, pulmonary embolism, and stroke with tamoxifen therapy.

Chemotherapy. Combination chemotherapy decreases the rate of recurrence and mortality from breast cancer in both node-positive and node-negative patients. The maximum benefit seems to be in node-positive women younger than 50 years of age. A commonly used combination chemotherapy regimen includes cyclophosphamide, methotrexate, and fluorouracil. The chemotherapy dose is an important determinant of cell kill. Conventional adjuvant chemotherapy usually begins within a few months of surgery. Chemotherapy or radiation before surgery may be used in selected patients in an attempt to decrease tumor size and improve breast conservation. In high-risk women with multiple positive lymph nodes, high-dose chemotherapy with alkylating drugs combined with autologous bone marrow transplantation may be considered.

Chemotherapy for breast cancer has adverse effects that typically resolve following treatment such as nausea and vomiting, hair loss, and bone marrow suppression. The most serious late sequelae of chemotherapy are leukemia and doxorubicin-induced cardiac impairment. Patients with symptoms of cardiac disease or congestive heart failure should be evaluated with an ECG and echocardiography. Myelodysplastic syndromes or acute myeloid leukemia can arise after chemotherapy, but the incidence is low (< 1%). High-dose radiation therapy may be associated with brachial plexopathy or nerve damage, pneumonitis, and/or pulmonary fibrosis.

Supportive Treatment

Palliation of symptoms and prevention of complications are primary goals when treating advanced breast cancer. The most common site of breast cancer metastases is bone. Regular administration of bisphosphonates in addition to hormone therapy or chemotherapy can decrease bone pain and lower the incidence of bone complications by inhibiting osteoclastic activity. Adequate pain control is usually achieved with sustained-release oral and/or transdermal opioid preparations.

Management of Anesthesia

Preoperative evaluation includes a review of potential side effects related to chemotherapy. Placement of intravenous catheters in the arm at risk of lymphedema is avoided because of the potential to exacerbate lymphedema and the susceptibility to infection. It is also necessary to protect that arm from compression (as from a blood pressure cuff) and heat exposure. The presence of bone pain and pathologic fractures is noted when considering regional anesthesia and when positioning patients during surgery. Selection of anesthetic drugs, techniques, and special monitoring is influenced more by the planned surgical procedure than by the presence of breast cancer. Of note, if isosulfan blue dye is injected during the surgical procedure, it is likely that pulse oximetry will demonstrate a transient spurious decrease in the measured Spo_2 value, usually a 3% decrease.

LESS COMMON CANCERS ENCOUNTERED IN CLINICAL PRACTICE

Less commonly encountered cancers include cardiac tumors, head and neck cancer, and cancers involving the endocrine glands, liver, gallbladder, genitourinary tract, and reproductive organs. Lymphomas and leukemias are examples of cancers involving the lymph glands and blood-forming elements.

Cardiac Tumors

Cardiac tumors may be primary or secondary, benign or malignant. Metastatic cardiac involvement occurs 20 to 40 times more often than a primary malignant cardiac tumor. Among the most common forms of cancer to metastasize to the heart include melanoma, lung cancer, and breast cancer. Secondary cardiac involvement is also fairly common with leukemias and lymphomas. Cardiac myxomas account for 40% to 50% of benign cardiac tumors that occur in adults. About three-quarters of cardiac myxomas occur in the left atrium, and the remaining 25% occur in the right atrium. Myxomas often demonstrate considerable movement within the cardiac chamber during the cardiac cycle.

Signs and symptoms of cardiac myxomas reflect interference with filling and emptying of the involved cardiac chamber. Left atrial myxoma may mimic mitral valve disease with development of pulmonary edema. Right atrial myxoma often mimics tricuspid disease and can be associated with impaired venous return and evidence of right heart failure. Emboli occur in about a third of patients with cardiac myxomas. These emboli are composed of myxomatous material or thrombi that have formed on the tumor. About 80% of cardiac myxomas are located in the left atrium; as a result, systemic embolism is particularly frequent and often involves the retinal and cerebral arteries. Cardiac myxomas may occur as part of an autosomal dominant disorder called the Carney complex that includes cutaneous myxomas, myxoid fibroadenomas of the breast, pituitary adenomas, and adrenocortical hyperplasia with Cushing syndrome. Echocardiography can determine the location, size, shape, attachment, and mobility of cardiac myxomas.

Surgical resection of cardiac myxomas is usually curative. After the diagnosis has been established, prompt surgery is indicated because of the possibility of embolic complications and sudden death. In most cases, cardiac myxomas can be easily removed because they are pedunculated. Intraoperative fragmentation of the tumor must be avoided. All chambers of the heart are examined to rule out the existence of multifocal disease. Mechanical damage to a heart valve or adhesion of the tumor to valve leaflets may necessitate valvuloplasty or valve replacement.

Anesthetic considerations in patients with cardiac myxomas include the possibility of low cardiac output and arterial hypoxemia due to obstruction at the mitral or tricuspid valve. Symptoms of obstruction may be exacerbated by changes in body position. The presence of a right atrial myxoma prohibits placement of right atrial or pulmonary artery catheters. Supraventricular cardiac dysrhythmias may follow surgical removal of atrial myxomas. In some patients, permanent cardiac pacing may be required because of atrioventricular conduction abnormalities.

Head and Neck Cancers

Head and neck cancers account for approximately 3% to 4% of all cancers in the United States, with a predominance in men older than 50 years of age. Risk factors include cigarette smoking, alcohol consumption, HPV, and Epstein-Barr virus. The most common sites of metastases are lung, liver, and bone. Integrated PET/CT scan is one of the most sensitive tests available for the detection of metastases. Preoperative nutritional therapy may be indicated before surgical resection. The goal of chemotherapy, if selected, is to decrease the bulk of the primary tumor or known metastases, thereby enhancing the efficacy of subsequent surgery or radiation. A secondary goal is eradication of occult micrometastases.

Anesthetic considerations in patients with head and neck cancers include the possibility of distorted airway anatomy, which may not be appreciated on external airway examination. Available imaging and the report of nasal fiberoptic examination should be reviewed preoperatively. Preparation for the possibility of difficult ventilation and/or intubation is necessary even if the airway examination is benign.

Thyroid Cancer

Papillary and follicular thyroid carcinomas are among the most curable of all cancers. Thyroid cancers are more frequent in women. External radiation to the neck during childhood increases the risk of papillary thyroid cancer as does a family history of the disease. Medullary thyroid cancers may be associated with pheochromocytomas in an autosomal dominant disorder known as multiple endocrine neoplasia type 2. This type of thyroid cancer typically produces large amounts of thyrocalcitonin, which provides a sensitive measure of the presence of the disease as well as its cure.

Subtotal and total thyroidectomy result in lower recurrence rates than more limited partial thyroidectomy. Even with total thyroidectomy, some thyroid tissue remains, as detected by postoperative scanning with radioactive iodine. Risks of total thyroidectomy include recurrent laryngeal nerve injury (2%) and permanent hypoparathyroidism (2%). Patients with papillary thyroid cancers require dissection of paratracheal and tracheoesophageal lymph nodes. The growth of papillary and follicular tumor cells is controlled by thyrotropin, and inhibition of thyrotropin secretion with thyroxine improves long-term survival. Postoperative thyroid hormone therapy is also required for patients who undergo total thyroidectomy. Radioiodine may also be administered after thyroidectomy in high-risk patients to ablate residual thyroid tissue. External beam radiation can be used for palliative treatment of obstructive and bony metastases.

Esophageal Cancer

Esophageal cancer exists in two histologic subtypes: squamous cell and adenocarcinoma. Excessive alcohol consumption and chronic cigarette smoking are independent risk factors for the development of squamous cell carcinoma of the esophagus. The risk of adenocarcinoma is highest in people with Barrett esophagus, a complication of gastroesophageal reflux disease. Dysphagia and weight loss are the initial symptoms of esophageal cancer in most patients. The dysphagia may be associated with malnutrition. Difficulty swallowing may result in regurgitation and increase the risk of aspiration. The disease has usually metastasized by the time clinical symptoms are present. The lack of a serosal layer around the esophagus and the presence of an extensive lymphatic system are responsible for the rapid

spread of tumor to adjacent lymph nodes. However, in patients with Barrett esophagus who undergo routine endoscopic surveillance, the disease can be diagnosed at a very early stage.

Despite aggressive treatment, the 5-year survival rate for patients with squamous cell carcinoma of the esophagus is only 15% to 20%. Esophagectomy is often performed for carcinoma of the esophagus and is associated with significant morbidity and mortality. Chemotherapy and radiation may be instituted prior to attempting surgical resection. Adenocarcinomas are not sensitive to radiotherapy, but chemotherapy and surgery may improve survival. Palliation may include surgical placement of a feeding tube, bougienage for the treatment of esophageal strictures, or endoscopic stent placement.

The likelihood of underlying alcohol-induced liver disease and chronic obstructive pulmonary disease from cigarette smoking are considerations during anesthetic management of patients with esophageal cancer. Patients with esophageal disease are at high risk of pulmonary aspiration, therefore it is prudent to consider using full stomach precautions and a rapid-sequence intubation technique. One-lung ventilation may be necessary if a thoracotomy or thoracoscopy is planned. Extensive weight loss often parallels a decrease in intravascular fluid volume and manifests as hypotension during induction and maintenance of anesthesia.

Gastric Cancer

The incidence of gastric cancer has decreased dramatically since 1930 when it was the leading cause of cancer-related death among men in the United States. Achlorhydria (loss of gastric acidity), pernicious anemia, chronic gastritis, and *Helicobacter* infection contribute to the development of gastric cancer. The presenting features of gastric cancer (indigestion, epigastric distress, anorexia) have considerable overlap with those of benign peptic ulcer disease. Approximately 90% of gastric cancers are adenocarcinomas. Gastric cancer is usually far advanced when signs and symptoms such as weight loss, palpable epigastric mass, jaundice, or ascites appear; only about 50% of patients have localized disease at the time of diagnosis.

Complete surgical eradication of gastric tumors with resection of adjacent lymph nodes is the only treatment that may be curative. Resection of the primary lesion also offers the best palliation. Both neoadjuvant and postoperative chemotherapy or chemoradiotherapy are commonly employed to improve disease-free survival.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) occurs most often in men with chronic liver disease caused by hepatitis B or hepatitis C virus, alcohol consumption, or hemochromatosis. Initial manifestations are typically abdominal pain, palpable abdominal mass, and constitutional symptoms such as anorexia and weight loss. There may be compression of the inferior vena cava and/or portal vein, lower extremity edema, ascites, and jaundice. Laboratory studies reflect the abnormalities associated with underlying chronic liver disease. Liver function tests are likely to be abnormal. CT and MRI can determine the anatomic location of the tumor, although angiography may be more useful for distinguishing hepatocellular cancer (hypervascular) from hepatic metastases (hypovascular) and for determining whether a tumor is resectable. Surgical resection is the mainstay of therapy, although many patients are not surgical candidates because of extensive cirrhosis, impaired liver function, or the presence of extrahepatic disease. Anesthesia for hepatic resection carries significant morbidity and mortality, especially in patients with preexisting liver disease. The Child-Pugh classification and the Model for End-Stage Liver Disease (MELD) score are two measures used to evaluate a patient's surgical risk. Hemorrhage, coagulopathy, hypotension, and liver failure are among the most serious complications. Several alternatives to surgery have emerged. These include radiofrequency ablation, transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and liver transplantation. Systemic chemotherapy has traditionally not been used in the treatment of HCC; however, newer molecularly targeted agents such as sorafenib, lenvatinib, and nivolumab have been demonstrated to improve survival in patients with advanced HCC.

Pancreatic Cancer

Pancreatic cancer, despite its low incidence, is the fourth most common cause of cancer-related death in men and women in the United States. Approximately 95% of pancreatic cancers are exocrine tumors—specifically ductal adenocarcinomas—most commonly occurring in the head of the pancreas. Endocrine tumors, also called neuroendocrine or islet cell tumors, are considerably less common; these tumors may be nonfunctional or they may secrete hormones, including insulin, glucagon, gastrin, and somatostatin. There is no evidence linking this cancer to caffeine ingestion, cholelithiasis, or diabetes mellitus, but cigarette smoking, obesity, and chronic pancreatitis show a positive correlation. Abdominal pain, anorexia, and weight loss are the usual initial symptoms. Pain suggests retroperitoneal invasion and infiltration of splanchnic nerves. Jaundice reflects biliary obstruction in patients with tumor in the head of the pancreas. Diabetes mellitus is rare in patients who develop pancreatic cancer.

Pancreatic cancer may appear as a localized mass or as diffuse enlargement of the gland. Biopsy is needed to confirm the diagnosis. Complete surgical resection is the only effective treatment. Neoadjuvant chemotherapy is sometimes recommended in patients with borderline resectable tumors. Patients most likely to have resectable lesions are those with tumors in the head of the pancreas that cause painless jaundice. Extrapancreatic spread eliminates the possibility of surgical cure. The most commonly employed surgical resection techniques are pancreaticoduodenectomy (Whipple procedure) and subtotal or total pancreatectomy. Pancreaticoduodenectomy is the preferred approach for tumors that involve the pancreatic head or uncinated process, while resection of the distal pancreas is the procedure of choice for tumors in the body or tail of the pancreas. Total pancreatectomy is technically easier but has the disadvantage of producing brittle diabetes mellitus and malabsorption, associated with significant morbidity. Even when surgical resection can be performed, only about 10% of patients with node-positive and 30% with node-negative disease survive

for 5 years. For patients with unresectable disease, palliative procedures include radiation, chemotherapy, and surgical diversion of the biliary system to relieve obstruction. Celiac plexus block is the most effective intervention for treating visceral pain associated with pancreatic cancer. This neurolytic block may be performed using cryotherapy, radiofrequency thermal coagulation, or the injection of caustic agents such as phenol or alcohol. The celiac plexus can be accessed using CT or ultrasound guidance or percutaneously using fluoroscopy. A complication of celiac plexus block is hypotension due to sympathetic denervation in these often hypovolemic patients.

Renal Cell Carcinoma

Renal cell carcinoma (RCC) most often originates in the renal cortex and manifests as hematuria, mild anemia, and flank pain. Risk factors include a family history of RCC and cigarette smoking. RCC is also significantly more common among patients on dialysis who develop acquired cystic disease. Renal ultrasonography can help to distinguish benign renal cysts from more complex masses, and CT and MRI are useful for determining the presence and extent of disease. Laboratory testing may reveal anemia or liver function abnormalities. Paraneoplastic syndromes, especially hypercalcemia due to ectopic PTH secretion and erythrocytosis due to ectopic erythropoietin production, are not uncommon. The only curative treatment for RCC confined to the kidneys is radical nephrectomy with regional lymphadenectomy. Cytoreductive or debulking nephrectomy also improves survival in patients with advanced disease. Surgical resection of isolated metastatic tumors is also sometimes performed. In addition, patients with locally advanced or metastatic disease are candidates for systemic immunotherapy or molecularly targeted therapies such as antiangiogenic chemotherapies.

Bladder Cancer

Bladder cancer occurs more often in men and is associated with cigarette smoking and chronic exposure to chemicals used in the dye (aniline), leather, and rubber industries. The most common presenting feature is hematuria.

Treatment of noninvasive bladder cancer includes endoscopic resection and intravesical chemotherapy, often with BCG. Carcinoma in situ of the bladder often behaves aggressively and may require cystectomy to help prevent muscle invasion and metastatic spread. In men, radical cystectomy includes removal of the bladder, prostate, and proximal urethra. In women, a hysterectomy, oophorectomy, and partial vaginectomy are required. Urinary diversion is either by ureteroileostomy (ileal conduit) or creation of an artificial bladder (neobladder) from segments of small bowel. Traditional treatments for metastatic disease include radiation and chemotherapy.

Testicular Cancer

Although testicular cancer is rare, it is the most common cancer in young men and represents a tumor that can be cured even when distant metastases are present. Testicular cancer usually presents as a painless testicular mass. When the diagnosis is suspected, an inguinal orchiectomy is performed, and the diagnosis is histologically confirmed. A transscrotal biopsy is not performed because disruption of the scrotum may predispose to local recurrence and/or metastatic spread to inguinal lymphatics. Men with a history of cryptorchidism are at higher risk of testicular cancer even if orchiopexy is performed. Germ cell cancers, which account for 95% of testicular cancers, can be subdivided into seminomas and nonseminomas. Seminomas metastasize through regional lymphatics to the retroperitoneum and mediastinum, and nonseminomas spread hematogenously to viscera, especially the lungs.

Radical orchiectomy is the treatment of choice for testicular malignancies. Semen cryopreservation prior to surgery may be performed for preservation of fertility. Cisplatin-based chemotherapy and/or radiation therapy may be offered to patients with advanced-stage seminomas. Nonseminomas are not radiation sensitive; they are treated with retroperitoneal lymph node dissection and combination chemotherapy.

Cervical and Uterine Cancer

Cervical cancer is the most common gynecologic malignancy in females aged 15 to 34 years. HPV is detectable in nearly all cases and plays a major role in the pathogenesis of the disease. Vaccination against these viruses is expected to reduce the incidence of cervical cancers in future generations; however, in developing countries, cervical cancer is likely to remain one of the leading causes of cancer-related mortality in women. Carcinoma in situ detected by cervical cytology (Papanicolaou smear) is treated with a conization, whereas more extensive local disease or disease that has metastasized is treated with some combination of surgery, radiation therapy, and/or chemotherapy.

Cancer involving the uterine endometrium occurs most frequently in women 50 to 70 years of age. Risk factors include estrogen replacement therapy at menopause, more than 5 years of tamoxifen treatment for breast cancer, obesity, and nulliparity. Endometrial cancer is often diagnosed at an early stage because 75% to 90% of patients present with postmenopausal or irregular bleeding. The initial evaluation of these patients involves endometrial biopsy or dilation and curettage. In the absence of metastatic disease, a total abdominal hysterectomy and bilateral salpingo-oophorectomy with or without pelvic lymph node evaluation is recommended. Vaginal brachytherapy or pelvic radiation may also be recommended. Patients with high-risk disease may also be treated with adjuvant chemotherapy using carboplatin and paclitaxel.

Ovarian Cancer

Ovarian cancer is the most deadly of the gynecologic malignancies. Ovarian cancer is most likely to develop in women who experience early menarche or late menopause or who have a family history of ovarian cancer. The presence of the *BRCA1* or *BRCA2* gene mutation confers a significant risk of ovarian cancer. Early ovarian cancer is usually asymptomatic, so advanced disease is often present by the time the cancer is discovered. Widespread intraabdominal metastases to lymph nodes, omentum, and peritoneum are frequently present. Surgery is the treatment of choice for both early-stage and advanced ovarian

cancer. Aggressive tumor debulking, even if all cancer cannot be removed, improves the length and quality of survival. Intraperitoneal chemotherapy is indicated postoperatively in most women and is usually well tolerated.

Skin Cancer

Skin cancer is the most common cancer in the United States. Skin cancers are either melanomas or nonmelanomas. Nonmelanomas include basal cell carcinoma and squamous cell carcinoma. Basal cell carcinoma is the most common type of skin cancer. Most of these cancers grow superficially and rarely metastasize, so local treatment (excision, topical chemotherapy, cryotherapy) is usually curative.

Melanoma accounts for only about 5% of all skin cancers, but 75% of skin cancer deaths. The incidence of cutaneous melanoma is increasing. The initial treatment of a suspected lesion is wide and deep excisional biopsy often with sentinel node mapping. Melanoma can metastasize to virtually any organ. Treatment of metastatic melanoma is directed at palliation and can include resection of a solitary metastasis, simple or combination chemotherapy, and/or immunotherapy.

Sunlight (ultraviolet light) is an important environmental factor in the pathogenesis of all times of skin cancer. Other risk factors include skin that easily burns, family history of skin cancer, and immunosuppression.

Bone Cancer

Primary bone malignancies are much less common than benign bone tumors but are associated with significant morbidity and mortality and commonly occur among children and young adults. Bone tumors are classified based on cytology. Among the most common types of bone cancers are multiple myeloma (also called plasma cell myeloma), osteosarcoma, Ewing sarcoma, and chondrosarcoma.

Multiple Myeloma

Multiple myeloma is a malignant neoplasm characterized by poorly controlled growth of a single clone of plasma cells that produce a monoclonal immunoglobulin (M protein). The diagnosis is usually made through detection of the M protein by serum and urine protein electrophoresis. Multiple myeloma accounts for approximately 17% of hematologic cancers and 1% to 2% of all cancers in the United States. The disease is more common in elderly patients (median age at time of diagnosis is 66 years), and it is two to three times more common in blacks compared to whites.

The most frequent manifestations of multiple myeloma are bone pain (often from vertebral collapse), anemia, renal failure, and hypercalcemia. Extramedullary plasmacytomas can produce compression of the spinal cord. This occurs in approximately 10% of patients. Other extramedullary sites of tumor invasion include the liver, spleen, ribs, and skull. Inactivation of plasma procoagulants by myeloma proteins may interfere with coagulation. These proteins coat the platelets and interfere with platelet function. The presence of hypercalcemia from excessive bone destruction should be suspected in patients with myeloma who develop nausea, fatigue, confusion, or polyuria. Renal insufficiency occurs in approximately 25% of patients with multiple myeloma either due to deposition of an abnormal protein (Bence-Jones protein) in renal tubules or the development of acute renal failure. Amyloidosis or immunoglobulin deposition can cause nephrotic syndrome or contribute to renal failure. The combination of hypogammaglobulinemia, granulocytopenia, and depressed cell-mediated immunity increases the risk of infection. Development of fever in patients with multiple myeloma is an indication for antibiotic therapy. In an estimated 20% of patients, multiple myeloma is diagnosed by chance in the absence of symptoms when screening laboratory studies reveal increased serum protein concentrations.

Treatment of overt symptomatic multiple myeloma most often includes autologous stem cell transplantation and chemotherapy. Palliative radiation is limited to patients who have disabling pain and a well-defined focal process that has not responded to chemotherapy. The median duration of remission is approximately 2 years and the median survival approximately 3 years, but these vary depending on cytogenetic characteristics of the myeloma cells. Signs of spinal cord compression due to an extramedullary plasmacytoma require early confirmation and prompt radiation. Urgent decompressive laminectomy to avoid permanent paralysis may be needed if radiation is not effective. Chemotherapy reverses mild renal failure in many patients with multiple myeloma, but temporary hemodialysis may be necessary until chemotherapy becomes effective. Erythropoietin therapy may be indicated to treat anemia. Hypercalcemia requires prompt treatment with volume expansion and saline dieresis. Bed rest is avoided because inactivity leads to further mobilization of calcium from bone and increases the risk for deep venous thrombosis.

The presence of compression fractures requires caution when positioning patients during anesthesia and surgery. Fluid therapy will depend on the degree of renal insufficiency and/or hypercalcemia. Pathologic fractures of the ribs may impair ventilation and predispose to the development of pneumonia. Hyperviscosity syndrome is a rare complication of multiple myeloma. Symptoms include oropharyngeal bleeding, neurologic symptoms, and heart failure. Plasmapheresis is the treatment of choice. Patients with multiple myeloma are also at increased risk of venous thromboembolism, especially when treated with immunomodulatory drugs such as thalidomide. Prophylaxis with warfarin, low-molecular-weight heparin, or aspirin is often advised.

Osteosarcoma

Osteosarcoma occurs in a bimodal age distribution, with a peak in early adolescence and in adults over the age of 65. Pain is a frequent presenting complaint, and lesions occur most commonly in the distal femur or proximal tibia. A genetic predisposition is suggested by the association of this tumor with retinoblastoma. In older patients, osteosarcoma commonly occurs in the context of Paget disease or previously irradiated bone. MRI is used to assess the extent of the primary lesion and the existence of metastatic disease, especially in the lungs. Serum alkaline phosphatase concentrations are likely to be

increased, and the levels correlate with prognosis. Treatment consists of combination chemotherapy followed by limb salvage surgery or amputation. Pulmonary resection may be indicated in patients with solitary metastatic lesions. Localized disease has a 70% to 80% 5-year survival rate.

Ewing Sarcoma

Ewing sarcoma (also classified as a peripheral primitive neuroectodermal tumor) usually occurs in children and young adults and most often involves the pelvis, femur, or tibia. Ewing sarcoma is highly malignant, and metastatic disease is often present at the time of diagnosis. Specific risk factors are largely unknown. Treatment consists of surgery, chemotherapy, and adjuvant radiation therapy.

Chondrosarcoma

Chondrosarcoma is a slow-growing tumor that is characterized by the production of chondroid cartilage. It usually involves the pelvis, ribs, or upper end of the femur or humerus and is most common in young or middle-aged adults. Surgical excision is the only potentially curable treatment. Radiation therapy is also sometimes employed. These tumors tend to be chemoresistant so chemotherapy is rarely utilized.

LYMPHOMAS AND LEUKEMIAS

Hodgkin Lymphoma

Hodgkin lymphoma is a lymphoma that seems to have infective (Epstein-Barr virus), genetic, and environmental associations. Another factor that appears to predispose to the development of lymphoma is impaired immunity as seen in patients after organ transplantation or in patients infected with the human immunodeficiency virus. The most useful diagnostic test in patients with suspected lymphoma is lymph node biopsy.

Hodgkin lymphoma is a lymph node–based malignancy, and presentation consists of lymphadenopathy in predictable locations, including the neck and anterior mediastinum. Characteristic systemic symptoms also occur, including pruritus, night sweats, and unexplained weight loss. Moderately severe anemia is often present. Peripheral neuropathy and spinal cord compression may occur as a direct result of tumor growth. Bone marrow and central nervous system involvement is unusual in Hodgkin lymphoma but not in other lymphomas.

Staging of the disease is accomplished by CT and PET scanning of the chest, abdomen, and pelvis, biopsy of available nodes, and bone marrow biopsy. Characteristic findings on microscopy include the presence of Reed-Sternberg (also called Hodgkin) cells. Precise definition of the extent of nodal and extranodal disease is necessary to select the proper treatment strategy. Patients are usually treated with a combination of chemotherapy and radiation. Cure can be achieved with 20-year survival rates approaching 90%, especially in younger patients.

Non-Hodgkin Lymphoma

Non-Hodgkin lymphomas (NHLs) are divided into subtypes based on cell type and immunophenotypic and genetic features. They can be of B-cell, T-cell, or NK-cell origin. Treatment and prognosis vary widely depending on subtype. Chemotherapy is the first-line treatment for most NHLs. Hematopoietic stem cell transplantation can be used in refractory cases.

Leukemia

Leukemia is the uncontrolled production of leukocytes owing to cancerous mutation of lymphogenous or myelogenous cells. Lymphocytic leukemias begin in lymph nodes and are named according to the type of hematopoietic cells that are primarily involved. Myeloid leukemia begins as cancerous production of myelogenous cells in bone marrow with spread to extramedullary organs. The principal difference between normal hematopoietic stem cells and leukemia cells is the ability of the latter to continue to divide. The result is an expanding mass of cells that infiltrate the bone marrow, rendering patients functionally aplastic. Eventually bone marrow failure is the cause of fatal infections or hemorrhage due to thrombocytopenia. Leukemia cells may also infiltrate the liver, spleen, lymph nodes, and meninges, producing signs of dysfunction at these sites. Extensive use of nutrients by rapidly proliferating cancerous cells depletes amino acid stores, leading to patient fatigue and metabolic starvation of normal tissues.

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (or acute lymphoblastic lymphoma) is the most common childhood malignancy but also occurs in adults. Hepatomegaly, splenomegaly, lymphadenopathy, fever, bone pain, and bleeding are among the most common presenting symptoms. The definitive diagnosis is made via analysis of spinal fluid. Affected patients are highly susceptible to life-threatening opportunistic infection, including that due to *Pneumocystis carinii* and cytomegalovirus. Patients should receive annual influenza vaccination but should only be given inactive immunizations while receiving chemotherapy. Chemotherapy induces remission in more than 90% of children and 40% of adults.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is characterized by the proliferation of monoclonal B lymphocytes. It is the most common leukemia in adults and is more common in men than women. This form of leukemia rarely occurs in children; the median age at diagnosis is approximately 70 years. The diagnosis of CLL is confirmed by the presence of lymphocytosis and lymphocytic infiltrates in bone marrow. Signs and symptoms are highly variable, with the extent of bone marrow infiltration often determining the clinical course. Lymphadenopathy may be prominent. On the other hand, most patients are asymptomatic and are diagnosed when routine blood work reveals lymphocytosis. Autoimmune hemolytic anemia and hypersplenism that results in pancytopenia may occur. Corticosteroids may be useful in treating the hemolytic anemia, but splenectomy may occasionally be necessary. Radiation therapy is often used to treatment localized disease, while chemotherapy is recommended for advanced disease. Five-year survival approximates 75% to 80%.

Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is characterized by an increase in the number of myeloid cells in bone marrow and arrest of their maturation, frequently resulting in hematopoietic insufficiency (granulocytopenia, thrombocytopenia, anemia). It is the most common acute leukemia in adults, and it rarely occurs in children. Clinical signs and symptoms of AML are diverse and nonspecific, but they are usually attributable to leukemic infiltration of the bone marrow. In some patients fever due to infection is the initial presenting symptom. Other patients will present with complaints of fatigue, bleeding gums or nose bleeds, pallor, and/or headache. Dyspnea on exertion is common due to severe anemia. Leukemic infiltration of various organs (hepatomegaly, splenomegaly, lymphadenopathy), bones, gingiva, and the central nervous system can produce a variety of signs. Hyperleukocytosis (L 100,000 cells/mm^3) can result in signs of leukostasis with ocular and cerebrovascular dysfunction or bleeding. Metabolic abnormalities may include hyperuricemia and hypocalcemia.

Chemotherapy is administered to induce remission. Five-year survival varies from 15% to 70% depending on tumor cell cytogenetics and age at diagnosis. Bone marrow transplantation may be a consideration in patients who do not achieve an initial remission or who relapse after chemotherapy.

Differentiation syndrome (also called retinoic acid syndrome [RAS]) is a unique, potentially lethal complication of induction therapy in patients with acute promyelocytic leukemia. It is often but not exclusively associated with treatment with all-*trans* retinoic acid (tretinoin) and/or arsenic trioxide. Respiratory distress, pulmonary infiltrates, fever, and hypotension are common presenting symptoms. The etiology is unclear but may be related to release of cytokines from myeloid cells, which causes capillary leak syndrome. High-dose corticosteroid administration is the most commonly employed treatment for RAS.

Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) manifests as myeloid leukocytosis with splenomegaly. In most cases there is a prolonged dormant phase in which patients are asymptomatic. The disease then progresses through an accelerated phase followed by blast crisis. This latter condition resembles acute leukemia and signals a poor prognosis. High leukocyte counts may predispose to vascular occlusion. Hyperuricemia is common and is treated with allopurinol. Cytoreduction therapy with hydroxyurea, chemotherapy, leukapheresis, and splenectomy may be necessary. CML is often treated with tyrosine kinase inhibitors such as imatinib, which target the constitutively active BCR-ABL tyrosine kinase implicated in the pathogenesis of CML. This class of drugs is successful in the vast majority of patients. Hematopoietic stem cell transplantation or other combination chemotherapies are alternatives if primary treatment is unsuccessful.

Hematopoietic Stem Cell Transplantation

HSCT offers an opportunity for cure for several otherwise fatal diseases. Hematopoietic stem cells can be obtained from various sources, including peripheral blood, umbilical cord blood, or bone marrow. Autologous bone marrow transplantation entails collection of the patient's own bone marrow for subsequent reinfusion, whereas allogeneic transplantation uses bone marrow or peripheral blood elements from an immunocompatible donor. Syngeneic transplants refer to the use of hematopoietic progenitor cells from an identical twin. Regardless of the type of bone marrow transplantation, recipients must undergo a preprocedural regimen designed to achieve functional bone marrow ablation. This is produced by a combination of total body radiation and chemotherapy. Although in recent years the use of mobilized stem cells from peripheral blood has become more common, bone marrow harvesting remains a well-established method of stem cell harvesting. Bone marrow is usually harvested by repeated aspirations from the posterior iliac crest. For allogeneic bone marrow transplantation with major AB incompatibility between donor and recipient, it is necessary to remove mature erythrocytes from the graft to avoid a hemolytic transfusion reaction. Removal of T cells from the allograft can decrease the risk of graft-versus-host disease (GVHD).

Processing of the harvested bone marrow may take 2 to 12 hours. The condensed bone marrow volume (approximately 200 mL) is then infused into the recipient through a central venous catheter. From the systemic circulation the bone marrow cells pass into the recipient's bone marrow, which provides the microenvironment necessary for maturation and differentiation of the cells. The time necessary for bone marrow engraftment is usually 10 to 28 days, during which time protective isolation of the patient is required.

Anesthesia for Bone Marrow Transplantation

General or regional anesthesia is used during aspiration of bone marrow from the iliac crests. Nitrous oxide might be avoided in the donor because of potential bone marrow depression associated with this drug. However, there is no evidence that nitrous oxide administered during bone marrow harvesting adversely affects marrow engraftment and subsequent function. Substantial fluid losses may accompany this procedure. Blood replacement may be necessary, either with autologous blood transfusion or by reinfusion of separated erythrocytes obtained during the harvest. Perioperative complications are rare, although discomfort at bone puncture sites is predictable.

Complications of Bone Marrow Transplantation

In addition to prolonged myelosuppression, bone marrow transplantation is associated with several specific complications.

Graft-versus-host disease. GVHD is a life-threatening complication of bone marrow transplantation manifesting as organ system dysfunction that most often involves the skin, liver, and gastrointestinal tract. Severe rash, jaundice, and diarrhea are usually seen. This response occurs when immunologically competent T lymphocytes from the donor graft target proteins on the recipient's cells. These proteins are usually human leukocyte antigens (HLAs), which are encoded by the major histocompatibility complex. Even when the patient and host are matched by HLA identity, minor histocompatibility antigens can also provoke GVHD.

Classically, GVHD was defined as acute if it occurred within the first 100 days after transplantation and chronic if symptoms arose more than 100 days after transplantation. However, this convention has been challenged in recent years with recognition that either illness may occur outside of these time periods. As a result, the current preference is to define the disease based on clinical symptoms (Table 27.6).

The incidence of acute GVHD is directly associated with the degree of incompatibility between HLA proteins. It ranges from 35% to 45% in fully matched sibling donors to 60% to 80% in patients with a single HLA mismatch. Patients undergoing allogeneic bone marrow transplantation receive prophylaxis to prevent acute GVHD. These treatments are mainly directed at minimizing the host's immune response. Examples include methotrexate and cyclosporine or tacrolimus. These agents inhibit T-cell activation. Glucocorticoids are the standard therapy for acute GVHD. Extracorporeal photopheresis is an emerging treatment for acute GVHD, which involves removal of a patient's white blood cells, exposure to ultraviolet-A light, followed by reinfusion into the patient. This process induces cellular apoptosis, which in turn prompts an acute antiinflammatory response that appears to reduce the risk of graft rejection.

Chronic GVHD shares features typical of autoimmune diseases. Symptoms include sclerosis of the skin, xerostomia, fasciitis, myositis, transaminitis, pericarditis, nephritis, and restrictive lung disease. The pathophysiology of chronic GVHD is poorly understood, so treatments are limited. Prophylaxis against acute GVHD appears to reduce the risk of chronic GVHD. Extracorporeal photopheresis has shown benefit in some studies. Steroids remain the mainstay of treatment.

Graft rejection. Graft rejection occurs when immunologically competent cells of host origin destroy the cells of donor origin. This is rarely seen in well-matched related-donor transplants but can be seen in transplants from alternative donors.

TABLE 27.6 Manifestations of Acute and Chronic Graft-Versus-Host Disease

Acute	Chronic
Desquamation, erythroderma, maculopapular rash	Lichen planus, systemic sclerosis, poikiloderma
Gastritis, diarrhea, abdominal cramping	Hyperkeratotic oral lesions, mucositis
Mucositis, anorexia, nausea, vomiting	Alopecia, nail dystrophy
Elevated bilirubin, hepatomegaly	Conjunctivitis
Nephritis, nephrotic syndrome	
Interstitial pneumonitis	

Pulmonary complications. Pulmonary complications following HSCT include infection, adult respiratory distress syndrome, chemotherapy-induced lung damage, and interstitial pneumonitis. When interstitial pneumonitis occurs 60 days or more after bone marrow transplantation, it is most likely due to cytomegalovirus or fungal infection.

Sinusoidal obstruction syndrome. Sinusoidal obstruction syndrome (formerly venoocclusive disease) of the liver may occur following allogeneic and autologous HSCT. Risk factors include preexisting liver disease, exposure to high-dose cyclophosphamide, or radiation. Primary symptoms include jaundice, tender hepatomegaly, ascites, and weight gain. The syndrome can manifest within days or as late as 1 year after HSCT. Progressive hepatic and multiorgan failure can develop, and the mortality approaches 50%.

Cancer is a common disease with major consequences to perioperative care. A thorough preoperative evaluation, which includes understanding the implications of the underlying cancer as well as its treatments, is critical for minimizing the risks of surgery and anesthesia.

KEY POINTS

- The fundamental event that causes cells to become malignant is an alteration in the structure of DNA. Tobacco accounts for more cases of cancer than all other known carcinogens combined.
- A commonly used staging system for solid tumors is the TNM system based on tumor size (T), lymph node involvement (N), and distant metastasis (M). This system further groups patients into stages ranging from the best prognosis (stage I) to the poorest prognosis (stage IV).
- Drugs and radiation administered for cancer treatment may produce significant side effects, including cardiomyopathy, pulmonary fibrosis, and peripheral neuropathy. These side effects may have important implications for the management of anesthesia during surgical procedures for cancer treatment as well as operations unrelated to the cancer.
- Induction chemotherapy or high-dose radiation can destroy large numbers of tumor cells and result in tumor lysis syndrome, a major feature of which is acute hyperuricemic nephropathy due to precipitation of uric acid crystals and calcium phosphate in the renal tubules.
- Many patients with cancer exhibit paraneoplastic syndromes. Examples include the syndrome of inappropriate antidiuretic hormone, Cushing syndrome, and Lambert-Eaton syndrome.
- Cancer is the most common cause of hypercalcemia in hospitalized patients, reflecting local osteolytic activity from bone metastases (especially breast cancer) or ectopic parathyroid hormonal activity associated with tumors that arise from the kidneys, lungs, pancreas, or ovaries.
- Mass effects of tumor or metastases can cause life-threatening oncologic crises. Superior vena cava syndrome is caused by spread of cancer into the mediastinum or caval wall that causes engorgement of the jugular and upper extremity veins and diminished venous return to the heart. Increased

intracranial pressure as a result of increased cerebral venous pressure can cause nausea, seizures, and/or diminished consciousness. Superior mediastinal syndrome exists when tracheal compression accompanies superior vena cava syndrome.

- Cancer patients may experience acute pain associated with surgery, chemotherapy, radiation, pathologic fractures, and tumor invasion. Patients with cancer who experience frequent and significant pain often exhibit signs of depression and anxiety.
- Mild to moderate cancer pain is initially treated with acetaminophen and/or NSAIDs. Opioids are indicated in the management of moderate to severe pain. Opioid rotation is one approach to managing opioid tolerance. Alternatives to opioids include serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressant drugs, and gabapentin.
- A neurolytic procedure is an option of last resort for refractory cancer pain in patients with limited life expectancy.
- Hematopoietic stem cell transplantation is a potentially life-saving treatment for many types of cancer, but it has serious potential complications. Graft-versus-host disease occurs when immunologically competent T lymphocytes from a donor graft target proteins on the recipient's cells and incite a profound immune response.

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28

Chronic Pain

Oscar Coppes, Maunak Rana

OUTLINE

Chronic pain is a major health issue throughout the world and is an increasingly challenging preoperative issue for anesthesiologists. Throughout the 1990s, the health care system in the United States began to encourage more routine assessment of pain in patients, leading to the emergence of pain as the "fifth vital sign." This resulted in the release of new pain management standards for hospitals by The Joint Commission in 2001, to encourage appropriate pain assessment and management. As the number of surgeries performed annually continues to grow, there is an increased need to manage patients with a long-standing history of chronic pain throughout their hospital course. Proper management of postoperative pain is critical for perioperative practitioners, as high levels of pain are associated with delirium, chronic pain syndrome, increased hospital stay, low patient satisfaction, and increased opioid use. This chapter offers a review of chronic pain conditions and their impact on anesthetic management. Patients with chronic pain present with unique considerations, including opioid tolerance and opioid-induced hyperalgesia (OIH), central sensitization, concomitant psychiatric conditions that may affect coping skills, and potential implants and devices that impact anesthetic techniques. A brief review of chronic pain in the parturient patient is offered for anesthesiologists working in the obstetric field, as these patients present unique challenges during their delivery. A comprehensive understanding of chronic pain conditions allows anesthesiologists to adjust medication doses and potential regional anesthesia techniques, address issues such a dosing of opioids and continuation of preoperative pain regimens, and optimize multimodal pain therapy, thereby ensuring safe and individualized patient management.

KETAMINE INFUSION

Ketamine, derived from phencyclidine, has been used extensively as an anesthetic agent since the 1960s. At subanesthetic doses, this agent has analgesic effects due to a variety of mechanisms of action. For chronic pain it is thought to reverse central sensitization and enhance descending modulatory pathways; in the acute pain setting the analgesic action is thought to be related to its efficacy as an N-methyl-d-aspartate (NMDA) receptor antagonist. Indications for ketamine infusions include patients at high risk for chronic postsurgical pain and OIH, opioid-tolerant patients, and patients with a history of sleep apnea. Various dosing recommendations for perioperative ketamine have been suggested, and a starting dose regimen is included in Table 28.1. The American Society of Regional Anesthesia (ASRA), American Academy of Pain Medicine (AAPM), and American Society of Anesthesiologists (ASA) released consensus guidelines for intravenous (IV) ketamine infusions for acute pain management in 2018. Recommendations include limiting IV ketamine boluses to 0.35 mg/kg and infusions to 1 mg/kg for patients who do not have intensive monitoring; patient-specific factors may warrant higher doses. Relative contraindications include pregnancy, and patients with active psychosis, poorly controlled cardiovascular disease, and severe liver disease; ketamine can be used in caution in patients with moderate liver disease. Intranasal (IN) ketamine can be a beneficial adjunct for acute pain management in pediatric patients or those with challenging IV access and can be used for amnesia and procedural sedation. Although patient-controlled analgesia (PCA) is a useful tool for helping manage acute pain, the consensus guidelines concluded that the evidence for ketamine IV PCA as the sole analgesic treatment for acute pain was limited, while more robust evidence supported the addition of ketamine to an opioid-based IV PCA.

LIDOCAINE INFUSION

Lidocaine was introduced clinically by Dr. Torsten Gordh, Sweden's first anesthesiologist, in the 1940s. With the trend toward

TABLE 28.1 Perioperative Ketamine Dosing

Short Duration Surgery	Short Duration Surgery	Postoperative Infusion
0.1–0.3 mg/kg intravenous (IV) bolus at anesthesia induction	0.1–0.3 mg/kg IV bolus at anesthesia induction Bolus 0.1–0.3 mg/kg q30-60 min intraoperatively	0.1–0.2 mg/kg IV bolus at anesthesia induction 0.1–0.2 mg/kg/hr infusion Continue infusion for 24–72 hr

TABLE 28.2 Lidocaine Infusion Dosing

Intraoperative Use	Nonoperative Use	Monitoring
Bolus: 1–1.5 mg/kg Ideal Body Weight (IBW) over 10 min Continuous: 0.5–3 mg/kg/hr (IBW), reduce to 1 mg/kg/hr during wound closure	Patients 70–100 kg: 0.5 mg/min Patients 70–100 kg: 0.75 mg/min Patients 101–100 kg: 1 mg/min	Therapeutic concentration: 1.5–6 μg/mL First level obtained when patient either arrives to postanesthesia care unit or 12 hr after initiating therapy, subsequent levels with daily morning labs and/or with dose adjustment Continuous telemetry for dysrhythmia monitoring

opioid-sparing perioperative management, systemic infusions have increasingly been used as an adjunct in the management of acute perioperative pain. Reported benefits include reductions in pain, nausea, ileus duration, opioid requirement, and length of hospital stay (Fig. 28.1). The clinical benefits of lidocaine have been reported to exceed its half-life by more than five times (8–24 hours), thus unlikely to be completely explained by its sodium channel blockade action. These long-lasting effects are believed to be secondary to a modulation of inflammatory signals seen during trauma and surgery. In vitro preclinical studies evaluating systemic administration of lidocaine have shown an impact on several inflammatory mediators, including NMDA receptors and calcium channels. Lidocaine inhibits the priming of polymorphonuclear granulocytes (PMNs), which have a crucial role in the release of proinflammatory cytokines and reactive oxygen species. Local anesthetics have been shown to block PMN priming when the cells are exposed for an extended period of time, even at low concentration. Animal studies have also shown suppression of wide dynamic range (WDR) neurons and inhibition of C fibers, which may help explain lidocaine's antinociceptive actions.

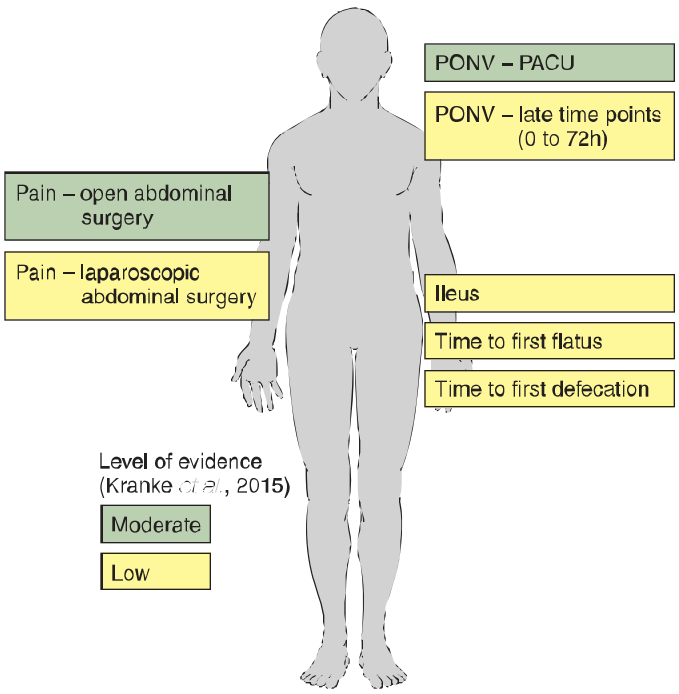

Fig. 28.1 Effects of intravenous lidocaine. *PACU*, Post-anesthesia care unit; *PONV*, postoperative nausea and vomiting. (From Dunn LK, Durieux ME. Perioperative use of intravenous lidocaine. *Anesthesiology*. 2017; 126(4):729–737. doi:10.1097/ALN.0000000000001527.)

Perioperative lidocaine infusion reduces visual analogue scale (VAS) pain scores in patients who have undergone open or laparoscopic abdominal surgery and decreases opioid consumption. Additionally, it can lead to decreased postoperative nausea and vomiting (PONV) and a reduction in the duration of postoperative ileus. Lidocaine infusion also appears to decrease postoperative pain in prostatectomies, colorectal surgery, and thoracic surgery, and reduce postanesthesia care unit (PACU) opioid requirements and pain scores in several ambulatory surgical procedures. Notably there has been no demonstrated association between perioperative lidocaine infusion and delayed discharge from PACU. Long-term benefits of lidocaine infusions include reduction in the incidence of chronic postsurgical pain after mastectomy and an improved quality of life months after major spine surgery. The current optimal dose of lidocaine is still under investigation, and, although rare, patients should be monitored for potential side effects. An example of a protocol from our institution's Acute Pain Service can be seen in Table 28.2. Mild side effects may include visual disturbances and dizziness, while more serious side effects include cardiac toxicity and neurologic changes. Rates of at least 2 mg/kg/hour appear to be associated with a greater reduction in opioid consumption and lower pain scores when compared to lower doses. Monitoring plasma lidocaine levels may help guide dosing to avoid toxic levels (5 μg/mL) and should be considered for patients with hepatic or renal dysfunction who may have decreased metabolism and/or excretion.

PATIENTS WITH CHRONIC OPIOID USE

OIH refers to increased sensitivity to pain in patients exposed to chronic or acute opioid therapy. It is characterized by worsening pain compared to prior opioid use or the development of new pain without evidence of new pathology. Patients with OIH often report a new onset of generalized, burning pain frequently extending beyond the area of initial discomfort. The

physician must exercise caution not to confuse suspected hyperalgesia with inadequate analgesia due to undertreatment. In the latter case, pain reduction should be seen with increasing doses of the medication, whereas in the former further opioid prescribing is largely futile. The mechanism behind this phenomenon appears to be both central and peripheral, and likely results from increased production of nociceptive neurotransmitters, substance P, and calcitonin gene-related peptide (CGRP) within the dorsal root ganglia. There is also sensitization of peripheral nerve endings mediated by excitatory neurotransmitters and activation of the descending signaling pathways leading to up-regulation of spinal dynorphins. In the acute setting, OIH has been mostly reported for patients treated with short-acting opioids, such as remifentanil infusions, with some evidence of elevated pain scores and morphine requirements postoperatively. The precise etiology of OIH with remifentanil when compared to other opioid agonists has yet to be elucidated, but it may be related to its fast onset and offset of action. Meta-analysis of randomized control trials indicates that remifentanil-induced OIH peaks around 1 hour after surgery and may last for up to 24 hours.

In the chronic setting, experimental studies have documented hyperalgesia to heat pain after even just 1 month of opioid therapy. In recent systematic reviews it has been reported that although OIH is evident for patients on chronic opioid therapy, the findings are dependent on the pain modality and assessment measures, with decreased pain tolerance to thermal stimuli but not electrical. Preoperative considerations for these patients include weaning of opioids prior to surgery as tolerated, which is often managed by the patient's opioid prescriber. A preoperative opioid rotation to reduce adverse reactions while simultaneously maintaining adequate analgesia can also be attempted. Preemptive analgesia to prevent an acute onset of hyperalgesia in the immediate or early postoperative period should be utilized. Ketamine, which has been demonstrated to prevent OIH in both animal and human studies, should be strongly considered along with other strategies, including magnesium sulfate and nitrous oxide. Adding opioid-sparing medications can aid in OIH management while reducing opioid needs. In patients suffering from long-lasting OIH, an opioid agonist with concomitant NMDA receptor antagonism such as methadone or a partial opioid agonist and ¯ antagonist such as buprenorphine can be alternative pharmacologic options (Fig. 28.2).

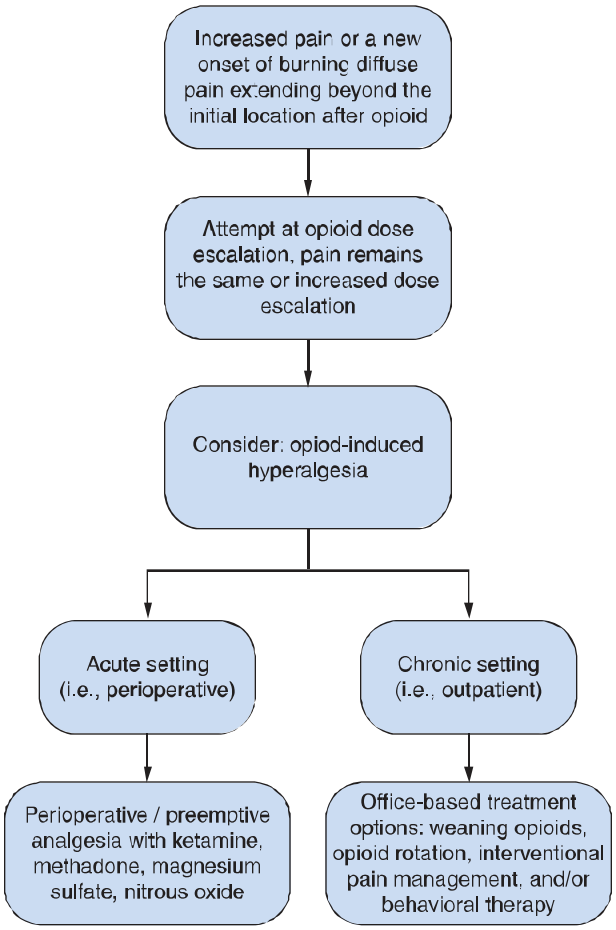

Fig. 28.2 Approach to diagnosis and treatment of opioid-induced hyperalgesia (OIH).

PATIENTS ON BUPRENORPHINE THERAPY

Buprenorphine is a partial _ receptor agonist and ⊥ and ⊔ receptor antagonist; it has a high receptor affinity and slow dissociation. It has been available in both sublingual and oral (PO) formulations since the 1970s. In 2000, the Drug Addiction Treatment Act was passed, allowing for qualified physicians to treat opioid addiction with narcotic medications, including buprenorphine. Buprenorphine is also prescribed for the management of chronic pain; therefore not all patients who present to the operating room (OR) on this medication have a history of opioid misuse. A common sublingual combination formulation is buprenorphine coadministered with naloxone, which can be administered in a film or tablet. The most common buprenorphine-naloxone combination is mixed in a 4:1 ratio. Because naloxone has poor bioavailability when taken sublingually, minimal amounts enter the bloodstream when the combined medication is taken appropriately. However, if taken IN or IV, a significantly larger portion of naloxone enters the bloodstream, thereby acting as a deterrent to potential abuse.

Given buprenorphine's high receptor affinity, it can displace opioid agonists from receptors. The long half-life, up to 6 hours for the IV formulation, and reported analgesic ceiling effect provide further potential for uncontrolled postoperative pain. Patients taking buprenorphine in any form scheduled for elective surgery should be evaluated, and a perioperative plan should be formed in conjunction with their buprenorphine prescriber. A thorough discussion regarding the risks and benefits of either discontinuing or continuing buprenorphine preoperatively must take place. Discontinuing buprenorphine may result in challenging postoperative pain management. Possible risks with discontinuation of buprenorphine include delaying surgery to allow for an adequate taper, opioid abuse relapse, overdose during buprenorphine discontinuation, and opioid withdrawal during reinduction onto buprenorphine. Recent protocols have been published that offer recommendations

based on the urgency of surgery and the level of anticipated postsurgical pain; the majority recommend continuing buprenorphine through the perioperative period. Other recommendations include tapering doses down to 12 to 16 mg/day and returning to preoperative doses as soon as possible.

Managing acute pain in patients who are on buprenorphine can present a unique challenge. The US Center for Substance Abuse Treatment (CSAT) stated in the Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction: Treatment Improvement Protocol (TIP) report that "it may be difficult to achieve analgesia with short-acting opioids in patients who have been maintained on buprenorphine, and higher doses of short-acting opioids may be required." They recommend noncombination opioid analgesics given the potential risk of salicylate or acetaminophen toxicity when administering these medications at the higher doses, which are likely required for patients on chronic opioids. The clinical practice guidelines from ASRA, the ASA Committee on Regional Anesthesia, and the American Pain Society provide recommendations that should be strongly considered in these patients. They include the use of multimodal analgesia with both pharmacologic and nonpharmacologic interventions, PCA for postoperative systemic analgesia when a parenteral route of opioids is needed, and single-injection or continuous regional analgesia when possible (Box 28.1).

PHANTOM LIMB PAIN

The incidence of chronic postoperative pain varies between different surgical procedures, with reports ranging anywhere between 6% and 85%. Limb amputations are notable for a high reported incidence of chronic postoperative pain, occurring in 50% to 80% of patients. Some surveys of amputees claim nearly all (95%) of patients reported experiencing one or more types of amputation-related pain. These symptoms can include phantom limb pain (PLP), a painful sensation in the distribution of the deafferented body area; phantom sensations (PS), nonpainful stimuli originating from the site of amputation; or residual limb pain (RLP), also known as stump pain, sensations felt along and derived from the residual body tissue rather than the amputated limb. The complex pathophysiology underlying PLP has yet to be fully understood; currently both peripheral and central mechanisms are thought to be involved. Peripherally, it is hypothesized that nerve trauma during amputation results in deafferentation, creating neuromas from the proximal severed nerve. This aberrancy ultimately results in an increase in spontaneous spinal cord afferent input. Central mechanisms are thought to derive from both the brain and spinal cord. In the spinal cord, pain likely derives from central sensitization and up-regulation of receptors at the dorsal horn of the spinal cord leading to "wind up phenomenon." At the level of the brain, it is thought that cortical somatosensory reorganization, where the cortical areas of the amputated extremity were taken over by adjacent zones, is a major cause for PLP.

Treatments for PLP include a variety of pharmacologic and procedural options; however, given the overall low evidence of most trials, the best first-line therapy is controversial. Acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) are commonly reported as initial therapy for PLP, although few patients report significant levels of benefit. NMDA receptor antagonists, such as ketamine and memantine, which may halt the sensitization of dorsal horn neurons, are often trialed in these patients, with conflicting results reported. Various trials and case reports have also evaluated the efficacy of antidepressants, which increase norepinephrine and serotonin in the synaptic cleft at supraspinal and spinal levels and result in reinforcement of the descending inhibitory pathways. These include tricyclic antidepressants (TCAs), such as amitriptyline and doxepin, as well as serotonin–norepinephrine reuptake inhibitors (SNRIs), including milnacipran and duloxetine. Anticonvulsants, such as gabapentin and pregabalin, which are commonly used for various peripheral neuropathic pain syndromes, may also offer some benefit, although no studies to date have compared their efficacy. Capsaicin, a member of the vanilloid family, which binds to the vanilloid receptor subtype 1 (TRPV1), can be applied as a patch and may reduce pain intensity. Calcitonin, which may act through either specific binding sites in the central nervous system (CNS) or by impacting descending serotonergic modification on C afferent sensory transmission, has also been trialed for PLP pain relief. A 2016 Cochrane review reported that while the effectiveness of medication management on clinically relevant outcomes remained unclear, morphine, gabapentin, and ketamine demonstrated favorable short-term analgesic efficacy compared with placebo while memantine and amitriptyline may not be effective for PLP. It was cautioned that since the results were largely based on a small number of trials with limited sample size, they should be interpreted with caution and larger, more rigorous randomized controlled trials were needed to reach more definitive conclusions.

Nonpharmacologic treatment includes mirror therapy, first reported in 1996 when Ramachandran and Rogers-Ramachandran used a "virtual reality box" with mirrors reflecting the patient's intact limb, which has been reported as effective in both lower and upper limb amputees. Other complementary therapies may include visual-kinesthetic feedback, hypnosis, and acupuncture. Finally, there is growing literature that neuromodulation may offer benefits to patients with intractable PLP. Motor cortex stimulation, electrical stimulation of the precentral gyrus, has been reported effective in treating patients with various forms of chronic pain and has led to improved pain in patients with PLP. Spinal cord stimulators may offer relief for patients with intractable PLP,

BOX 28.1 Buprenorphine

- Analgesic and addiction-treatment drug with partial receptor agonist at the μ receptor and antagonist at the κ and δ receptors available in oral and sublingual formulations; commonly combined with naloxone.
- May lead to opioid agonist displacement from receptors; has a long half-life (24–42 hr).
- Consider the use of multimodal analgesics and regional anesthesia when appropriate in the perioperative setting.

as may electroconvulsive therapy. There is also some evidence of decreased PLP development in patients who are treated with transcutaneous electrical nerve stimulation after major amputation, although the results were not sustained at the 1-year mark.

As perioperative physicians, anesthesiologists are in a unique position to help decrease the potential development of PLP. Poorly controlled severe pain prior to surgery increases the risk of chronic postsurgical pain, and both preamputation pain and acute PLP intensity are independent predictors for the development of chronic PLP. Perioperative neuraxial regional anesthetic techniques with a variety of infusions, including local anesthetics, clonidine, ketamine, and opioids, may help decrease the development of PLP. Other regional anesthetic techniques, such as continuous local anesthetic infusion through a peripheral nerve catheter, are frequently used in extremity amputations to help with perioperative pain. Although associated with reduced postoperative opioid consumption, a systematic review and meta-analysis found no clear benefit on the development of PLP or stump pain. It should be noted that the quality of evidence for all outcomes was reported as very low, and once again further large trials are required. Perioperative medication management for planned amputations has included ketamine infusions, oral memantine, and oral gabapentin, which may help decrease postoperative pain intensity and rate of PLP development.

PLP continues to be a challenging condition to manage in patients with a history of amputations. Larger trials with longer follow-up are still needed to provide high-quality data that will guide management of this complex and difficult-to-treat condition (Box 28.2).

CANCER

As the global population continues to age and the incidence of cancer increases, anesthesiologists find themselves more frequently anesthetizing patients with a known history of cancer. Up to 40% of patients with cancer suffer from pain, and in advanced disease up to 80% to 90% of patients report moderate to severe pain. Despite optimized use of systemic analgesics, 10% to 30% of people with advanced cancer still report inadequate pain control. The etiology of pain may be from disease progression, iatrogenic, or unrelated to their cancer (e.g., myofascial pain from deconditioning, diabetic neuropathy, or osteoarthritis). Patients with a cancer diagnosis also frequently exhibit signs of depression and increased anxiety, which increases the risk for increased postoperative pain.

Patients with cancer may present to the anesthesiologist when they require diagnostic or therapeutic procedures for their cancer or unrelated surgeries. Optimizing postoperative pain management requires individualized assessment and, if available, a preoperative consultation with a pain physician can help create a plan for symptom management. Often these patients are on preoperative opioid analgesics, which can result in tolerance and/or hyperalgesia. Therefore they may require higher doses of intraoperative opioids, an escalation of the opioid dose in the immediate postoperative period, as well as adjuncts such as intraoperative methadone or ketamine. Many cancer patients may present in the preoperative setting with concerns about postoperative pain management, and every effort should be made to address these concerns prior to surgery. It is critical to review the possible systemic effects of the malignancy and treatment and how it may impact pain management. Cerebral metastatic disease burden, as well as electrolyte abnormalities and malnutrition, may affect the patient's mental status and sometimes require adjustments in analgesic agents. Renal or hepatic disease may impact metabolism or effect of commonly administered analgesic medications, notably acetaminophen and NSAIDs. NSAIDs in particular may be contraindicated in patients with thrombocytopenia or impaired renal function from cancer or ongoing therapy such as platinum-based chemotherapy agents (i.e., cisplatin, carboplatin, and oxaliplatin), which are nephrotoxic and can cause either acute or chronic renal disease. Any disease burden that involves the liver or hepatic blood supply may result in alterations in coagulation; therefore appropriate lab work, including platelets, INR, prothrombin time (PT)/partial thromboplastin time (PTT), must be drawn prior to regional or neuraxial procedures. The potential for CNS or epidural metastatic disease should be investigated, as this may preclude spinal or epidurals (Box 28.3).

FIBROMYALGIA

Fibromyalgia is a chronic pain condition characterized by widespread musculoskeletal pain. Although the disease process has an unknown etiology, it appears to be triggered or aggravated

BOX 28.2 Phantom Limb Pain (PLP)

- Limb amputations have high reported incidence of chronic postoperative pain, occurring in 50% to 80% of patients.
- PLP: a painful sensation in the distribution of the deafferented body area
- Phantom sensations: nonpainful stimuli originating from the site of amputation
- Residual limb pain (or stump pain): felt along and derived from the residual body tissue rather than the amputated limb
- PLP has both central and peripheral mechanisms.
- The short- and long-term effectiveness for medical treatment of PLP is not fully clear; morphine, gabapentin, and ketamine demonstrate favorable short-term analgesic efficacy.
- Larger and more rigorous randomized control trials are needed to work up prevention and treatment.

BOX 28.3 Cancer Pain

- Up to 40% of patients with cancer suffer from pain, and despite optimized use of systemic analgesics, 10% to 30% of people with advanced cancer still report inadequate pain control.
- Often these patients are on preoperative opioid analgesics, which can result in tolerance and/or hyperalgesia.
- Review the possible systemic effects of the malignancy and treatment, including electrolyte abnormalities, malnutrition, and metastatic disease to central nervous system, kidneys, and liver.

by emotional and physical stressors or trauma and does appear to have a component of genetic predisposition. Traditionally it has been clinically diagnosed using the 1990 American College of Rheumatology (ACR) fibromyalgia classification criteria, which required widespread pain present on both sides of the body and both above and below the waist, and physical findings at 11 of 18 defined tender points. In 2010, the ACR approved revised diagnostic criteria, which were further modified in 2011 and 2016. The diagnosis is now fulfilled based on the Widespread Pain Index and a symptom severity scale score, with symptoms present for 3 months or greater and no other disorder that would explain the patient's symptoms.

There has been significant literature describing treatment options for these patients' chronic pain; the American Pain Society Fibromyalgia Panel recommended a multidisciplinary clinical approach, including education, physical training, cognitive behavioral strategies, and pharmacologic therapy. Although it is possible that patients suffering from fibromyalgia may be at a greater risk of chronic postoperative pain, there is very little data to help guide the management of these patients in the perioperative setting. In addition to pain symptoms, these patients often have medical comorbidities that are known to increase the intensity of acute postoperative pain such as anxiety, depression, and poor physical conditioning. Of note there is no evidence that fibromyalgia increases the risk of in-hospital cardiovascular complications in patients undergoing procedures. Similar to other chronic pain conditions, these patients benefit from a comprehensive multimodal approach. Prior to surgery, a history and physical exam should include a detailed report of current symptoms, including location and severity, as well as a thorough list of current and historic medication use. Patients with fibromyalgia are often on pharmacologic medications, including antidepressants, anticepileptic agents, and muscle relaxants, and if possible these should be continued throughout the perioperative period. Gabapentin and pregabalin, which interfere with central sensitization, may be beneficial in the perioperative period and can be started preoperatively if the patient is not taking these medications. The gabapentinoids have also been used to treat generalized anxiety, which may provide anxiolysis for fibromyalgia patients with coexisting anxiety. There is some concern that opioids may have decreased effectiveness in fibromyalgia patients, therefore they should be uptitrated cautiously. Furthermore, ketamine and other NMDA receptor antagonists are useful adjuvants either preoperatively or in the immediate postoperative period, especially for patients on long-term opioid therapy. Since the psychomimetic side effects are particularly undesirable in fibromyalgia patients who present with concurrent psychological symptoms, a benzodiazepine should be administered if needed. Regional anesthesia should strongly be considered as either a primary anesthetic or an adjunct to manage pain, with concurrent continuation of the patient's usual pain medications.

COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome (CRPS) is a chronic neurologic condition characterized by severe pain, most commonly in a limb, with associated sensory, autonomic, motor, and trophic impairment. It is a clinical diagnosis, which can be made following the Budapest Clinical Diagnostic Criteria for Complex Regional Pain Syndrome by the International Association for the Study of Pain (IASP). CRPS type I occurs without direct damage to a nerve, while CRPS type II occurs in a defined region after injury of a nerve or one of its major branches innervating that region. Considerations for operative care include delaying elective surgical procedures until CRPS symptoms are under good control, minimizing operative and tourniquet time, and using minimally invasive approaches to surgery when feasible. Patients with a diagnosis of CRPS often require aggressive pain management postoperatively, and a regional or neuraxial technique with a catheter and infusion of local anesthetic can help manage symptoms. Ketamine infusions at subanesthetic doses have been reported beneficial in treating chronic CRPS symptoms, as have α_2-adrenergic agonists such as clonidine and dexmedetomidine. Therefore, although there is little data on perioperative use of these agents on CRPS patients, they can be considered useful adjuncts to prevent or treat pain symptoms. IV magnesium sulfate infusions may also act to decrease CRPS symptoms and can be utilized as an additional intraoperative infusion to attempt to minimize postoperative symptoms. An increasingly common outpatient management for CRPS patients is spinal cord stimulation, and special considerations may be warranted for intraoperative managements of these patients (see Neuromodulation Devices, later). Postoperatively, patients should be resumed on their home medications as soon as it is deemed safe along with additional medications for acute pain. Indwelling peripheral or neuraxial nerve catheters can help with difficult-to-treat postoperative pain and should be considered as an option if not placed preoperatively. If the patient requires opioid at discharge, methadone can be considered, as the NMDA receptor antagonist actions are beneficial in treating neuropathic pain. Both psychological and physical rehabilitation are useful in helping to manage postoperative chronic pain, with desensitization therapy in particular having been shown to decrease pain in CRPS.

PATIENTS WITH SEVERE OBESITY

The World Health Organization (WHO) uses a class system to define obesity by body mass index (BMI), the ratio of weight (in kilograms) to the square of height (in meters), where a BMI of 30 kg/m^2 or more is generally considered obese. Oftentimes regional anesthesia techniques should be considered in patients with severe obesity, particularly those with concurrent obstructive sleep apnea (OSA), in an effort to reduce the potential for airway-related and respiratory complications. Peripheral nerve blocks and neuraxial techniques allow for reduced need for postoperative opioids, and subsequently a decreased risk of drug-induced respiratory depression. Ultrasound may be required to assist when landmarks are less palpable. Although sedation can be offered during these techniques, a light level of sedation may be prudent. For perioperative opioid dosing, clinical effect has been found to be poorly related to the plasma concentration, therefore it is recommended to start dosing

using lean body weight and then titrate to effect after the patient is awake and protecting their airway. Optimizing multimodal analgesia with NSAIDs, acetaminophen, local anesthetics, and adjunctive medications such as systemic lidocaine, ketamine, and $_2$ agonists allow for an opioid-sparing pain regimen. Various studies have reported a decrease in postoperative pain scores and opioid use after weight loss surgery when protocols, including local anesthetic wound infiltration and NSAIDs, were used. Intraoperative lidocaine infusion as well as a single preoperative dose of gabapentin or pregabalin seem to provide a reduction in pain reported after bariatric surgery as well. For all medications, including those administered for pain relief, intramuscular injections should be used cautiously because of unpredictable absorption.

INTRATHECAL DRUG DELIVERY SYSTEMS

Intrathecal drug delivery systems (IDDS) were first developed in the early 1980s with the goal of increasing flexibility and ability of administering intrathecal opiates. The US Food and Drug Administration (FDA) has approved two implantable and programmable IDDS: Prometra and Medstream. Opioid therapy through IDDS is now offered to patients who suffer from cancer or noncancer chronic pain. Common indications for noncancer pain include chronic back pain, notably patients with failed back syndrome, as well as CRPS, neuropathies, rheumatoid arthritis, and chronic pancreatitis. IDDS are also used to treat chronic spasticity; common patient populations include those with multiple sclerosis and spinal cord injury–induced spasticity. At this time three medications are approved by the FDA for administration via IDDS: morphine, ziconotide, and baclofen; however, fentanyl, hydromorphone, bupivacaine, and clonidine are also regularly utilized.

Anesthesiologists must be prepared for appropriate perioperative management of patients with IDDS, both in the OR and when working in out-of-OR locations. A frequent concern is that these patients may be prone to excessive sedation and respiratory depression with the administration of further parenteral sedating medication. Further issues may include interference with the intrathecal catheter with regional anesthetic techniques, using the IDDS to provide postoperative pain management, and the interference of the pump itself with surgical access. The ASRA Neuromodulation Special Interest Group released recommendations for the perioperative management of these patients. Preoperatively it is recommended that the surgical team creates a perioperative plan with the patient's pain physician or with the hospital's pain service. If intrathecal (IT) medication doses are known, this information should be conveyed to the anesthesia team. Escalation of IT doses prior to surgery should be avoided. Further preoperative recommendations include the use of regional anesthesia whenever feasible. If peripheral or neuraxial continuous catheter techniques are used, they must be done under strict sterile technique. For lumbar epidural analgesia, the procedure should be done under image guidance with the goal of avoiding the implanted device. In obstetric patients undergoing cesarean delivery, the IT catheter entry point must be known, and the entry point for neuraxial anesthesia should be caudad to the catheter. Otherwise, general anesthesia is recommended.

Intraoperatively, the anesthetic plan may include opioids if clinically indicated; however, caution is recommended with continuous opioid infusions. Strong consideration should be given to adjunct therapies, including NSAIDs, ketamine (administered as a bolus of 0.5 mg/kg with a subsequent intraoperative infusion), steroids, and acetaminophen. If the IT pump or catheter is inadvertently damaged during surgery and repair is not feasible, the pump should be turned off and analgesia administered parenterally.

In the postoperative stage, a multimodal pain treatment plan with adjuncts as mentioned earlier and short-acting opioids should be favored over the use of long-acting opioids. PCA, if needed, can be used although a basal rate should be avoided. Apnea monitors and continuous pulse oximetry is recommended, and a transition to short-acting oral opioids is advised. Furthermore, close follow-up with the patient's primary pain physician (preferably within 2 weeks) should be arranged.

Special care should be taken while performing non-OR anesthesia (NORA) for patients with IDDS. MRI procedures can affect the device by causing a temporary motor stall, which resolves after 20 minutes to 24 hours. It is recommended that the pump be interrogated before and after an MRI, and that patients bring an identification card to alert staff of the IDDS prior to imaging. Although rare, complete pump failure has been reported. The Medtronic IDDS is reported as fully MRI compatible in up to 3.0-T scanners, while the Prometra pump (Flowonix) is MRI compatible only with an empty reservoir. Hyperbaric therapy has also been linked to pump motor stall and a risk of variation in drug delivery. It has been advised to avoid pressures above 2.0 atmospheres and to fill IT pumps to capacity prior to any hyperbaric treatment. For patients undergoing radiation therapy, it is recommended the pump be interrogated immediately following the treatment. Medtronic further recommends that high radiation sources (cobalt 60 or radiation) should not be directed at the pump, and if radiation therapy is to be targeted near the pump lead shielding should be used. Recommendations from Medtronic are summarized in Table 28.3.

Box 28.4 provides additional information on IDDS.

NEUROMODULATION DEVICES

Neuromodulation through spinal cord stimulation (SCS), first clinically utilized in the 1960s, has grown as an increasingly common practice for patients with chronic pain. It is critical that anesthesia providers are knowledgeable about perioperative management of these devices. Neuromodulation applies an electrical current, generated in the battery within the implantable pulse generator (IPG), which travels to the electrodes within the epidural space. There are several major companies that produce SCS devices, and information about the management of these devices is found in the labeling information of the manufacturer. It is recommended that prior to all procedures the device be reprogrammed to the lowest amplitude and turned off prior to induction, which decreases the risk of

TABLE 28.3 Medtronic Recommendations for Intrathecal Drug Delivery Systems (IDDS)

Diathermy	Shortwave diathermy should not be used within 30 cm (12 in) of the pump or catheter
Magnetic resonance imaging (MRI)	The pump must be checked after the MRI to confirm it is still working properly. Pump performance has not been tested for MRI using ≥ 3.0 Tesla (T).
Defibrillation or cardioversion	External defibrillation is unlikely to damage the pump; however, after external defibrillation the pump should be interrogated to confirm it is working.
Radiation therapy	High radiation (including cobalt 60 or γ radiation) should not be directed at the pump. If radiation is required near the pump, lead shielding should be used.
Therapeutic magnets (magnetic mattresses, blankets, wrist wraps, elbow wraps)	Keep therapeutic magnets at least 25 cm (10 in) away from the pump.
Radiofrequency or microwave ablation	Safety has not been established.
Psychotherapeutic procedures (electroconvulsive therapy, transcranial magnetic stimulation)	Safety has not been established.
High-output ultrasonics or lithotripsy	Not recommended in patients with IDDS. If lithotripsy must be used, the beam should not be focused within 15 cm (6 in) of the pump.
Computed tomography scan, diagnostic ultrasound, diagnostic x-rays or fluoroscopy, positron emission tomography (PET) scans, magnetoencephalography (MEG)	Unlikely to affect the IDDS.

inadvertent reprogramming during surgery from electromagnetic interference (EMI). If electrosurgical instrument use is planned, it is recommended to avoid monopolar devices; if this is not possible, the electrosurgical unit should be on the lowest setting and the dispersion (grounding) pad should be on the contralateral side of the IPG with as much distance away from the stimulator as possible.

For the NORA anesthesiologist, the SCS can present issues related to possible interaction with the equipment and risk to both the patient and the device. Most manufacturers have recommended avoiding lithotripsy in patients with SCS; however, recommendations are provided if this procedure is unavoidable. These include ensuring the SCS is off prior to the procedure and ensuring functionality afterwards, as well as avoidance of the lithotripsy beam within 15 cm of the implanted device. It is estimated that over 80% of patients with an implanted SCS will require at least one MRI within 5 years of device placement, and between 50% and 70% will require a non-spine MRI within 10 years. If a patient with a SCS is undergoing an MRI, the theoretical risks include magnetic pull on the device, damage to the device, unwanted stimulation, and thermal injury from heating of the epidural leads. Several SCS have conditional MRI compatibility; these can be either full body or only for specific body parts under certain conditions. Furthermore, patients may be implanted with devices that are several years old and have different MRI compatibility than current models. It is recommended that prior to an MRI the device manufacturer and model are identified, and the device representative can provide information about under what MRI conditions the device can be scanned. If a patient is presenting for an elective MRI, it is recommended the scan be delayed until adequate information can be obtained. Finally, for computed tomography (CT) scanning it is recommended that the SCS be turned off during the scan and evaluated for proper function after the scan is completed, as high levels of radiation have resulted in reports of device lead malfunction and shocklike sensations. While the FDA stresses that the presence of an electronic device should not preclude a medically indicated CT and the risk of an adverse event is extremely low, it does state that "when a CT scanner directly irradiates the circuitry of certain implantable or wearable electronic medical devices (i.e., when the device is visible in the resulting CT image), it can cause sufficient electronic interference to affect the function and operation of the medical device."

Radiation therapy (RT), in which a beam of high-dose ionizing radiation is targeted at a tumor site, can damage implanted devices such as pacemakers and SCS, which can lead to device failure. Since there are no studies evaluating RT on SCS systems, recommendations have been extrapolated from implanted cardiovascular device case reports, where the dose limit recommendation has been 5 gray (Gy), with the beam at least 1 cm away from the IPG (Box 28.5).

BOX 28.4 Intrathecal Drug Delivery Systems

- Create a perioperative plan of care with the patient's pain physician or with the hospital's pain service.
- If peripheral or neuraxial continuous catheter techniques are used, maintain strict sterile conditions.
- For lumbar epidural analgesia, the procedure should be done under image guidance with the goal of avoiding implanted devices.
- In the operating room, caution is recommended with continuous opioid infusions, and strong consideration should be given to adjunct medication.
- In the postoperative stage, patient-controlled analgesia can be used if needed; if possible avoid a basal rate of opioids.
- Magnetic resonance imaging (MRI) procedures can affect the device by causing a temporary motor stall; therefore it is recommended the pump be interrogated before and after the MRI.

BOX 28.5 Neuromodulation Devices

- Neuromodulation applies an electrical current generated by a battery and travels to electrodes within the epidural space.
- It is recommended that prior to all procedures the device be reprogrammed to the lowest amplitude and turned off prior to induction for surgeries utilizing electrosurgical tools.
- Avoid monopolar electrosurgery when possible.
- Prior to magnetic resonance imaging (MRI), identify the device manufacturer and model to determine if the device is MRI compatible.

BOX 28.6 Pregnancy

- For obstetric patients with chronic pain, it is recommended to minimize or avoid the use of opioids.
- For those already on chronic opioid therapies, continued opioid agonist therapy is recommended and preferable to supervised withdrawal.
- Pregnant patients on methadone, especially during the third trimester, may require dose adjustments.
- Infants born to women on opioid therapy during pregnancy should be monitored by a pediatric trained health care provider after birth for neonatal abstinence syndrome.
- Although there are no studies examining the effect of spinal cord stimulation (SCS) on human fetal development, the current recommendation of SCS manufacturers is to inactivate the device at gestation.

PREGNANCY

The parturient patient offers unique challenges to anesthesiologists (Box 28.6). For those patients suffering from chronic pain, special attention must be paid to managing them through their pregnancy safely. Antepartum maternal opioid use has become more prevalent, with a near fivefold increase from 2000 to 2009, and substance use has been identified as a major risk factor for pregnancy-associated mortality. The American College of Obstetricians and Gynecologists (ACOG) released a committee opinion in 2017 on opioid use and opioid use disorder in pregnancy. Overall, it is concluded that early universal screening, brief interventions, and referral for treatment of pregnant women with opioid use disorder lead to improved infant and maternal outcomes. While it should be noted that studies evaluating the link between opioid pharmacotherapy during pregnancy and risks of birth defects have been conflicting, this must be balanced against the clear risks associated with the ongoing misuse of opioids by a pregnant woman. Screening for substance use, including opioid use, should be done by the obstetric physician at the first prenatal visit. For obstetric patients with chronic pain, it is recommended to minimize or avoid the use of opioids, with special attention to be given to alternative therapies, including nonopioid pharmacology and nonmedical therapies. For those already on chronic opioid therapies, continued opioid agonist therapy is recommended and preferable to supervised withdrawal, which is associated with high relapse rates and could result in worse outcomes in both the pregnant patient and fetus. Overall, continued opioid pharmacotherapy along with prenatal care reduces the risk of obstetric complications. For pregnant patients on methadone, pharmacokinetic and physiologic changes that occur during may require dose adjustments, most notably in the third trimester, when increased metabolism may require more frequent dosing. There is evidence supporting the use of buprenorphine for opioid use disorder in this patient population, and while the monoproduct without any adjunctive naloxone has been recommended to avoid potential prenatal exposure to naloxone, especially if injected, recent studies that evaluated the use of buprenorphine with naloxone found no adverse effects in the obstetric population. It is recommended that infants born to women on opioid therapy during pregnancy should be monitored by a pediatric trained health care provider after birth for neonatal abstinence syndrome. After delivery, breastfeeding is not contraindicated for patients on stable opioid doses.

Obstetric chronic pain patients with implanted SCS present a unique consideration for the anesthesiologist. It is critical that practitioners who care for obstetric patients familiarize themselves with indications and management of SCS in this population. There is an accumulation of both preclinical and clinical data that seem to suggest low-frequency electric and magnetic fields (EMF) do not adversely affect fertility and pregnancy; however, the continued concern for possible teratogenic and aborticide effects of neuromodulation have not been excluded. Therefore, although there are no studies examining the effect of SCS on human fetal development, the current recommendation of SCS manufacturers is to inactivate the device at gestation. The current location of the leads and battery should be ascertained by reviewing previous imaging. There are several case reports of successful neuraxial anesthetic techniques utilized during which a meticulous sterile technique is essential to minimize any potential infection risk. Intrathecal medications have no documented impact on SCS function, and medications injected intrathecally or epidurally are not likely to lead to SCS lead migration given that fibrous deposits form around the leads in the epidural space, which decrease the risk of inadvertent movement.

KEY POINTS

- Understanding of chronic pain allow anesthesiologist to offer multimodal techniques to optimize perioperative care in a challenging patient population.
- Buprenorphine has gained increased use in chronic pain patients, anesthesiologists must be aware of extended half life of this agent and its impact on managing acute pain.
- Phantom Limb Pain is a challenging perioperative condition and requires addressing both central and peripheral mechanisms with the use of multimodal therapies and regional techniques.
- Cancer patients presenting pre-operatively may have iatrogenic and disease related phenomenon leading to tolerance and hyperalgesia, which affects perioperative pain management.
- Patients on intrathecal therapy require caution when considering long acting or continuous opioids, as well as other agents that may lead to sedation.

- It is recommended for spinal cord stimulators to be reprogrammed prior to induction for surgeries utilizing electrosurgical tools.
- The judicious use of opioids in obstetric patients with chronic pain should be followed with close care to monitor the effects of this therapy on the patient and the developing fetus.

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29

Psychiatric Disease, Substance Use Disorders, and Drug Overdose

Melissa B. Weimer, Roberta L. Hines

OUTLINE

The prevalence of mental illness and substance use disorders in the United States is about 30%, so these conditions are often present in patients undergoing anesthesia and surgery. Effects of and potential drug interactions with psychotropic medications are important perioperative considerations, as are potential behavioral issues. In addition, substance use and suicide represent significant occupational hazards for anesthesiologists.

MOOD DISORDERS

Mood is defined as a temporary state of mind, temper, or feeling. Thus moods are transient. Mood disorders are characterized by disturbances in the regulation of mood, behavior, and affect that are longer lasting or even lifelong. They are typically divided into three classes: (1) depressive disorders, (2) bipolar disorders, and (3) depression associated with medical illness or substance use.

Depression

Depression is a common psychiatric disorder, affecting 6% to 7% of the population (Fig. 29.1). It is distinguished from normal sadness and grief by the severity and duration of the mood disturbance. There is a familial pattern to major depression, and females are affected more often than males. A significant number of patients with major depression attempt suicide, and about 15% are successful. Pathophysiologic causes of major depression are unknown, although abnormalities of amine neurotransmitter pathways are the most likely etiologic factors.

Diagnosis

The diagnosis of major depression is based on the persistent presence of at least five of the symptoms noted in Table 29.1 for a period of at least 2 weeks that is a change from previous functioning and not attributed to another medical condition. There is a profound loss of pleasure in previously enjoyable activities (anhedonia). Organic causes of irritability or mood changes and a normal reaction to a major loss (e.g., death of a loved one, loss of a job) must be excluded. Depressive symptoms often are present in patients with cardiac disease, cancer, neurologic diseases, diabetes mellitus, hypothyroidism, and human immunodeficiency virus (HIV) infection. This depression can be a situational depression caused by patients' reaction to the health condition with which they are now confronted, which may compromise both the quality and quantity of their life. It could also be directly related to the medical illness itself or be a side effect of medications used to treat the medical illness.

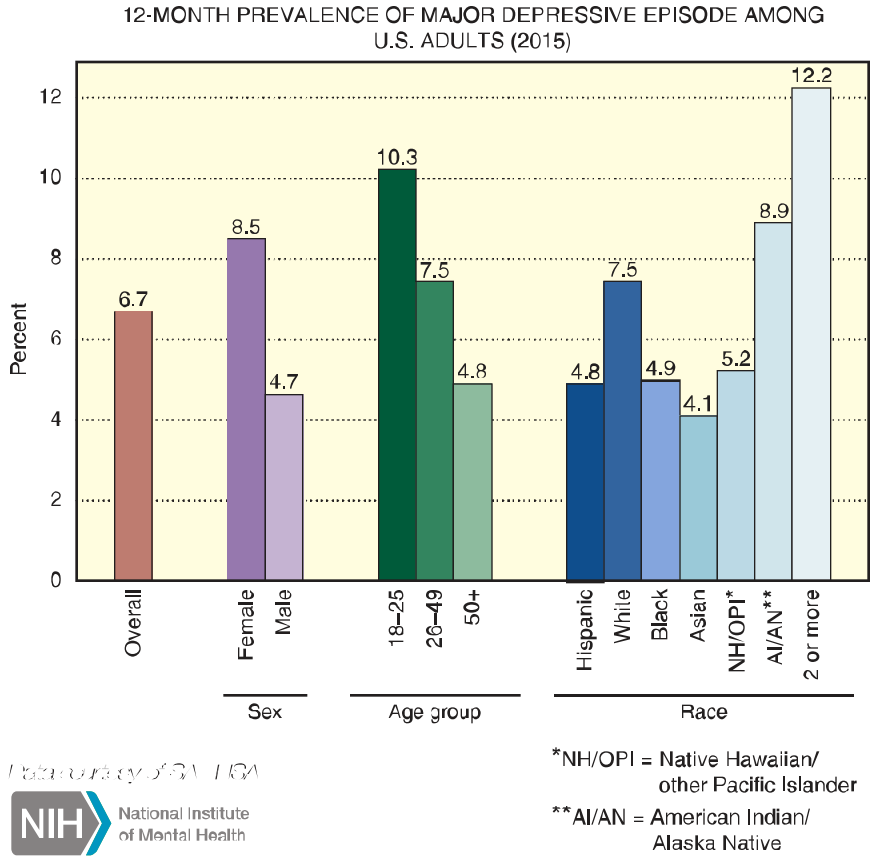

Fig. 29.1 Twelve-month prevalence of depressive episodes among US adults (2015). (Data courtesy of Substance Abuse and Mental Health Services Administration from the National Institute of Mental Health website. http://www.nimh.nih.gov/health/statistics/prevalence/.)

TABLE 29.1 Characteristics of Severe Depression

Depressed mood*
Markedly diminished interest or pleasure in almost all activities*
Fluctuations in body weight and appetite
Insomnia or hypersomnia
Psychomotor agitation or retardation
Fatigue
Feelings of worthlessness or guilt
Decreased ability to concentrate
Suicidal ideation

*These must be present. Exclude symptoms attributed to another medical condition.

All patients with depression should be evaluated for suicide risk. Suicide is the 10th leading cause of death among Americans, with about 45,000 deaths per year due to this cause. Interestingly, physicians have moderately higher to much higher suicide rates than the general population. Most individuals who commit suicide have been under the care of a physician (not necessarily a psychiatrist) within the month before their death, which emphasizes the need for physicians in all specialties to recognize patients at risk. Hopelessness is the most important aspect of depression associated with suicide.

Treatment

Depression can be treated with antidepressant medications, psychotherapy, electroconvulsive therapy (ECT), and other nonpharmacologic measures. An estimated 70% to 80% of patients respond to pharmacologic therapy, and most who do not respond to antidepressants do respond favorably to ECT or one of the alternative measures. ECT is typically reserved for patients with depression resistant to antidepressant drugs or those with medical contraindications to treatment with these drugs. Patients with depression plus psychotic symptoms (delusions, hallucinations, catatonia) require both antidepressant and antipsychotic drugs.

Approximately 50 years ago, neurochemical hypotheses regarding depression postulated that decreased availability of norepinephrine and serotonin at specific synapses in the brain is associated with depression and, conversely, that an increased concentration of these neurotransmitters is associated with mania. Subsequent studies have generally supported this hypothesis that norepinephrine and serotonin metabolism are important in mood states, although the exact mechanisms remain to be elucidated. Almost all drugs with antidepressant properties affect the availability of catecholamines and/or serotonin in the central nervous system (CNS) (Table 29.2). These include selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs),

TABLE 29.2 Commonly Used Antidepressant Medications Listed by Class

Drug Class	Generic Name	Trade Name
SSRIs	Fluoxetine	Prozac
	Paroxetine	Paxil
	Sertraline	Zoloft
	Citalopram	Celexa
	Escitalopram	Lexapro
SNRIs	Duloxetine	Cymbalta
	Venlafaxine	Effexor
	Desvenlafaxine	Pristiq
NDRI	Bupropion	Wellbutrin
MAOIs	Phenelzine	Nardil
	Tranylcypromine	Parnate
	Selegiline	Emsam
Atypical	Trazodone	Desyrel
	Vortioxetine	Trintellix
	Mirtazapine	Remeron

MAOIs, Monoamine oxidase inhibitors; *NDRI*, norepinephrine-dopamine reuptake inhibitor; *SNRIs*, serotonin-norepinephrine reuptake inhibitors; *SSRIs*, selective serotonin reuptake inhibitors.

norepinephrine-dopamine reuptake inhibitors (NDRIs), atypical antidepressants, monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants.

SSRIs block reuptake of serotonin at presynaptic membranes but have relatively little effect on adrenergic, cholinergic, histaminergic, or other neurochemical systems. As a result, they are associated with few side effects.

Venlafaxine, desvenlafaxine, and duloxetine (SNRIs) are methylamine antidepressants that selectively inhibit reuptake of norepinephrine and serotonin without affecting other neurochemical systems. Bupropion inhibits reuptake of serotonin and dopamine. Other atypical antidepressants have a diverse range of activity ranging from antagonism of specific serotonin receptors, dopamine receptor blockade, presynaptic α_2 blockade resulting in increases in norepinephrine and serotonin release, and histamine receptor blockade

MAOIs are inhibitors of either or both the A and B forms of brain MAO and change the concentration of neurotransmitters by preventing breakdown of catecholamines and serotonin. They are not considered first-line drugs in the treatment of depression because of their adverse effect profile, which includes the risk of hypertensive crises from consumption of tyramine-containing foods and the risk of serotonin syndrome if they are used concomitantly with SSRIs.

Before the availability of SSRIs, tricyclic antidepressants were the most commonly prescribed drugs for treatment of depression. They were thought to affect depression by inhibiting synaptic reuptake of norepinephrine and serotonin. However, they also affect other neurochemical systems, including histaminergic and cholinergic systems. They are now rarely used as first-line therapy for depression but are used more commonly as adjuvant therapy for patients with chronic pain syndromes. Their principal advantage is the existence of well-defined correlations between dosage, plasma concentration, and therapeutic response for nortriptyline, imipramine, and desipramine. Adverse effects include sedation, anticholinergic effects, and cardiovascular abnormalities, including orthostatic hypotension and cardiac dysrhythmias.

There has been a resurgence in the use of amphetamine and its congeners in treating depression. Typically these drugs are used in small dosages in combination with SSRIs. The effects on mood can be remarkable. However, because of their status as class II controlled substances, they are not widely used.

SSRIs. Serotonin is produced by hydroxylation and decarboxylation of l-tryptophan in presynaptic neurons, then stored in vesicles that are released and bound to postsynaptic receptors when needed for neurotransmission. A reuptake mechanism allows for return of serotonin to the presynaptic vesicles. Metabolism is by MAO type A. Serotonin-specific reuptake inhibitors, as their name implies, inhibit reuptake of serotonin from the neuronal synapse without having significant effects on reuptake of norepinephrine and/or dopamine.

SSRIs comprise the most widely prescribed class of antidepressants and are the drugs of choice to treat mild to moderate depression. These drugs are also effective for treating panic disorders, posttraumatic stress disorder, bulimia, dysthymia, obsessive-compulsive disorder, and irritable bowel syndrome. Common side effects include insomnia, agitation, headache, nausea, diarrhea, dry mouth, and sexual dysfunction. Appetite suppression is associated with fluoxetine therapy, though this effect is usually transient. Abrupt cessation of SSRI use, especially use of paroxetine and fluvoxamine, which have short half-lives and no active metabolites, can result in a discontinuation syndrome that can mimic serious illness and can be distressing and uncomfortable. Discontinuation symptoms typically begin 1 to 3 days after abrupt cessation of SSRI use and may include dizziness, irritability, mood swings, headache, nausea and vomiting, dystonia, tremor, lethargy, myalgias, and fatigue. Symptoms are relieved within 24 hours of restarting SSRI therapy.

Among SSRIs, fluoxetine is a potent inhibitor of certain hepatic cytochrome P450 enzymes. As a result, this drug may increase plasma concentrations of drugs that depend on hepatic metabolism for clearance. For example, addition of fluoxetine to treatment with tricyclic antidepressant drugs may result in twofold to fivefold increases in plasma concentrations of tricyclic drugs. Some cardiac antidysrhythmic drugs and some β-adrenergic antagonists are also metabolized by this enzyme system, and fluoxetine inhibition of enzyme activity may result in potentiation of their effects.

Serotonin syndrome. Serotonin syndrome is a potentially life-threatening adverse drug reaction that may occur with therapeutic drug use, overdose, or interactions between serotoninergic drugs. A large number of drugs have been associated with serotonin syndrome. These include SSRIs, atypical and cyclic antidepressants, MAOIs, opiates, cough medicine, antibiotics, antiemetic drugs, antimigraine drugs, drugs of abuse (especially Ecstasy), and herbal products (Table 29.3).

Typical symptoms of serotonin syndrome include agitation, delirium, autonomic hyperactivity, hyperreflexia, clonus, and hyperthermia (Fig. 29.2). Additional syndromes to consider in the differential diagnosis of serotonin syndrome are listed in

TABLE 29.3 Drugs Known to Be Associated With Serotonin Syndrome

Selective serotonin reuptake inhibitors
Selective serotonin-norepinephrine reuptake inhibitors
Bupropion
Atypical antidepressants
Monoamine oxidase inhibitors
Tricyclic antidepressants
Drugs of abuse: ecstasy, lysergic acid diethylamide (LSD), amphetamines
Antiemetic drugs: ondansetron, granisetron, metoclopramide, droperidol
Analgesics: meperidine, fentanyl, tramadol
Lithium
Muscle relaxant: cyclobenzaprine
Antimigraine drugs: triptans
Anticonvulsant drugs: valproate
Antibiotics: linezolid, ritonavir
Cough medicine: dextromethorphan
Dietary supplements: nutmeg, ginseng, St. John wort

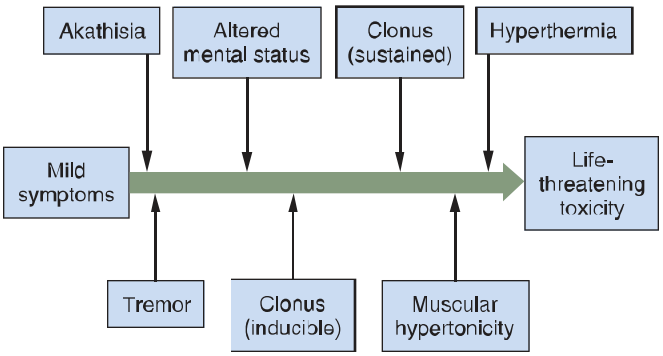

Fig. 29.2 Spectrum of clinical findings in serotonin syndrome. Manifestations range from mild to life threatening. Vertical arrows suggest the approximate point at which clinical findings initially appear in the spectrum of the disease. (Adapted from Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med.* 2005;352:1112–1120. Copyright 2005 Massachusetts Medical Society. All rights reserved.)

Table 29.4. Treatment includes supportive measures and control of autonomic instability, excess muscle activity, and hyperthermia. Cyproheptadine, a 5-hydroxytriptamine (serotonin) type 2A ($5\text{-}HT_{2A}$) antagonist, can be used to compete for and bind to serotonin receptors. It is available only for oral use.

Monoamine oxidase inhibitors. Patients whose depression does not respond to other antidepressant drugs may benefit from treatment with MAOIs. MAOIs inhibit norepinephrine and serotonin and tyramine breakdown, so there is more norepinephrine and serotonin available for release. Selegiline is a subtype A MAOI that is reversible and specifically catabolizes serotonin, norepinephrine, and tyramine, the substances most directly linked to MAOI antidepressant activity. It is used in a transdermal preparation that limits enterohepatic MAO inhibition and may help eliminate the need for dietary tyramine restriction.

The principal clinical problems associated with use of MAOIs, especially the nonselective irreversible forms, include the need for dietary restrictions, the potential for drug interactions, and adverse side effects. Probably the most dreaded occurrence is very significant systemic hypertension if patients ingest foods containing tyramine (cheeses, wines) or receive sympathomimetic drugs. Both tyramine and sympathomimetic drugs are potent stimuli for norepinephrine release. Interestingly, however, orthostatic hypotension is the most common adverse effect observed in patients being treated with MAOIs (Table 29.5). The mechanism for this hypotension is unknown, but it may involve accumulation of false neurotransmitters such as octopamine that are less potent than norepinephrine. This mechanism may also explain the antihypertensive effects observed with long-term use of MAOIs.

Adverse interactions between MAOIs and serotoninergic drugs have been observed. In the anesthetic environment the interaction between MAOIs and the opioid meperidine has been the most notable.

Management of anesthesia. Anesthesia can be safely conducted in patients being treated with MAOIs despite earlier recommendations that these drugs be discontinued 14 days

TABLE 29.4 Drug-Induced Hyperthermic Syndromes

Syndrome	Time to Onset	Causative Drugs	Outstanding Features	Treatment
Malignant hyperthermia	Within minutes	Succinylcholine, inhalation anesthetics	Muscle rigidity, severe hypercarbia	Dantrolene, supportive care
Neuroleptic malignant syndrome	24–72 hr	Dopamine antagonist antipsychotic drugs	Muscle rigidity, stupor or coma, bradykinesia	Bromocriptine or dantrolene, supportive care
Serotonin syndrome	Up to 12 hr	Serotoninergic drugs	Clonus, hyperreflexia, agitation; possible muscle rigidity	Cyproheptadine, supportive care
Sympathomimetic syndrome	Up to 30 min	Cocaine, amphetamines	Agitation, hallucinations, myocardial ischemia, dysrhythmias, no rigidity	Vasodilators, α- and β-blockers, supportive care
Anticholinergic poisoning	Up to 12 hr	Atropine, belladonna	Toxidrome of hot, red, dry skin; dilated pupils; delirium; no rigidity	Physostigmine, supportive care
Cyclic antidepressant overdose	Up to 6 hr	Cyclic antidepressants	Hypotension, stupor or coma, polymorphic ventricular tachycardia, no rigidity	Serum alkalinization, magnesium

TABLE 29.5 Adverse Effects of Monoamine Oxidase Inhibitors

Sedation
Blurred vision
Orthostatic hypotension
Tyramine-induced hypertensive crisis
Excessive effects of sympathomimetic drugs
Potential for serotonin syndrome

before elective surgery to permit time for regeneration of new enzyme. Proceeding with anesthesia and surgery in patients being treated with MAOIs influences selection and doses of drugs to be administered. Benzodiazepines are acceptable for pharmacologic treatment of preoperative anxiety. Induction of anesthesia can be safely accomplished with most intravenous (IV) induction agents, but it should be kept in mind that CNS effects and depression of ventilation may be exaggerated. Ketamine, a sympathetic stimulant, should be avoided. Serum cholinesterase activity may decrease in patients treated with phenelzine, so the dose of succinylcholine may need to be reduced. A volatile anesthetic with or without nitrous oxide is acceptable for maintenance of anesthesia. Anesthetic requirements may be increased because of increased concentrations of norepinephrine in the CNS. Fentanyl has been administered intraoperatively to patients being treated with MAOIs without apparent adverse effects. The choice of nondepolarizing muscle relaxants is not influenced by treatment with MAOIs. Spinal or epidural anesthesia is acceptable, although the potential of these anesthetic techniques to produce hypotension and the consequent need for vasopressors may argue in favor of general anesthesia. Addition of epinephrine to local anesthetic solutions should probably be avoided.

During anesthesia and surgery, it is important to avoid stimulating the sympathetic nervous system as, for example, by light anesthesia, topical application of cocaine spray, or injection of indirect-acting vasopressors to decrease the incidence of systemic hypertension. If hypotension occurs and vasopressors are needed, use of a direct-acting drug such as phenylephrine is recommended. The dose should probably be decreased to minimize the likelihood of an exaggerated hypertensive response.

Postoperative care. Provision of analgesia during the postoperative period is influenced by the potential adverse interactions between opioids, especially meperidine and MAOIs, which can result in serotonin syndrome. If opioids are needed for postoperative pain management, morphine is a preferred drug. Alternatives to opioid analgesics such as nonopioid analgesics, nonsteroidal antiinflammatory drugs (NSAIDs), and peripheral nerve blocks should be considered. Neuraxial opioids provide effective analgesia, but experience is too limited to permit recommendations regarding use of this approach in patients being treated with MAOIs.

Nonpharmacologic treatments of depression. For patients who do not respond well to antidepressant drug therapy, there are several forms of treatment for severe depression that do not include antidepressant medications but rather rely on various forms of brain stimulation. At the present time these alternatives include transcranial magnetic stimulation and ECT. Magnetic seizure therapy (MST) is in investigational trials.

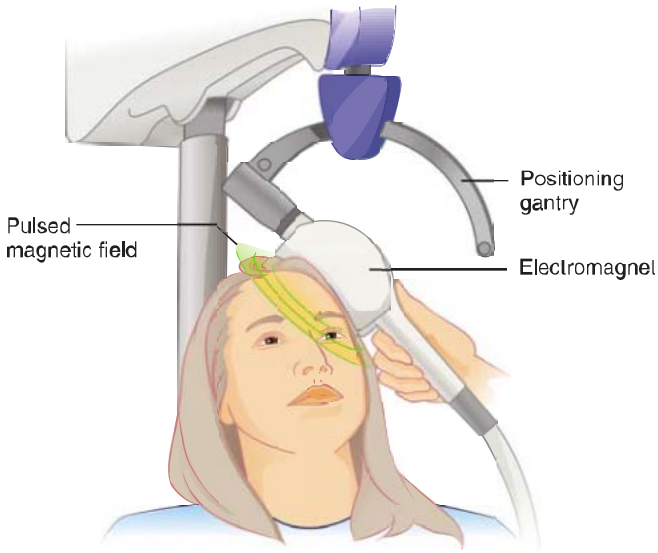

Fig. 29.3 Repetitive transcranial magnetic stimulation (rTMS). This modality uses a magnet instead of an electric current to activate the brain. Typically the magnetic field is centered over either prefrontal cortex.

Repetitive transcranial magnetic stimulation (rTMS) uses a magnet instead of electric current to activate the brain. An electromagnetic coil is placed against the forehead near the region of the brain thought to be involved in regulation of mood (Fig. 29.3). Then short electromagnetic impulses are administered through the coil. These cause small electric currents that stimulate cells in the targeted region. The impulses can apparently not travel farther than about 2 inches from the point of origin, so the treatment is localized to the area of interest, which is typically the left or right prefrontal cortex. The impulses have about the same strength as those in use during an magnetic resonance imaging (MRI) exam. A major advantage of this treatment is that anesthesia is not needed. Most complications consist of headaches and scalp discomfort. In 2008, the US Food and Drug Administration (FDA) approved rTMS for treatment of depression in patients who have failed treatment with at least one antidepressant medication.

MST uses elements of both rTMS and ECT. It uses a magnetic pulse instead of electricity to stimulate a target area in the brain, but it uses a higher frequency of electromagnetic stimulation, with the aim of inducing a seizure. Because of this, an anesthetic is required in a manner similar to that needed for ECT. There is some evidence that MST may reduce the incidence and severity of cognitive side effects compared to traditional ECT.

Despite many decades of use of ECT, the exact mechanism for its therapeutic effect remains unknown. Alterations in neurophysiologic, neuroendocrine, and neurochemical systems are thought to be involved but have not been clearly elucidated. What is evident is that electrically induced seizures of at least 25 sec duration are necessary for a therapeutic effect. ECT is

indicated for treatment of severe depression in patients who show no response to drug therapy, cannot tolerate the adverse effects of psychotropic drug therapy, or are suicidal. The electric current may be administered to both hemispheres or only to the nondominant hemisphere (which may reduce memory impairment). The electrical stimulus produces a grand mal seizure consisting of a brief tonic phase followed by a more prolonged clonic phase. The electroencephalogram shows changes similar to those present during spontaneous grand mal seizures. Typically patients undergo 6 to 12 induction treatments during hospitalization and then may continue weekly, biweekly, or monthly maintenance therapy. More than two-thirds of patients receiving ECT show significant improvement in their depressive symptoms.

In addition to the seizure and its neuropsychiatric effects, ECT produces significant cardiovascular and CNS effects (Table 29.6). The typical cardiovascular response to the ECT stimulus consists of 10 to 15 sec of parasympathetic stimulation producing bradycardia with a reduction in blood pressure, followed by sympathetic nervous system activation resulting in tachycardia and hypertension lasting several minutes. These changes may be undesirable in patients with ischemic heart disease. Indeed, the most common causes of death associated with ECT are myocardial infarction and cardiac dysrhythmias, although overall mortality rates are extremely low, approximately 1 in 5000 treatments. Transient myocardial ischemia, however, is not an uncommon event. Other cardiovascular changes in response to ECT include decreased venous return caused by the increased intrathoracic pressure that accompanies the seizure and/or positive pressure ventilation and ventricular premature beats that presumably reflect excess sympathetic nervous system activity. Patients with acute coronary syndromes, decompensated congestive heart failure, significant dysrhythmias, and severe valvular heart disease require cardiologic consultation prior to initiation of ECT.

Cerebrovascular responses to ECT include marked increases in cerebral blood flow (up to sevenfold) and cerebral blood flow velocity (more than double) compared with pretreatment values. Cerebral oxygen consumption increases as well. The rapid increase in systemic blood pressure may transiently overwhelm cerebral autoregulation and result in a dramatic increase in intracranial pressure. Thus the use of ECT is prohibited in patients with known space-occupying lesions or head injury. The cerebral hemodynamic changes are also associated with increased wall stress on cerebral aneurysms, and intracranial aneurysm disease is another contraindication to ECT.

Increased intraocular pressure is an inevitable side effect of electrically induced seizures. Increased intragastric pressure also occurs during seizure activity. Transient apnea, postictal confusion or agitation, nausea and vomiting, and headache may follow the seizure. The most common long-term effect of ECT is memory impairment.

Management of anesthesia. Anesthesia for ECT must be brief, provide the ability to monitor and limit the physiologic effects of the seizure, and minimize any interference with seizure activity or duration. Patients must fast before the procedure. IV administration of glycopyrrolate 1 to 2 min before induction of anesthesia and delivery of the electric current may be useful in decreasing excessive salivation and bradycardia. The magnitude of treatment-induced hypertension can be ameliorated with use of nitroglycerin intravenously, sublingually, or transdermally. Likewise, esmolol 1 mg/kg IV administered just before induction of anesthesia can attenuate the tachycardia and hypertension associated with ECT, and it does so better than labetalol. Many other drugs, including calcium channel blockers, ganglionic blockers, $\bar{}_2$-agonists and antagonists, and direct-acting vasodilators, have been used to treat the sympathetic overactivity during ECT, but they do not appear to offer any specific advantages over esmolol or nitroglycerin therapy.

Methohexital (0.5–1 mg/kg IV) is the traditional drug used for induction of anesthesia for ECT. It has a rapid onset, short duration of action, minimal anticonvulsant effects, and rapid recovery. Because of shortages of barbiturates in the United States, other induction drugs are now commonly used for ECT. Propofol is an alternative to methohexital and is associated with a lower blood pressure and heart rate response to ECT. Recovery time is similar after administration of methohexital and propofol, but the anticonvulsant effect of propofol can be manifested as a shortened seizure duration. Ketamine and etomidate improve the quality and duration of the electrically induced seizure, but ketamine is associated with a prolonged reorientation time after the procedure, and etomidate is associated with more hypertension after the seizure and the possibility of spontaneous seizures before the electrical stimulus is delivered.

IV injection of succinylcholine promptly after induction is intended to attenuate the potentially dangerous skeletal muscle contractions and bone fractures that can result from seizure activity. Doses of 0.3 to 0.5 mg/kg IV are sufficient to attenuate skeletal muscle contractions and still permit visual confirmation of seizure activity. The most reliable method to confirm electrically induced seizure activity is the electroencephalogram. Alternatively, tonic and clonic movements in an extremity that has been isolated from the circulation by applying a tourniquet before administration of succinylcholine are evidence that a seizure has occurred. Succinylcholine-induced myalgias are remarkably uncommon, occurring in only about

TABLE 29.6 Adverse Effects of Electroconvulsive Therapy

Parasympathetic nervous system stimulation
Bradycardia
Hypotension
Sympathetic nervous system stimulation
Tachycardia
Hypertension
Dysrhythmias
Increased cerebral blood flow
Increased intracranial pressure
Increased intraocular pressure
Increased intragastric pressure

2% of patients undergoing ECT. There is no evidence that succinylcholine-induced release of potassium is increased by ECT. Ventilatory support and oxygen supplementation are continued as necessary until there is complete recovery to pretreatment cardiopulmonary status. Because repeated administration of anesthetics is necessary, it is possible to establish the exact doses of the anesthetic induction drug and succinylcholine that produce the most predictable and desirable effects in each patient.

Occasionally ECT is necessary in a patient with a permanent cardiac pacemaker or cardioverter-defibrillator. Fortunately most of these devices are shielded and not adversely affected by the electric currents necessary to produce seizures, but it is prudent to have a magnet available to ensure the pacemaker can be converted to an asynchronous mode should malfunction occur in response to the delivered electric current or to myopotentials from the succinylcholine or the seizure. Monitoring the electrocardiogram (ECG) and the plethysmographic waveform of the pulse oximeter and palpation of peripheral arterial pulses will document uninterrupted function of a cardiac pacemaker. Implantable cardioverter-defibrillators should be turned off before ECT and reactivated when the treatment is finished.

Safe and successful use of ECT has been described in patients following cardiac transplantation. In such patients, lack of vagal innervation to the heart eliminates the risk of bradydysrhythmias. However, the sympathetic responses still occur.

Bipolar Disorder

Bipolar disorder, previously called manic-depressive disorder, is characterized by marked mood swings from depressive episodes to manic or hypomanic episodes, with normal behavior often seen between these episodes. Between 8% and 10% of patients with bipolar disorder commit suicide. The manic phase of bipolar disorder is manifested clinically by sustained periods of expansive euphoric mood in which the patient expresses grandiose ideas and plans. The mood disturbance may be sufficiently severe to cause impairment in occupational functioning, social activities, and relationships, so there is risk of harm to self and others. Irritability and hyperactivity are also present; in severe cases, psychotic delusions and hallucinations may appear that are indistinguishable from those of schizophrenia (Table 29.7).

Genetic patterns in bipolar disorders suggest autosomal dominance with variable penetrance. Presumably there are abnormalities in neuroendocrine pathways that result in aberrant regulation of one or more amine neurotransmitter systems. Thus the pathophysiology of bipolar disorder—to the extent it is known—is similar to that of major depressive illness. Note that evaluation of mania must exclude the effects of substance abuse drugs, medications, and concomitant medical conditions.

TABLE 29.7 Manifestations of Mania

Expansive euphoric mood
Inflated self-esteem
Decreased need for sleep
Flight of ideas
Greater talkativeness than usual
Distractibility
Psychomotor agitation

Treatment

Mania necessitates prompt treatment, usually in a hospital setting to protect patients from potential harmful actions. Lithium remains a mainstay of treatment, but antiepileptic drugs such as carbamazepine and valproate are often used. Olanzapine is another treatment option. When manic symptoms are severe, lithium may be administered in combination with an antipsychotic drug until the acute symptoms abate.

Lithium. Lithium is an alkali metal, a monovalent cation, and is minimally protein bound. It does not undergo biotransformation and is excreted by the kidneys. Lithium is efficiently absorbed after oral administration. Its therapeutic serum concentration for acute mania and for prophylaxis is approximately 0.8 to 1.2 mEq/L. Because of this narrow therapeutic window, the serum lithium concentration must be monitored to prevent toxicity. The therapeutic effects of lithium are most likely related to actions on second-messenger systems based on phosphatidylinositol turnover. Lithium also affects transmembrane ion pumps and has inhibitory effects on adenylate cyclase.

Common adverse effects of lithium therapy include cognitive dysfunction, weight gain, and tremor. Lithium inhibits release of thyroid hormone and results in hypothyroidism in about 5% of patients. Long-term administration of lithium may also result in polyuria due to a form of vasopressin-resistant diabetes insipidus. Cardiac problems may include sinus bradycardia, sinus node dysfunction, atrioventricular block, T-wave changes, and ventricular irritability. Leukocytosis in the range of 10,000 to 14,000 cells/mm^3 is common.

Toxicity occurs when the serum lithium concentration exceeds 2 mEq/L, with signs of skeletal muscle weakness, ataxia, sedation, and widening of the QRS complex. Atrioventricular heart block, hypotension, and seizures may accompany severe lithium toxicity. Hemodialysis may be necessary in this medical emergency.

Lithium is excreted entirely by the kidneys. Reabsorption of lithium occurs in the proximal tubule in exchange for sodium, so diuretic use can affect the serum lithium concentration. Thiazide diuretics trigger an increase in lithium reabsorption in the proximal tubule, whereas loop diuretics do not promote lithium reabsorption. Administration of sodium-containing solutions or osmotic diuretics enhances renal excretion of lithium and results in lower lithium levels. Concomitant administration of NSAIDs and/or angiotensin-converting enzyme (ACE) inhibitors increases the risk of lithium toxicity.

Management of anesthesia. Evidence of lithium toxicity is an important consideration during the preoperative evaluation. The most recent serum lithium concentration should be reviewed, and inclusion of a lithium level in measurements of the patient's serum electrolyte concentrations during the perioperative period is very useful. To prevent significant renal reabsorption of lithium, it is reasonable to administer sodium-containing IV solutions during the perioperative period. Stimulation of urine output with thiazide diuretics must be

avoided. The ECG should be monitored for evidence of lithium-induced conduction defects or dysrhythmias. The association of sedation with lithium therapy suggests that anesthetic requirements may be decreased in these patients. Monitoring the effects of neuromuscular blockade is indicated because the duration of action of both depolarizing and nondepolarizing muscle relaxants may be prolonged in the presence of lithium.

SCHIZOPHRENIA

Schizophrenia (Greek for "split mind") is the major psychotic mental disorder. It is characterized by abnormal reality testing or thought processes. The essential features of the illness include two broad categories of symptoms. Positive symptoms are those that reflect distortion or exaggeration of normal behavior and include delusions and hallucinations. Negative symptoms represent a loss or diminution in normal function and include flattened affect, apathy, social or occupational dysfunction (including withdrawal), and changes in appearance and hygiene. Subtypes of schizophrenia include paranoid type, disorganized type, catatonic type, and undifferentiated type. In some patients the disorder is persistent, whereas in others there are exacerbations and remissions.

Treatment

The dopamine hypothesis concerning the etiology of schizophrenia suggests the disorder is a result of neurotransmitter dysfunction, specifically dysfunction of the neurotransmitter dopamine. This hypothesis is based on the discovery that agents that diminish dopaminergic activity also reduce the acute signs and symptoms of psychosis, especially agitation, anxiety, and hallucinations. Drugs that affect dopaminergic function by blocking dopamine receptors, especially D_2 and D_4 receptors, have demonstrated the ability to improve a variety of psychotic symptoms, especially positive symptoms. Conventional antipsychotic drugs have broad-spectrum dopamine receptor–blocking properties affecting all dopamine receptor subtypes. As a result, these drugs have significant adverse motor effects. These troubling side effects include tardive dyskinesia (choreoathetoid movements), akathisia (restlessness), acute dystonia (contraction of skeletal muscles of the neck, mouth, and tongue), and parkinsonism. Some of these effects diminish over time, but some persist even after drug discontinuation. Concurrent administration of anticholinergic medication may lessen some of these motor abnormalities. Acute dystonia resolves with administration of diphenhydramine 25 to 50 mg IV.

Newer antipsychotic drugs, also called atypical antipsychotic drugs, have variable effects on dopamine receptor subtypes and serotonin receptors, especially the 5-HT_{2A} receptor. These newer drugs appear to be quite effective in relieving the negative symptoms of schizophrenia and have fewer extrapyramidal side effects than traditional drugs.

Management of Anesthesia

For the anesthesiologist, important effects of antipsychotic medications include Γ-adrenergic blockade causing postural hypotension, prolongation of the QT interval (potentially producing ventricular dysrhythmias), seizures, elevations in hepatic enzyme levels, abnormal temperature regulation, and sedation. Drug-induced sedation may decrease anesthetic requirements.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome is a rare, potentially fatal complication of antipsychotic drug therapy that probably reflects dopamine depletion in the CNS. This syndrome can occur anytime during the course of antipsychotic treatment but often is manifest during the first few weeks of therapy or after an increase in drug dosage. Clinical manifestations usually develop over 24 to 72 hours and include hyperpyrexia, severe skeletal muscle rigidity, rhabdomyolysis, autonomic hyperactivity (tachycardia, hypertension, cardiac dysrhythmias), altered consciousness, and acidosis. Skeletal muscle spasm may be so severe that mechanical ventilation becomes necessary. Renal failure may occur as a result of myoglobinuria and dehydration.

Treatment of neuroleptic malignant syndrome requires immediate cessation of antipsychotic drug therapy and supportive therapy (mechanical ventilation, hydration, cooling). Bromocriptine (5 mg orally every 6 hours) or dantrolene (up to 10 mg/kg daily as a continuous infusion) may decrease skeletal muscle rigidity. Mortality rates approach 20% in untreated patients, with death resulting from cardiac dysrhythmias, congestive heart failure, hypoventilation, or renal failure. Patients who have had this syndrome are likely to experience a recurrence when treatment with antipsychotic drugs is resumed, so a switch is usually made to a less potent antidopaminergic drug or to an atypical antipsychotic medication.

Because there are similarities between neuroleptic malignant syndrome and malignant hyperthermia, the possibility that patients with a history of neuroleptic malignant syndrome are vulnerable to developing malignant hyperthermia is an important issue to consider. At the present time there is no evidence of a pathophysiologic link between the two syndromes, and there is no familial pattern or evidence of inheritance in neuroleptic malignant syndrome. However, until any association between neuroleptic malignant syndrome and malignant hyperthermia is clearly disproved, careful metabolic monitoring during general anesthesia is recommended. Note that succinylcholine has been used without problems for ECT in patients with a history of neuroleptic malignant syndrome.

ANXIETY DISORDERS

Anxiety disorders are the most prevalent form of psychiatric illness in the general community. Anxiety is defined as a subjective sense of unease, dread, or foreboding. It can be a primary psychiatric illness, a reaction to or result of a medical illness, or a medication side effect. Anxiety is associated with distressing symptoms such as nervousness, insomnia, hypochondriasis, and somatic complaints. It is useful clinically to consider anxiety disorders as occurring in two different patterns: (1) generalized anxiety disorder and (2) episodic, often situation-dependent, anxiety. The Γ-aminobutyric acid (GABA)

neurotransmitter system has been implicated in the pathogenesis of anxiety disorders.

Anxiety resulting from identifiable stressors is usually self-limited and rarely requires pharmacologic treatment. Performance anxiety (stage fright) is a type of situational anxiety that is often treated with β blockers, which do not produce sedation or allay anxiety but do eliminate the motor and autonomic manifestations of anxiety. The presence of unrealistic or excessive worry and apprehension may be cause for drug therapy. Buspirone, a partial 5-HT_{2A} receptor antagonist, is a nonbenzodiazepine anxiolytic drug that is not sedating and does not produce tolerance or drug dependence. However, its slower onset of action (several weeks until full effect is reached) and the need for thrice-daily dosing have limited its use. Short-term and often dramatic relief is afforded by almost any benzodiazepine, which is not surprising since these drugs bind to GABA receptors. Other drugs with GABAergic properties such as gabapentin, pregabalin, and divalproex may also be effective in treating anxiety disorders. Supplemental cognitive-behavioral therapy, relaxation techniques, hypnosis, and psychotherapy are also very useful in treating anxiety disorders.

Panic disorders are qualitatively different from generalized anxiety. The patient typically experiences recurrent and unprovoked episodes of intense fear and apprehension associated with physical symptoms and signs such as dyspnea, tachycardia, diaphoresis, paresthesias, nausea, chest pain, and fear of impending doom or dying. Such episodes can be confused with, or indeed caused by, certain medical conditions such as angina pectoris, epilepsy, pheochromocytoma, thyrotoxicosis, hypoglycemia, and cardiac dysrhythmias. Several classes of medications are effective in reducing panic attacks, including SSRIs, benzodiazepines, cyclic antidepressants, and MAOIs. These drugs have comparable efficacy. Psychotherapy and education increase the effectiveness of drug treatment.

EATING DISORDERS

Eating disorders are traditionally classified as anorexia nervosa, bulimia nervosa, and binge-eating disorder (Table 29.8). Bulimia nervosa and binge-eating disorder are more common than anorexia nervosa. All these disorders are characterized by serious disturbances in eating (fasting or binging) and excessive concerns about body weight. Eating disorders typically occur in adolescent girls or young women, although 5% to 15% of cases of anorexia nervosa and bulimia and 40% of binge-eating disorders occur in boys and young men.

Anorexia Nervosa

Anorexia nervosa is a relatively rare disorder, with an incidence of 5 to 10 cases per 100,000 and a mortality rate of 5% to 10%. Approximately half of deaths result from medical complications associated with malnutrition, and the remainder are due to suicide. The disease is characterized by a dramatic decrease in food intake and excessive physical activity in the obsessive pursuit of thinness. Bulimic symptoms may be part of the syndrome. Weight loss often exceeds 25% of normal body weight, but patients perceive that they are still obese despite this dramatic weight loss.

TABLE 29.8 Diagnostic Criteria for Eating Disorders

Anorexia Nervosa
Body mass index <17.5 kg/m²
Fear of weight gain
Inaccurate perception of body shape and weight
Amenorrhea
Bulimia Nervosa
Recurrent binge eating (twice weekly for 3 mo)
Recurrent purging, excessive exercise, or fasting
Excessive concern about body weight or shape
Binge-Eating Disorder
Recurrent binge eating (2 days/wk for 6 mo)
Eating rapidly
Eating until uncomfortably full
Eating when not hungry
Eating alone
Guilt feelings after a binge
No purging or excessive exercise

Adapted from Becker AE, Grinspoon SK, Klibanski A, et al. Eating disorders. *N Engl J Med.* 1999;340:1092–1098.

Signs and Symptoms

Marked unexplained weight loss in adolescent girls is suggestive of anorexia nervosa. Among the more serious medical complications seen in these patients are those that affect the cardiovascular system. Such changes include a decrease in cardiac muscle mass and depressed myocardial contractility. Cardiomyopathy due to starvation or to abuse of ipecac (used to induce vomiting) may be present. Sudden death has been attributed to ventricular dysrhythmias, presumably reflecting the effects of starvation or associated hypokalemia. ECG findings may include low QRS amplitude, nonspecific ST-T–wave changes, sinus bradycardia, U waves, and a prolonged QT interval (another possible association with sudden death). Hyponatremia, hypochloremia, and hypokalemia can be present along with metabolic alkalosis from vomiting and laxative and diuretic abuse. Amenorrhea is often seen in patients with anorexia.

Physical examination reveals emaciation, dry skin that may be covered with fine body hair, and cold, cyanotic extremities. Decreased body temperature, orthostatic hypotension, bradycardia, and cardiac dysrhythmias may reflect alterations in autonomic nervous system activity. Bone density is decreased as a result of poor nutrition and low estrogen concentrations, and long bones or vertebrae may fracture as a result of osteoporosis. Gastric emptying may be slowed, which leads to complaints of gastric distress after eating. In addition, starvation may impair cognitive function. Occasionally patients develop a fatty liver and abnormal liver function tests. Renal complications may reflect long-term dehydration resulting in damage to the renal tubules. Parturient women are at increased risk of delivering low-birthweight infants. Anorexic patients are often anemic, neutropenic, and thrombocytopenic.

Treatment

Treatment of patients with anorexia nervosa is complicated by the patient's denial of the condition. Pharmacologic

treatment has not been predictably successful, but SSRIs that are effective in treating obsessive-compulsive disorder, particularly fluoxetine, may have some value. Most therapy involves medical management of the malnutrition-related symptoms and signs, dietary counseling, and family and/or individual psychotherapy.

Management of Anesthesia

There is a paucity of information relating to management of anesthesia in patients with this eating disorder. Preoperative evaluation is based on the known pathophysiologic effects of starvation. Electrolyte abnormalities, hypovolemia, and delayed gastric emptying are important preanesthetic considerations. There is a risk of perioperative cardiac dysrhythmias. Experience is too limited to permit recommendations regarding specific anesthetic drugs, muscle relaxants, and anesthetic techniques.

Bulimia Nervosa

Bulimia nervosa is characterized by episodes of binge eating, purging, and dietary restriction. Binges are most often triggered by a negative emotional experience. Purging usually consists of self-induced vomiting that may be facilitated by laxatives and/or diuretics. In most patients this disorder is chronic, with relapses and remissions. Depression, anxiety disorders, and substance abuse commonly accompany bulimia nervosa.

Signs and Symptoms

Findings on physical examination suggestive of bulimia nervosa include dry skin, evidence of dehydration, and bilateral painless hypertrophy of the salivary glands. Resting bradycardia is often present. The most common laboratory finding is an increased serum amylase concentration, presumably of salivary gland origin. Metabolic alkalosis due to purging is frequently seen. Dental complications are common, especially enamel loss from repeated vomiting and exposure of the lingual surface of the teeth to gastric acid.

Treatment

The most effective treatment of bulimia nervosa is cognitive-behavioral therapy. Pharmacotherapy may be helpful in selected patients. Potassium supplementation may be necessary in the presence of hypokalemia caused by recurrent self-induced vomiting.

Binge-Eating Disorder

Binge-eating disorder resembles bulimia nervosa, but in contrast to patients with bulimia, those with binge-eating disorder do not purge, and periods of dietary restriction are shorter. The diagnosis of binge-eating disorder should be suspected in morbidly obese patients, particularly obese patients with continued weight gain or marked weight cycling. The disease is chronic and accompanied by weight gain. Like anorexia nervosa and bulimia nervosa, this disorder is frequently accompanied by depression, anxiety, and personality disorders. The principal medical effects of binge-eating disorder are severe clinical obesity and its associated complications: hypertension, diabetes mellitus, hypercholesterolemia, and degenerative joint disease. Antidepressant medications may be useful for treatment of binge-eating disorders.

SUBSTANCE USE AND SUBSTANCE USE DISORDERS

Approximately 11% of patients admitted to the hospital may have a substance use disorder, though current trends in substance use suggest that that number is higher. Alcohol is the leading cause of substance use–related hospitalization, but hospitalizations related to opioids have risen by 64% since 2005. The high prevalence of substance use and substance use disorders makes it very important for hospital-based clinicians to be able to accurately screen and differentiate substance use, unhealthy substance use, and substance use disorders.

Screening for Unhealthy Substance Use

Hospitalization is an opportunity to identify and intervene on substance use disorders. Substance use disorders refers to a spectrum of substance use that increases the risk of health consequences and ranges from hazardous/risky use to severe substance use disorders, or addiction. Without employing universal screening strategies, clinicians are at risk to underrecognize substance use. There are evidence-based screening questions that can be implemented in a variety of health care settings, and all clinicians should be familiar with them (Table 29.9). In addition to using these evidence-based screening questions, patients with medical conditions that can be related to drug use such as infectious endocarditis, hepatitis, HIV, opioid overdose, alcohol withdrawal, or trauma should have careful evaluation for substance use disorders. In all drug use inquiry or screening, it is important to maintain a nonjudgmental and empathetic approach with the understanding that substance use disorders are a medical condition that deserves appropriate evaluation and treatment.

Tobacco is the leading cause of preventable disease, disability, and death in the United States and remains a large problem in hospitalized patients. All patients should be screened for tobacco use. For active tobacco use, patients should be offered medication treatment such as nicotine replacement therapy, varenicline, or bupropion and referral to care for ongoing tobacco cessation counseling.

Alcohol is the third leading cause of preventable death in the United States, and alcohol-related deaths have doubled in the

TABLE 29.9 Screening for Substance Use

Tools	Substance(s) Included	Purpose of Tool
SISQ-Alc (Single-Item Screening Questions for Alcohol)	Alcohol	Screen for unhealthy alcohol use
SISQ-Drug (Single-Item Screening Questions for Drug Use)	Prescription drugs, other drugs	Screen for unhealthy drug use
TAPS (Tobacco, Alcohol, Prescription Medication, and Other Substance Use)	Tobacco, alcohol, prescription drugs, other drugs	Risk assessment for unhealthy drug and alcohol use

last two decades. When screening for unhealthy alcohol use, a clinician can use the Single-Item Screening Question for Alcohol (SISQ-Alc), which asks, "How many times in the last year have you had 5 or more drinks (for men) or 4 or more drinks (for women)?" Any answer response other than "never" is a positive test. If patients screen positive with the SISQ-Alc, follow-up testing to assess patient's alcohol use risk should occur using either the Alcohol Use Disorders Identification Test (AUDIT) or a formal diagnostic evaluation of alcohol use disorder via the Diagnostic Criteria for a Substance Use Disorder (DSM-5). Patients who are identified to have unhealthy alcohol use or an alcohol use disorder should be further evaluated, offered treatment, and referred for ongoing care. Some hospitals settings have addiction medicine or addiction psychiatry teams that can help with further evaluation and treatment while patients are hospitalized.

Illicit drug use, particularly use of opioids and cannabis, have also been increasing over the last 2 decades. Opioid use, particularly of nonpharmaceutic fentanyl, has worsened the current epidemic of opioid overdose deaths. It is important to assess for illicit drug use, and this can be done using the Single-Item Screening Questions for Drug Use. If positive, this test should be followed with the Drug Abuse Screening Test (DAST). Individuals who have high scores on the DAST should be further evaluated and offered treatment. Individuals with opioid use should be evaluated formally for opioid use disorder using the DSM-5 and immediately offered medication treatment, the standard of care for opioid use disorder.

Diagnosis of Substance Use Disorder

Addiction is a treatable, chronic medical disease whose symptoms include compulsive use of substances and continued use of substances despite harms. Risk factors such as genetics, environment, and psychosocial factors such as trauma and adverse childhood experiences predispose individuals to addiction. As of 2013, the disease of addiction is diagnostically defined as severe substance use disorder. In 2013, the diagnostic criteria for substance use disorders were updated from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-4), to the Fifth Edition (DSM-5). This change eliminated the terms "substance abuse" and "substance dependence" for the new term "substance use disorders." With the DSM-5, the substance use disorder diagnosis is based on 11 criteria that broadly fit into the four categories of impaired control over substance use, social impairment, risky use, and physiologic changes (Box 29.1).

BOX 29.1 Opioid Use Disorder

Diagnostic Criteria:

A. A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects
4. Craving, or a strong desire or urge to use opioids
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school or at home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous
9. Continued opioid use despite the knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
    A. A need for markedly increased amounts of opioids to achieve intoxication or desired effect
    B. A markedly diminished effect with continued use of the same amount of an opioid.
    C. **Note:** This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.
11. Withdrawal, as manifested by either of the following:
    A. The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal, pp 547-548 (in DSM-5).
    B. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.
    C. **Note:** This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

Specify if:

In early remission: After full criteria for opioid use disorder were previously met, none of the criteria for opioid use disorder have been met for at least 3 months but for less than 12 months (with the exception that Criterion A4, "Craving, or a strong desire or urge to use opioids", may be met.

In sustained remission: After full criteria for opioid use disorder were previously met, none of the criteria for opioid use disorder have been met at any time during a period of 12 months or longer (with the exception that Criterion A4, "Craving, or a strong desire to use opioids", may be met).

Specify if:

On maintenance therapy: This additional specifier is used if the individual is taking a prescribed agonist medication such as methadone or buprenorphine and none of the criteria for opioid use disorder have been met for that class of medication (except tolerance to, or withdrawal from, the agonist). This category also applies to those individuals being maintained on a partial agonist, an agonist/antagonist, or a full antagonist such as oral naltrexone or depot naltrexone.

Coding based on current severity: Note for ICD-10-CM codes: If an opioid intoxication, opioid withdrawal, or another opioid-induced mental disorder is also present, do not use the codes below for opioid use disorder. Instead, the comorbid opioid use disorder is indicated in the 4th character of the opioid-induced disorder code (see the coding note for opioid intoxication, opioid withdrawal, or a specific opioid-induced mental disorder). For example, if there is comorbid opioid-induced depressive disorder and opioid use disorder, only the opioid-induced depressive disorder code is given, with the 4th character indicating whether the comorbid opioid use disorder is mild, moderate, or severe: F11.14 for mild opioid use disorder with opioid-induced depressive disorder or F11.24 for a moderate or severe opioid use disorder with opioid-induced depressive disorder

Specific current severity:

305.50 (F11.10) Mild: Presence of 2-3 symptoms.

304.00 (F11.20) Moderate: Presence of 4-5 symptoms.

304.00 (F11.20) Severe: Presence of 6 or more symptoms.

TABLE 29.10 Urine Drug Testing Information

Substance or Prescribed Medication	Detection in Urine (Days)	Result From Presumptive Testing	Result From Definitive Testing
Cannabis	2–30 days	Cannabis	Cannabis
Cocaine	1–3 days	Cocaine	Cocaine benzoylecgonine
Benzodiazepines	1–14 days	Benzodiazepines	Depends on the benzodiazepine
Codeine	1–3 days	Opiate	Codeine, morphine
Ethanol†	10–12 hr	Ethanol	n/a
Fentanyl	1–3 days	Fentanyl*	Fentanyl
Heroin	1–3 days	Opiate	6-monoacetylmorphine (MAM), morphine
Hydrocodone	1–3 days	Opiate	Hydrocodone, hydromorphone
Hydromorphone	1–3 days	Opiate	Hydromorphone
Methadone	3–5 days	Methadone*	Methadone, methadone metabolite
Methamphetamine	1–3 days	Amphetamine	Methamphetamine
Morphine	1–3 days	Opiate	Morphine
Oxycodone	1–3 days	Oxycodone*	Oxycodone, oxymorphone
Oxymorphone	1–3 days	Oxycodone*	Oxymorphone

*Methadone, oxycodone, and fentanyl require their own specific urine screening tests for methadone, oxycodone, and fentanyl, respectively.
†To detect ethanol in the urine for longer than 10 to 12 hours, perform ethyl glucuronide or PEth testing.

Individuals who have substance use disorders meet at least two criteria in a 12-month period; the severity of use is defined as mild (two to three criteria), moderate (four to five criteria), or severe (six or more criteria) (Table 29.10). Importantly, physical dependence and tolerance are not synonymous with substance use disorder. Physical dependence develops when the presence of a drug in the body is necessary for physiologic function, and the cessation of that drug causes physiologic withdrawal symptoms. Physical dependence to opioids, as an example, can occur in 1 to 2 weeks of daily use of 20 to 30 mg of morphine equivalents per day. Tolerance is a state in which tissues become accustomed to the presence of a drug, so increased dosages of that drug become necessary to produce effects similar to those experienced initially with smaller dosages. Understanding these principles is particularly important when evaluating patients who are prescribed long-term opioids or benzodiazepines, which can cause withdrawal symptoms with abrupt cessation.

A helpful tool to objectively identify substance use is the urine drug test. Though it alone is not indicative of a substance use disorder, the information provided can prompt further evaluation for substance use disorder and be essential to determine management of acute overdose or acute withdrawal.

Prior to interpreting the results of a urine drug test, it is important to recognize the differences between urine drug screening and definitive drug testing. Urine drug screening, or presumptive testing, refers to preliminary, rapid screening typically based on point of care or immunoassay testing and has lower sensitivity and/or specificity compared to definitive testing (see Table 29.10). Definitive urine drug testing refers to confirmatory testing that is generally done with gas chromatography/mass spectrometry. The results of definitive urine drug testing typically take a few days to result but provide more specific drug identification. If testing results are disputed by the patient, it is important to wait for definitive testing results as certain medications can cause false-positive results on urine drug screening tests. If you have questions regarding the interpretation of a urine drug test, it is important to seek expert advice from your laboratory or medical toxicology. Additional information can also be obtained at www.mytopcare.org. Finally, it is important to recognize that substance may continue to be detected in individuals' urine for longer than the substance has effect on the body. For instance, cocaine can be detected in the urine for up to 3 days after use; however, its half-life on the body and subsequent effect on anesthetic management is only 3 to 5 hours.

Perioperative Management of Patients With Substance Use Disorders

Recognition of substance use is important for anesthesiologists because significant substance use can cause cross-tolerance to medications used for analgesia or anesthesia. This cross-tolerance can make it difficult to predict analgesic and anesthetic requirements and can portend a need for increased analgesic and anesthetic requirements. Acute intoxication or acute withdrawal from opioids, benzodiazepines, alcohol, cocaine, or other stimulants can complicate perioperative management. In the following sections, considerations for each major substance will be discussed.

Alcohol

Overdose

Many drug overdoses involve alcohol in addition to other substances. When evaluating a patient with acute alcohol overdose, testing such as ethanol level, assessment for toxic alcohols, comprehensive metabolic panel, ECG, blood glucose concentration, and arterial blood gas is also important for acute management. The intoxicating effects of alcohol parallel its blood concentration. In patients without tolerance to alcohol, blood alcohol levels of 25 mg/dL are associated with impaired cognition and coordination. At blood alcohol concentrations higher than 100 mg/dL, signs of vestibular and cerebellar dysfunction (nystagmus, dysarthria, ataxia) are likely. Autonomic nervous system dysfunction may result in hypotension, hypothermia, stupor, and coma. Intoxication with alcohol is often defined as a blood alcohol concentration of more than 80 to 100 mg/dL, and levels above 500 mg/dL are usually fatal as a result of respiratory depression.

However, long-term tolerance from prolonged excessive alcohol ingestion may allow patients with alcohol use disorder to remain clinically stable despite potentially fatal blood alcohol concentrations. The critical aspect of treating life-threatening alcohol overdose is maintenance of ventilation. Electrolyte abnormalities, including hypoglycemia, hypomagnesemia, hypophosphatemia, and thiamine (vitamin B_1) deficiency, commonly occur in patients with severe alcohol use disorder. It is important to recognize these abnormalities quickly and provide hydration, electrolyte replacement, and high-dose thiamine replacement, typically by an intravenous or intramuscular route. It must be appreciated that other CNS-depressant drugs are often ingested simultaneously with alcohol.

The depth of CNS depression can be estimated based on the response to painful stimulation, activity of the gag reflex, presence or absence of hypotension, respiratory rate, and size and responsiveness of the pupils. Regardless of the drug(s) ingested, the manifestations may be similar. Assessment and treatment proceed simultaneously. The first step is to secure the airway and support ventilation and circulation. Absence of a gag reflex is confirmatory evidence that protective laryngeal reflexes are dangerously depressed. In this situation a cuffed endotracheal tube should be placed to protect the lungs from aspiration. Body temperature is monitored because hypothermia frequently accompanies unconsciousness as a result of drug overdose. Decisions to attempt removal of ingested substances (gastric lavage, forced diuresis, hemodialysis) depend on the drug ingested, time since ingestion, and degree of CNS depression. Gastric lavage may be beneficial if less than 4 hours have elapsed since ingestion. Gastric lavage or pharmacologic stimulation of emesis is not recommended when the ingested substances are hydrocarbons or corrosive materials or when protective laryngeal reflexes are not intact. After gastric lavage or emesis, activated charcoal can be administered to adsorb any drug remaining in the gastrointestinal tract. Hemodialysis may be considered when potentially fatal doses of drugs have been ingested, when there is progressive deterioration of cardiovascular function, or when normal routes of metabolism and excretion are impaired. Treatment with hemodialysis is of little value when the ingested drugs are highly protein bound or avidly stored in tissues because of high lipid solubility.

Acute Alcohol Withdrawal Syndrome

Physiologic dependence on alcohol produces a withdrawal syndrome when the drug is discontinued or there is a significant decrease in intake. The earliest and most common alcohol withdrawal syndrome is characterized by generalized tremors that may be accompanied by perceptual disturbances (nightmares, auditory or visual hallucinations), autonomic nervous system hyperactivity (tachycardia, hypertension, dysrhythmias), nausea, vomiting, insomnia, and mild confusion with agitation. Disruption and loss of equilibrium in the neurotransmitters GABA and norepinephrine caused by chronic alcohol exposure lead to alcohol withdrawal syndrome. Alcohol withdrawal symptoms usually begin within 6 to 8 hours after a substantial decrease in blood alcohol concentration and are typically most pronounced at 24 to 36 hours. Alcohol withdrawal syndrome can be complicated by seizure or delirium tremens (DTs). Risk factors for complicated alcohol withdrawal include age over 45 years, evidence of increased autonomic activity on admission, concomitant medical conditions, prior alcohol-related seizure or DTs, genetic predisposition, and concomitant benzodiazepine withdrawal. Patients who have undergone multiple alcohol withdrawal episodes are also at high risk for seizure and DTs due to a phenomenon called kindling. Alcohol withdrawal–related seizure usually occurs within 8 to 24 hours of the last alcohol use and occurs within 20% to 30% of patients. DTs occurs 2 to 4 days after cessation of alcohol ingestion and manifests as hallucinations, combativeness, hyperthermia, tachycardia, hypertension or hypotension, and grand mal seizures.

The Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) is a reliable, valid, and reproducible assessment tool to determine the severity of alcohol withdrawal in communicative patients. Patients who are admitted to the hospital for alcohol withdrawal can be monitored and treated utilizing the CIWA-Ar as an assessment tool. Typically, symptom-based treatment of alcohol withdrawal syndrome with benzodiazepines is the standard treatment for uncomplicated alcohol withdrawal syndrome. Diazepam or lorazepam are generally the preferred agents to use. Adjuvant medications such as clonidine, hydroxyzine, and trazodone as needed can help with the associated anxiety and insomnia that accompany alcohol withdrawal syndrome.

Treatment of complicated alcohol withdrawal syndrome or DTs must be aggressive with close monitoring and higher doses of scheduled benzodiazepines. Alternative treatments such as phenobarbital may be more effective for patients with severe alcohol withdrawal syndrome. Patients who are unstable or obtunded should be monitored for need for ventilatory support. Protection of the airway with a cuffed endotracheal tube may be necessary in some patients. Physical restraints may be necessary to decrease the risk of self-injury or injury to others. Even with aggressive treatment, mortality from DTs is approximately 10%, resulting from hypotension, dysrhythmias, or seizures.

Another complication of significant alcohol use is Wernicke-Korsakoff syndrome. This syndrome reflects a loss of neurons in the cerebellum (Wernicke encephalopathy) and a loss of memory (Korsakoff psychosis) resulting from lack of thiamine (vitamin B_1), which is required for the intermediary metabolism of carbohydrates. This syndrome is not an alcohol withdrawal syndrome, but its occurrence establishes that the patient likely has a significant alcohol use disorder. In addition to ataxia and memory loss, many patients exhibit global confusion, drowsiness, nystagmus, and orthostatic hypotension. An associated peripheral polyneuropathy is almost always present. Treatment of Wernicke-Korsakoff syndrome consists of high-dose IV administration of thiamine followed by normal dietary intake when possible. Because carbohydrate loads may precipitate this syndrome in thiamine-depleted patients, it is useful to administer thiamine before initiation of glucose infusions in malnourished or alcoholic patients.

Alcohol Use Disorder Treatment

Alcohol use disorders have high morbidity and mortality (Table 29.11). Alcohol use disorders have effective medication treatments to reduce heavy alcohol use and promote abstinence, yet many individuals with this disorder do not receive these

TABLE 29.11 Medical Problems Related to Alcohol Use Disorder

Central Nervous System Effects
Psychiatric disorders (depression, anxiety)
Nutritional disorders (Wernicke-Korsakoff syndrome)
Withdrawal syndrome
Cerebellar degeneration
Cerebral atrophy
Cardiovascular Effects (Cardiomyopathy, Cardiac Dysrhythmias)
Hypertension
Gastrointestinal and Hepatobiliary Effects
Esophagitis and gastritis
Pancreatitis
Hepatic cirrhosis
Portal hypertension
Skin and Musculoskeletal Effects (Myopathy, Osteoporosis)
Endocrine and Metabolic Effects
Decreased serum testosterone concentrations (impotence)
Decreased gluconeogenesis (hypoglycemia)
Ketoacidosis
Electrolyte abnormalities
Hematologic Effects (Bone Marrow Suppression)

treatments or other effective behavioral treatments. There are three FDA-approved medication treatments for alcohol use disorder, including acamprosate, disulfiram, and naltrexone. Topiramate and gabapentin also have evidence to reduce heavy drinking. Of the three FDA-approved medications, both acamprosate and naltrexone are associated with reduction in heavy alcohol drinking. When compared to each other, there were no significant differences for alcohol use outcomes, though the ease of daily naltrexone likely improves daily adherence. Acamprosate is dosed at 333 to 666 mg three times a day based on renal function and has a contraindication for patients with renal insufficiency (creatinine clearance [CrCl] ¯30). It is an ideal medication for patients with advanced decompensated liver disease if their renal function is normal. It is most effective when started after a period of alcohol abstinence. Naltrexone, an opioid antagonist, is available as an oral tablet and intramuscular injection. The oral tablet is dosed at 50 mg once daily, and the injection is a single intramuscular injection into the gluteal muscle of 380 mg once every 4 weeks. It should be used with caution for patients with decompensated liver disease. Patients must be completely opioid abstinent prior to initiation.

Disulfiram is an aversive alcohol treatment, meaning that it works by causing unpleasant symptoms (flushing, vertigo, diaphoresis, nausea, vomiting) when alcohol is ingested. These symptoms are caused by accumulation of acetaldehyde from oxidation of alcohol, which cannot be further oxidized because of disulfiram-induced inhibition of aldehyde dehydrogenase activity. Unlike acamprosate and naltrexone, disulfiram has not been documented to have advantages over placebo related to its lack of treatment adherence by patients with alcohol use disorders. Its use is contraindicated in pregnancy, cardiac dysfunction, and decompensated liver disease.

Anesthesia Considerations

Management of analgesia in patients treated with naltrexone can be challenging. Patients who are prescribed oral naltrexone should anticipate needing to discontinue oral naltrexone 72 hours prior to surgery. Patients prescribed intramuscular extended-release naltrexone should receive their last injection 4 weeks prior to surgery. Animal studies suggest that long-term opioid antagonism can increase the opioid receptor density in the brain, which may cause patients treated with naltrexone to be more sensitive to opioid agonists. Therefore patients who receive full opioid agonists after consistent naltrexone use should be monitored closely for side effects from opioid initiation and nonopioids used when possible. If patients are receiving naltrexone at the time of their surgery, higher affinity full opioid agonists such as fentanyl or hydromorphone with close monitoring will likely need to be utilized. Redosing naltrexone after receipt of full opioid agonists will require a minimum of 5 to 7 days of opioid abstinence prior to naltrexone reinitiation.

Management of anesthesia in patients being treated with disulfiram should consider the potential presence of disulfiram-induced sedation and hepatotoxicity. Decreased anesthetic drug requirements could reflect additive effects from coexisting sedation or the ability of disulfiram to inhibit metabolism of drugs other than alcohol. For example, disulfiram may potentiate the effects of benzodiazepines. Acute unexplained hypotension during general anesthesia could reflect inadequate stores of norepinephrine as a result of disulfiram-induced inhibition of dopamine β hydroxylase. This hypotension might respond to ephedrine, but direct-acting sympathomimetics such as phenylephrine produce a more predictable response in the presence of norepinephrine depletion. Use of regional anesthesia may be influenced by the presence of disulfiram-induced or alcohol-induced polyneuropathy. Alcohol-containing solutions, such as those used for skin cleansing, should probably be avoided in disulfiram-treated patients.

Cocaine

Cocaine is a stimulant that produces sympathetic stimulation by blocking presynaptic uptake of norepinephrine and dopamine and thereby increases postsynaptic concentrations of these neurotransmitters. Because of this effect, dopamine is present in high concentrations in synapses. Cocaine is well absorbed through the oral, nasal, gastrointestinal, rectal, vaginal mucosa and pulmonary alveoli following inhalation. It is generally used via nasal or pulmonary inhalation or injection, and the onset of action of cocaine through these routes ranges from less than 1 min to 5 min. The duration of action is generally 30 to 60 min, which accounts for its frequent use by individuals with cocaine use disorder. Injection cocaine use is commonly mixed with injection opioid use (aka speedball). Withdrawal from cocaine is generally mild and managed with symptomatic care. Symptoms associated with cocaine withdrawal include fatigue, depression, and increased appetite.

Acute cocaine administration has been known to cause coronary vasospasm, myocardial ischemia, myocardial infarction, and ventricular dysrhythmias, including ventricular fibrillation. Associated systemic hypertension and tachycardia further increase myocardial oxygen requirements at a time when coronary oxygen

delivery is decreased by the effects of cocaine on coronary blood flow. Cocaine use can cause myocardial ischemia and hypotension that lasts as long as 6 weeks after discontinuation of cocaine use. Excessive sensitivity of the coronary vasculature to catecholamines after long-term exposure to cocaine may be due in part to cocaine-induced depletion of dopamine stores. Lung damage and pulmonary edema have been observed in patients who smoke cocaine. Pregnant women who use cocaine are at higher risk of spontaneous abortion, abruptio placenta, and fetal malformations. Cocaine causes a dose-dependent decrease in uterine blood flow. It may also produce hyperpyrexia, which can contribute to seizures. There is a temporal relationship between use of cocaine and cerebrovascular accidents. Long-term cocaine use is associated with nasal septal atrophy, agitated behavior, paranoid thinking, and heightened reflexes. Death due to cocaine use has occurred with all routes of administration (intranasal, oral, IV, inhalational) and is usually due to apnea, seizures, or cardiac dysrhythmias. Persons with decreased plasma cholinesterase activity (elderly individuals, parturient women, those with severe liver disease) may be at risk of sudden death when using cocaine because this enzyme is essential for metabolizing cocaine.

Overdose

Cocaine overdose evokes overwhelming sympathetic stimulation. Uncontrolled hypertension may result in pulmonary and cerebral edema, and the effects of increased circulating catecholamines may include coronary artery vasoconstriction and platelet aggregation that can lead to myocardial infarction.

Treatment of cocaine overdose includes administration of nitroglycerin to manage myocardial ischemia. Although esmolol has been recommended for treating the tachycardia caused by cocaine overdose, there is evidence that β blockade can accentuate cocaine-induced coronary artery vasospasm. α-adrenergic blockade is quite effective in the treatment of coronary vasoconstriction caused by cocaine, with no notable adverse effects. Administration of IV benzodiazepines is effective in controlling seizures associated with cocaine toxicity. Active cooling may be necessary if hyperthermia is significant.

Treatment

There are no FDA-approved medications for the treatment of cocaine use disorder; however, topiramate has shown benefit for patients with this disorder. Other forms of treatment include contingency management and cognitive behavioral therapy delivered in the inpatient or outpatient addiction treatment setting.

Management of Anesthesia

Management of anesthesia in patients acutely intoxicated with cocaine must consider the vulnerability of these patients to myocardial ischemia and dysrhythmias, though it is important to recognize that the general duration of cocaine is no longer than 2 hours. Medically necessary surgeries should not be delayed unnecessarily due to recent cocaine ingestion or cocaine in a patient's urine drug test. Any event or drug likely to increase already enhanced sympathetic activity must be avoided. It seems prudent to have nitroglycerin readily available to treat signs of myocardial ischemia associated with tachycardia or hypertension. Increased anesthetic requirements may be present in acutely intoxicated patients, which presumably reflects increased concentrations of catecholamines in the CNS. Thrombocytopenia associated with cocaine abuse may influence selection of regional anesthesia.

In the absence of acute intoxication, long-term use of cocaine has not been shown to be associated with adverse anesthetic interactions, although the possibility of cardiac dysrhythmias remains a constant concern. Cocaine's rapid metabolism probably decreases the likelihood that an acutely intoxicated patient will come to the operating room.

Opioids

The opioid overdose epidemic that started in the 1990s has placed a spotlight on the use of opioids in the United States. Current overdose deaths are driven mainly by synthetic opioids such as nonpharmaceutic fentanyl and other high potency synthetic opioids. Prescription opioid use has fallen due to national efforts to reduce their use, and opioids for the treatment of acute postoperative pain do not appear to drive opioid overdose death. That said, individuals can develop physical dependence on opioids in less than 14 days if the opioid is given daily at a sufficient dose, so it is important to monitor individuals' use of opioids and develop taper plans in the postoperative setting.

When used in a risky manner, opioids can be used orally, subcutaneously, rectally, or intravenously. Intravenous use is the riskiest and is associated with injection-related medical harms such as infective endocarditis, osteomyelitis, and injection-related abscesses (Table 29.12). Evidence of these medical problems must be sought during the preoperative evaluation. An evaluation of opioid withdrawal and tolerance to opioids should also be evaluated as these issues are likely to influence perioperative analgesia and anesthesia. A patient who is withdrawing from opioids will likely have very difficult postoperative pain management and will need treatment of the withdrawal to stabilize the pain.

Overdose

The most obvious manifestation of overdose of an opioid (usually heroin or fentanyl/fentanyl analogues) is a slow respiratory rate with an increased tidal volume. Pupils are typically miotic,

TABLE 29.12 Medical Problems Associated With Opioid Use Disorder

Hepatitis
Opioid overdose
Opioid withdrawal syndrome
Cellulitis
Superficial skin abscesses
Septic thrombophlebitis
Injection drug use–related infective endocarditis
Systemic septic emboli
Acquired immunodeficiency syndrome
Aspiration pneumonitis
Malnutrition
Tetanus
Transverse myelitis

although mydriasis may occur if hypoventilation results in severe hypoxemia. CNS manifestations range from dysphoria to unconsciousness. Seizures are unlikely. Pulmonary edema occurs in a large proportion of patients with opioid overdose. The cause of this pulmonary edema is poorly understood, but hypoxemia, hypotension, neurogenic mechanisms, drug-related pulmonary endothelial damage, or the effects of other materials (contaminants) injected with the opioid may be responsible. Gastric atony is a predictable accompaniment of acute opioid overdose. Fatal opioid overdose is most often an outcome of fluctuations in the purity of illicit opioids or the combination of opioids with other CNS depressants such as alcohol or benzodiazepines. Naloxone is the specific opioid antagonist administered to maintain an acceptable respiratory rate. Currently it is customary for first responders—police, fire personnel, emergency medical technicians, and others—to carry naloxone nasal spray so it can be administered immediately to anyone suspected of an opioid overdose.

Withdrawal Syndrome

Although withdrawal from opioids is rarely life threatening, it is unpleasant and will complicate analgesic management during the perioperative period. In this regard it is useful to consider the time to onset, peak intensity, and duration of withdrawal symptoms after abrupt withdrawal of opioids. Opioid withdrawal symptoms develop within seconds after IV administration of naloxone. Conversely it is usually possible to abort the withdrawal syndrome by administering methadone or another full opioid agonist. To treat opioid withdrawal, methadone is typically dosed from 10 to 40 mg. The maximum dose of methadone on the first day of treatment is 40 mg; higher doses are likely to cause unintentional overdose in subsequent days. Another option for opioid withdrawal treatment is buprenorphine-naloxone. Both methadone and buprenorphine can be administered in the hospital setting without restriction. Clonidine may also attenuate opioid withdrawal symptoms, presumably by replacing opioid-mediated inhibition with E_2 agonist–mediated inhibition of the sympathetic nervous system in the brain.

Opioid withdrawal symptoms include manifestations of excess sympathetic activity such as diaphoresis, mydriasis, hypertension, and tachycardia. Craving for the drug and anxiety are followed by yawning, lacrimation, rhinorrhea, piloerection (origin of the term "cold turkey"), tremors, skeletal muscle and bone discomfort, and anorexia. Insomnia, abdominal cramps, diarrhea, and hyperthermia may also develop. Skeletal muscle spasms and jerking of the legs (origin of the term "kicking the habit") follow, and cardiovascular collapse is possible. Seizures are rare; their occurrence should raise suspicion of other causes of seizures, such as unrecognized withdrawal of other substances or underlying epilepsy. The Clinical Opioid Withdrawal Scale is an evidence-based assessment tool to evaluate the severity of opioid withdrawal.

Rapid opioid detoxification using high doses of an opioid antagonist administered during general anesthesia followed by naltrexone maintenance has been proposed as a cost-effective alternative to conventional detoxification approaches; however, data indicate that the detoxification from opioids achieved with this method is not associated with better long-term abstinence from opioids and is associated with adverse events, some of which can be life threatening. Indeed, a number of deaths have been reported in this regard. It is no longer a preferred treatment for opioid detoxification and should not be used.

Treatment

There are three FDA-approved medications for the treatment of opioid use disorder: buprenorphine, methadone, and naltrexone (Table 29.13). Despite 50 years of evidence showing they reduce opioid use, reduce mortality related to opioid use and all-cause mortality, decrease communicable disease risk, reduce criminal activity, and increase treatment retention, only approximately 20% of people with opioid use disorder receive these treatments. Hospitalization is an opportunity to initiate treatment for the disorder to improve patient outcomes.

Buprenorphine is a long-acting, lipid-soluble, semisynthetic alkaloid partial opioid agonist with high affinity for the opioid receptors. The half-life of buprenorphine is about 37 hours owing to its slow dissociation from the opioid receptors. Its onset is rapid, approximately 30 to 60 min with sublingual preparations and about 5 to 15 min with an IV preparation. For the treatment of opioid use disorder, buprenorphine is generally paired with naloxone to prevent IV use. IV use of combination buprenorphine-naloxone would cause opioid withdrawal because naloxone would block the effects of the buprenorphine.

In the United States, buprenorphine is a schedule III medication. It requires a waiver from the Drug Enforcement Administration (DEA) to prescribe to more than 30 patients in the outpatient setting. Recent legislation in 2021 allows all clinicians to prescribe it for less than 30 patients if they request a notice of intent to prescribe to the DEA. Federal regulations allow the use of buprenorphine in the inpatient hospital setting without restriction or need for an X waiver (Title 21 Code of Federal Regulations section 1306.07C). For patients with opioid use disorder, it is a first-line

TABLE 29.13 Medication Treatment for Opioid Use Disorder

Medication	Starting Dose	Effective Dose	Caution/Contraindication
Buprenorphine/naloxone (sublingual [SL] tablet or film)	2–4 mg SL Day 1: 8–12 mg	12–16 mg/day	Use of full opioid agonist treatment
Methadone (liquid, oral [PO])	10–30 mg PO Day 1: **NMT 40 mg**	60–80 mg/day	QTc prolongation drug–drug interactions
Extended release **naltrexone,** intramuscular (IM) (gluteal)	380 mg IM	380 mg IM	Use of full opioid agonist treatment

treatment that can be managed safely in the outpatient setting by trained clinicians. Buprenorphine is also an effective treatment for pain and can be an effective treatment for patients with chronic pain and opioid use disorder. Buprenorphine can be safely given to pregnant and breastfeeding women.

Due to the partial opioid agonist properties of buprenorphine, individuals would need to be in mild opioid withdrawal prior to initiation of the medication. Without this period of opioid abstinence, there is a risk that precipitated opioid withdrawal would occur. Newer strategies of buprenorphine induction using ultra low doses of buprenorphine (aka microdosing) are being developed to reduce the risk of precipitated opioid withdrawal.

Methadone is a full opioid agonist. For the treatment of opioid use disorder, it is federally regulated to be prescribed only in an opioid treatment program. Similar to buprenorphine, it can be started in the hospital without restriction, but ongoing treatment in the outpatient setting should be arranged. Methadone may be an ideal medication for patients who are undergoing surgical treatments and are not currently on opioid use disorder treatment. Methadone can quickly treat opioid withdrawal symptoms. A dose no greater than 40 mg on the first day of treatment should be given.

Naltrexone extended release (ER) is also indicated for the treatment of opioid use disorder. It is a complete opioid antagonist, so patients would have to be completely opioid abstinent prior to initiation. Patients who are using short-acting opioids must abstain for a minimum 3 to 5 days prior to initiation. Patients who are using long-acting opioids must abstain for a minimum 10 to 14 days prior to initiation. A urine drug test showing absent opioids as well as a naloxone challenge prior to initiation can confirm the safety of providing naltrexone without precipitating serious opioid withdrawal. The naloxone challenge involves giving up to 0.8 _g of naloxone via IV or IM route and confirms opioid abstinence prior to initiation.

Head-to-head trials comparing methadone and buprenorphine show that they are both equally effective to treat opioid use disorder at higher doses of buprenorphine with flexible dosing. Both buprenorphine and methadone decrease mortality by more than 50% in patients with opioid use disorder. Comparisons between buprenorphine and naltrexone ER show that they can both reduce opioid use, but more patients have difficulty initiating naltrexone ER than buprenorphine, and naltrexone has higher discontinuation rates than buprenorphine.

Management of Anesthesia

Patients who are maintained on methadone or buprenorphine in the perioperative setting should continue these medications. A conversation with the patient and the prescriber is helpful to determine the patient's questions and expectations for pain relief and postoperative management. Specifically, when patients are prescribed buprenorphine, it is important that they continue to receive this medication in the perioperative period. Though a new practice, it has become clear that discontinuing buprenorphine in the perioperative setting worsens patients' opioid use disorder and pain outcomes. It is recommended that each hospital develop a protocol for the management of buprenorphine in the perioperative setting that focuses on continuation of buprenorphine. Because buprenorphine has such high binding affinity at the opioid receptor, full opioid agonist medications such as fentanyl and hydromorphone will need to be used in addition to buprenorphine. Neuroimaging studies show that patients can receive analgesic benefit from other full opioid agonist medications in addition to buprenorphine doses of 12 to 16 mg/day. Other nonopioid medications such as ketamine along with multimodal treatment may need to be utilized for analgesia as well.

The clinician should assume a 20% to 30% increase in acute opioid requirements due to patients' higher tolerance for opioids. Multimodal treatment with nonopioids such as IV or oral NSAIDs, clonidine, ketamine, gabapentin, or pregabalin will be useful for analgesia. Opioid agonist-antagonist drugs are not recommended for perioperative use because they can precipitate acute withdrawal reactions. There is no advantage to trying to maintain anesthesia with opioids, since dosages greatly in excess of normal are likely to be required. Furthermore, long-term opioid use leads to cross-tolerance to other CNS depressants. This may manifest as a decreased analgesic effect from inhaled anesthetics. Conversely, acute opioid administration decreases anesthetic requirements. There is a tendency for perioperative hypotension to occur, which may reflect inadequate intravascular fluid volume due to chronic infection, fever, malnutrition, or adrenocortical insufficiency. Chronic liver disease may also be present.

Management of anesthesia in patients receiving opioid use disorder medication treatment often includes a volatile anesthetic. Regional anesthesia may have a role in some patients, but it is important to remember the tendency for hypotension to occur, the increased incidence of positive results on serologic testing for HIV, the occasional presence of peripheral neuritis, and the rare occurrence of transverse myelitis.

Postoperative pain can be safely and effectively treated with multimodal treatment, including opioids, NSAIDs, acetaminophen, and gabapentin. Alternative methods such as regional anesthesia with local anesthetics, neuraxial opioid analgesia, and transcutaneous electrical nerve stimulation may also be helpful. Opioid doses in the postoperative setting may need to be higher due to patients' higher opioid tolerance. Both methadone and buprenorphine have analgesic properties and can confer analgesic benefit, although they should not be expected to be sufficient alone for analgesia unless procedures are low complexity such as dental procedures.

Barbiturates

Barbiturates have been in medical use since about 1900 but became popular in the 1960s and 1970s as treatments for anxiety, insomnia, and seizure disorders. Indeed, barbiturates were the most commonly used preanesthetic medications during that time. They also became drugs of abuse. With the development of benzodiazepines, medicinal barbiturate use decreased dramatically. Misuse of barbiturates also declined substantially.

The pharmacology of barbiturates is quite different from many other drugs, so overdose or withdrawal of barbiturates presents unique management problems. Long-term barbiturate use is not associated with major pathophysiologic changes. These drugs are most commonly misused orally to treat anxiety, counter insomnia, and antagonize the stimulant effects of other drugs. There is tolerance to most of the actions of these drugs,

as well as cross-tolerance to other CNS depressants. Although the barbiturate doses needed to produce sedative or euphoric effects increase rapidly, lethal doses do not increase at the same rate or to the same magnitude. Thus the margin of error for individuals who abuse barbiturates, in contrast to that for those who use opioids or alcohol, decreases as barbiturate doses are increased to achieve the desired effect.

Overdose

CNS depression is the principal manifestation of barbiturate overdose. Barbiturate blood levels correspond to the degree of CNS depression (slurred speech, ataxia, irritability), with excessively high blood levels resulting in loss of pharyngeal and deep tendon reflexes and the onset of coma. No specific pharmacologic antagonist exists to reverse this barbiturate-induced CNS depression, and the use of nonspecific stimulants is not encouraged. Depression of ventilation may be profound. Maintenance of a patent airway, protection from aspiration, and support of ventilation using a cuffed endotracheal tube are often necessary. Barbiturate overdose may also be associated with hypotension because of central vasomotor depression, direct myocardial depression, and increased venous capacitance. This hypotension usually responds to fluid infusion, although occasionally vasopressors or inotropic drugs are required. Hypothermia is frequent. Acute renal failure resulting from hypotension and rhabdomyolysis may occur. Forced diuresis and alkalinization of urine promote elimination of phenobarbital but are of lesser value for many of the other barbiturates. Induced emesis or gastric lavage followed by administration of activated charcoal may be helpful in awake patients who ingested barbiturates less than 6 hours previously.

Withdrawal Syndrome

Abrupt cessation of excessive barbiturate ingestion is associated with potentially life-threatening responses. The time of onset, peak intensity, and duration of symptoms of withdrawal from barbiturates are delayed compared with those for opioids. Barbiturate withdrawal manifests initially as anxiety, skeletal muscle tremors, hyperreflexia, diaphoresis, tachycardia, and orthostatic hypotension. Cardiovascular collapse and hyperthermia may occur. The most serious problem associated with barbiturate withdrawal is the occurrence of grand mal seizures. Many of the manifestations of barbiturate withdrawal, particularly seizures, are difficult to abort once they develop. If available, pentobarbital may be administered to treat barbiturate withdrawal. Phenobarbital and benzodiazepines are useful in suppressing evidence of barbiturate withdrawal.

Benzodiazepines

Benzodiazepine use disorder has become a problem in the United States in the last 10 years as rates of benzodiazepine prescriptions have increased. As with barbiturates, tolerance and physical dependence occur with long-term benzodiazepine use. Benzodiazepines do not significantly induce microsomal enzymes. Symptoms of withdrawal generally occur later than with barbiturates and are less severe because of the prolonged elimination half-lives of most benzodiazepines and the fact that many of these drugs are metabolized to pharmacologically active metabolites that also have prolonged elimination half-lives. The Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B) is an evidence-based assessment tool for benzodiazepine withdrawal. Generally, patients who have developed a benzodiazepine use disorder may need to undergo a prolonged taper off of benzodiazepines to successfully discontinue them. Connection to outpatient treatment where they can have close monitoring and follow-up is recommended.

Acute benzodiazepine overdose is much less likely to produce ventilatory depression than an overdose with barbiturates and many other drugs of abuse. It must be recognized, however, that the combination of benzodiazepines and other CNS depressants (e.g., alcohol) can be life threatening. Supportive treatment usually suffices for treatment of a benzodiazepine overdose. Flumazenil, a specific benzodiazepine antagonist, is useful for managing a severe or life-threatening overdose. Seizure activity suppressed by benzodiazepines could be unmasked by administration of flumazenil.

Amphetamines

Amphetamines stimulate release of catecholamines, which results in increased alertness, appetite suppression, and a decreased need for sleep. Approved medical uses of amphetamines include treatment of narcolepsy, attention-deficit disorders, significant depression, and hyperactivity associated with minimal brain dysfunction in children. Tolerance to the appetite suppressant effects of amphetamines develops within a few weeks, making these drugs poor substitutes for proper dieting techniques. Physiologic dependence on amphetamines is profound, and dosages may be increased to several hundred times the therapeutic dosage. Long-term use of amphetamines results in depletion of body stores of catecholamines. Such depletion may manifest as somnolence and anxiety or a psychotic state. Other physiologic abnormalities reported with long-term amphetamine abuse include hypertension, cardiac dysrhythmias, and malnutrition. Amphetamines are most often used orally but can also be inhaled or used intravenously.

Overdose

Amphetamine overdose causes anxiety, a psychotic state, and progressive CNS irritability manifesting as hyperactivity, hyperreflexia, and occasionally seizures. Other physiologic effects include hypertension and tachycardia, dysrhythmias, decreased gastrointestinal motility, mydriasis, diaphoresis, and hyperthermia. Metabolic imbalances such as dehydration, lactic acidosis, and ketosis may occur.

Treatment of oral amphetamine overdose includes induced emesis or gastric lavage followed by administration of activated charcoal and a cathartic. Phenothiazines may antagonize many of the acute CNS effects of amphetamines. Similarly, diazepam may be useful for controlling amphetamine-induced seizures. Acidification of urine promotes elimination of amphetamines.

Withdrawal Syndrome

Abrupt cessation of amphetamine use is accompanied by extreme lethargy, depression that may be suicidal, increased

appetite, and weight gain. Benzodiazepines are useful in the management of withdrawal if sedation is needed, and ⊥ blockers may be administered to control sympathetic nervous system hyperactivity. Postamphetamine depression may last for months and require treatment with antidepressant medications.

Management of Anesthesia

Pharmacologic doses of amphetamines that have been administered long term for medically indicated uses (narcolepsy, attention-deficit disorder) need not be discontinued before elective surgery. Patients who require emergency surgery and who are acutely intoxicated from ingestion of amphetamines may exhibit hypertension, tachycardia, hyperthermia, and increased anesthetic requirements. Intraoperative intracranial hypertension and cardiac arrest have been attributed to amphetamine abuse. In animals, acute IV administration of dextroamphetamine produces dose-related increases in body temperature and anesthetic requirements. Thus it is prudent to monitor body temperature during the perioperative period. Long-term amphetamine abuse may be associated with markedly decreased anesthetic requirements presumably as a result of catecholamine depletion in the CNS. Refractory hypotension can reflect depletion of catecholamine stores. Direct-acting vasopressors, including phenylephrine and epinephrine, should be available to treat hypotension because the response to indirect-acting vasopressors such as ephedrine is attenuated by catecholamine depletion. Intraoperative monitoring of blood pressure using an intraarterial catheter should be considered. Postoperatively there is the potential for orthostatic hypotension once the patient begins to ambulate.

Designer/Club Drugs

MDMA (3-methoxy-4,5-methylenedioxyamphetamine, also known as Ecstasy), ketamine, rohypnol, phencyclidine (angel dust), ⊏-hydroxybutyrate (GHB), and synthetic cathinones (bath salts) are some examples of club drugs because they tend to be used by teenagers and young adults at nightclubs, bars, and concerts. They are also called designer drugs because they are synthetic substances, and some can be made with only a minimal knowledge of chemistry. They are becoming ever more popular, and because they are related to cocaine, amphetamines, and other hallucinogens they have the potential to cause serious, even life-threatening adverse effects. There are insufficient data in the medical literature at this time to offer recommendations regarding anesthetic management of persons intoxicated by these substances. However, spontaneous pneumothorax and/or pneumomediastinum has been reported in several patients who had taken MDMA.

Forced diuresis and acidification of urine promotes elimination of phencyclidine but also introduces the risk of fluid overload and electrolyte abnormalities, especially hypokalemia.

Hallucinogens

More traditional hallucinogens, as represented by lysergic acid diethylamide (LSD), are usually ingested orally. Although there is a high degree of psychological dependence, there is no evidence of physical dependence or withdrawal symptoms when LSD is abruptly discontinued. The effects of these drugs develop within 1 to 2 hours and last 8 to 12 hours. They consist of visual, auditory, and tactile hallucinations and distortions of the environment and body image. The ability of the brain to suppress relatively unimportant stimuli is impaired by LSD. Evidence of sympathetic nervous system stimulation includes mydriasis, increased body temperature, hypertension, and tachycardia. Tolerance to the behavioral effects of LSD occurs rapidly, whereas tolerance to the cardiovascular effects is less pronounced.

Overdose

Overdoses of LSD have not been associated with death, although patients may experience unrecognized injuries, which reflects the intrinsic analgesic effects of this drug. On rare occasions, LSD produces seizures and apnea. It can lead to an acute panic reaction characterized by hyperactivity, mood lability, and in extreme cases overt psychosis. Patients should be placed in a calm, quiet environment with minimal external stimuli. No specific antidote exists, although benzodiazepines may be useful for controlling agitation and anxiety reactions. Supportive care in the form of airway management, mechanical ventilation, treatment of seizures, and control of the manifestations of sympathetic nervous system hyperactivity may be needed.

Management of Anesthesia

Anesthesia and surgery have been reported to precipitate panic attacks in these patients. If such an event occurs, midazolam or diazepam is likely to be a useful treatment. Exaggerated responses to sympathomimetic drugs are likely. The analgesia and ventilatory depression of opioids are prolonged by LSD.

Cannabis

Cannabis use is on the rise in the United States with increased legalization for both medicinal and recreational use. Cannabis is usually used via smoking, which causes higher bioavailability of the primary psychoactive component, tetrahydrocannabinol (THC), than oral ingestion. Inhalation of cannabis causes increased sympathetic nervous system activity and decreased parasympathetic nervous system activity. The most consistent cardiac change is an increased resting heart rate. Orthostatic hypotension may occur. Long-term cannabis use leads to increased tar deposits in the lungs, impaired pulmonary defense mechanisms, and decreased pulmonary function, effects similar to cigarette smoking. There is an increased incidence of sinusitis and bronchitis. In some persons, marijuana may evoke seizures. Conjunctival reddening is evidence of vasodilation. Drowsiness is a common side effect. Tolerance to most of the psychoactive effects of THC has been observed. Although physical dependence on cannabis is not believed to occur, abrupt cessation after long-term use is characterized by mild withdrawal symptoms such as irritability, insomnia, diaphoresis, nausea, vomiting, and diarrhea.

Evidence of the medicinal effect of cannabis is limited to cancer-related nausea and HIV cachexia, though many people are increasing their use of cannabis for treatment of chronic pain. Current evidence does not show that cannabis is effective

for the treatment of chronic pain and has not been found to successfully reduce opioid use in patients with chronic pain.

Management of Anesthesia

The pharmacologic effects of inhaled THC occur within minutes but rarely persist longer than 2 to 3 hours, which decreases the likelihood that acutely intoxicated patients will be seen in the operating room. Management of anesthesia includes consideration of the known effects of THC on the heart, lungs, and CNS. Animal studies have demonstrated drug-induced drowsiness and decreased dose requirements for volatile anesthetics following IV administration of THC. Barbiturate and ketamine sleep times are prolonged in THC-treated animals, and opioid-induced respiratory depression may be potentiated.

Substance Abuse as an Occupational Hazard in Anesthesiology

Anesthesiologists represent 5.5% of all physicians in the United States. However, they are overrepresented in addiction treatment programs, enrolling at a rate approximately three times higher than that of any other physician group. In addition, anesthesiologists are at highest risk of relapse after drug addiction treatment. At the present time, 12% to 15% of all physicians in treatment are anesthesiologists. The encouraging news is that a survey performed in 1997 revealed that the apparent incidence of substance abuse among anesthesiology residents was 1.6%, with a faculty incidence of 1.0%. Both rates represented a decline in incidence since 1986.

Why Anesthesiologists?

Numerous factors have been proposed to explain the high incidence of substance use among anesthesiologists. These include:

- Easy access to potent drugs, particularly opioids
- High addictive potential of accessible drugs, particularly fentanyl and sufentanil
- Relative simplicity of diversion of these agents, since only small doses will initially provide the effect desired by the abusing physician
- Curiosity about patients' experiences with these substances
- Control-oriented personality

Demographic Characteristics of Anesthesiologists With Substance Use Disorders

The curriculum on drug use and addiction compiled by the American Society of Anesthesiologists Committee on Occupational Health is a highly recommended in-depth source of information on this important topic. This curriculum notes the following demographic characteristics of anesthesiologists who have a substance use disorder:

- Half are younger than age 35, but this may reflect the age distribution within the specialty.
- Residents are overrepresented, possibly because increased awareness of the high risk of substance use among anesthesiologists has led to more careful screening for signs of addiction in anesthesiology training programs. (Interestingly, a higher proportion of anesthesiology residents with substance use disorders are members of the Alpha Omega Alpha Honor Society.)
- Most people with substance use disorders are male (67%–88%) and white (75%–96%).
- Opiates are the drug of choice in 76% to 90%.
- One-third to one-half misuse more than one drug.
- One-third have a family history of addiction, most frequently alcohol use disorder.
- Two-thirds of anesthesiologists with a documented history of addiction are associated with academic departments.

Most Frequently Abused Drugs

Traditionally, opioids are the drugs selected for misuse by anesthesiologists. Fentanyl and sufentanil are the most commonly used drugs, followed by meperidine and morphine. This choice is particularly evident among anesthesiologists younger than age 35. Alcohol is the misused substance found in older anesthesiologists, probably because the time to produce impairment is significantly longer than that observed with opioid use disorder. The data also suggest that opioids are the substance of choice for use early in an anesthesiologist's career, whereas alcohol use is more frequently detected in anesthesia practitioners who have been out of residency for longer than 5 years.

Other drugs that have been misused include cocaine, benzodiazepines (midazolam), and more recently propofol. Over the past few years there has been a switch to needleless delivery of the abused drugs. This approach provides a cleaner alternative to the more traditional IV or intramuscular routes. Every possible route of administration has been tried, including unusual IV sites (hidden veins in the feet, groin, thigh, and penis), oral-nasal administration (benzodiazepines), and sublingual and rectal routes. Volatile anesthetics have entered the use arena as well, with sevoflurane reported as the drug of choice among inhalational anesthetics. Regardless of the drug used initially, after 6 months there is an increasing incidence of polydrug use.

Methods of Obtaining Drugs for Misuse

Anesthesiologists have developed numerous and often creative methods for obtaining drugs for misuse. The most frequently employed methods are falsely recording drug administration, improperly filling out the anesthesia record, and keeping rather than wasting leftover drugs. In addition, recent reports have highlighted a new practice involving secretly accessing multidose vials and then refilling and resealing them with other substances. It is important to be wary of the faculty member or resident who is too anxious to give breaks to others or who volunteers to take late cases. One of the most frequently reported retrospective markers of addiction was the desire to work overtime, particularly during periods when supervision might be reduced, such as evenings and weekends.

Signs and Symptoms of Addiction

Regardless of which drugs are misused, any unusual and persistent changes in behavior should be cause for alarm. Classically these behaviors include wide mood swings, such as periods of depression, anger, and irritability, alternating with

periods of euphoria. Key points to remember about addiction include:

- Denial is universal.
- Symptoms at work are the last to appear (symptoms appear first in the community and then at home).
- The pathognomonic sign is self-administration of drugs.
- Addiction is often first detected when an individual is found comatose.
- Individuals whose addiction remains untreated are often found dead.

The most frequently overlooked symptoms of addiction are:

- The desire to work alone
- Refusal of lunch relief or breaks
- Frequent offers to relieve others
- Volunteering for extra cases or calls
- Patient pain needs in the postanesthetic care unit that are disproportionately high given the opioids recorded as administered
- Weight loss
- Frequent bathroom breaks

Associated Risks of Physician Addiction

Although traditionally the risks related to substance use disorders were assigned to the individual physician, it is clear there are also significant risks to patients and potential risks to the hospital staff and administration when a physician develops a substance use disorder.

Physician. The principal risks to the anesthesia provider with substance use disorder are an increased risk of suicide by drug overdose and drug-related death. Unfortunately, the relapse rate for anesthesiologists after drug treatment is the highest among all physician groups with a history of addiction. The risk of relapse is greatest in the first 5 years and decreases as time in recovery increases. The positive news is that 89% of anesthesiologists who complete treatment and commit to aftercare remain abstinent for longer than 2 years. However, death is the primary presenting sign of relapse in an anesthesiologist with opioid use disorder.

Patients can be affected by addiction. The data show that impaired physicians (those who are actively misusing drugs) are at an increased risk of malpractice suits. Data from California and Oklahoma revealed a dramatic decrease in both the number and dollar value of claims filed after treatment for substance use disorder.

Most states have laws requiring that hospital and medical staff report any suspected behavior related to substance use disorders. Failure to report may have significant consequences depending on individual state statutes.

Process for Dealing With Suspected Substance Use Disorder

The process for dealing with suspected substance use by an anesthesiologist is significantly affected by the presence or absence of a physician assistance committee. If an institution does not have such a committee, one should be formed and policies developed so that the support required by an impaired physician is in place when it is needed. The membership of this committee should include an anesthesiologist. In addition, this group should have a consulting agreement with local addiction specialists with experience in treating and referring physicians with substance use disorders. Ideally this treatment group would also include a physician-counselor with experience and expertise in treating anesthesiologists. Finally, this committee should have a helpline telephone number and a point of contact with at least one preselected addiction treatment program.

Reporting and Intervention

Admission to an alcohol or drug addiction treatment program is not considered a reportable event by state or national agencies. It can be dealt with as a medical leave of absence. However, intervention must be initiated as soon as there is firm evidence that substances are being diverted for personal use. This evidence needs to be clear and convincing to the physician assistance committee.

The primary goal of intervention is to get the individual into a multidisciplinary medical evaluation process conducted by a team of experts at an experienced residential treatment program. One-on-one intervention must be avoided. The expertise of the hospital physician assistance committee and county or state medical society can be called upon to help with the intervention. After an individual has been confronted and is awaiting final disposition of the case, it is important not to leave the individual alone, because newly identified physicians with substance use disorders are at increased risk of suicide following this initial confrontation.

Treatment

The specifics of substance use disorder treatment for physicians are beyond the scope of this chapter, though physicians should be offered the same evidence-based treatments that are available to nonphysicians, including medication treatments. It is important that a member of the faculty, group, or impairment committee keep in contact with the physician and the treatment team. There is no cure for addiction, and recovery is a lifelong process. The most effective treatment programs are multidisciplinary and able to provide long-term follow-up for the impaired physician.

Acetaminophen Overdose

Acetaminophen overdose is the most common medicinal overdose reported to poison control centers in the United States. Patients typically have nausea and/or vomiting and abdominal pain at presentation. Acetaminophen toxicity is due to centrilobular hepatic necrosis caused by *N*-acetyl-*p*-benzoquinoneimine (NAPQI), which reacts with and destroys hepatocytes. Normally this metabolite constitutes only 5% of acetaminophen metabolic products and is inactivated by conjugation with endogenous glutathione. In overdose, the supply of glutathione becomes depleted, and NAPQI is not detoxified.

Treatment of acetaminophen overdose begins with determination of the time of drug ingestion and with administration of activated charcoal to impede drug absorption. At 4 hours after drug ingestion, plasma acetaminophen concentration should be measured and plotted on the Rumack-Matthew nomogram,

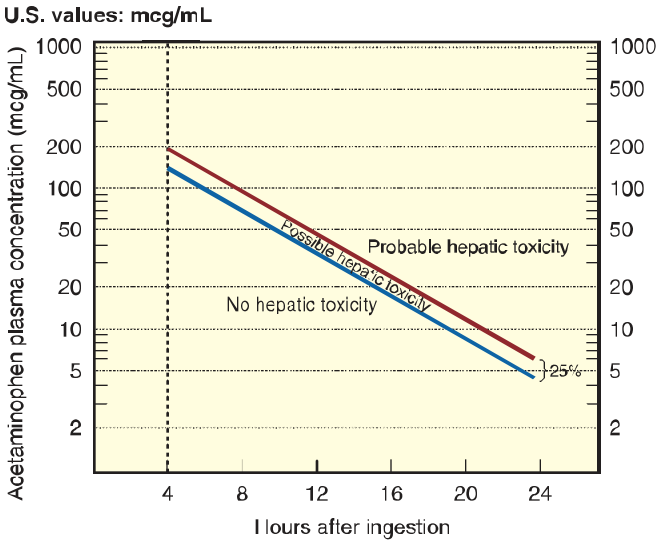

Fig. 29.4 Rumack-Matthew nomogram for acetaminophen toxicity. The plasma concentration of acetaminophen is measured and plotted according to the time the blood sample was drawn relative to the time of overdose ingestion. Position on the nomogram indicates whether hepatotoxicity is probable, possible, or unlikely. Concentrations are expressed as _g/mL. (Adapted from Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. *Pediatrics*. 1975;55:871–876.)

which stratifies patients into those who are not at risk of hepatotoxicity, those who are possibly at risk, and those who are probably at risk (Fig. 29.4). All patients who are possibly or probably at risk of hepatotoxicity and anyone for whom the time of ingestion is not known are treated with *N*-acetylcysteine, which repletes glutathione, combines directly with NAPQI, and enhances sulfate conjugation of acetaminophen. Administration of *N*-acetylcysteine is virtually 100% effective in preventing hepatotoxicity when administered within 8 hours of drug ingestion.

POISONING

Organophosphate Poisoning

Organophosphate pesticides, carbamate pesticides, and organophosphorus compounds (nerve agents developed for chemical warfare and used in terrorist attacks) all inhibit acetylcholinesterase, which results in cholinergic overstimulation. These chemicals are absorbed by inhalation, by ingestion, and through the skin. There are several important differences between the nerve agents and insecticides. The insecticides are oily, less volatile liquids with a longer time to onset of toxicity but longer-lasting effects. Nerve agents are typically watery and volatile, acting rapidly and severely but for a shorter period of time. They are highly toxic, stable, and easily dispersed. Carbamate insecticides have more limited penetration of the CNS, bind acetylcholinesterase reversibly, and result in a shorter, milder course of toxicity than organophosphates. All can be aerosolized and vaporized. The manifestations of pesticide and nerve agent poisoning are influenced by the route of absorption, with the most severe effects occurring after inhalation.

TABLE 29.14 Signs of Organophosphate Poisoning

Muscarinic Effects
Copious secretions
Salivation
Tearing
Diaphoresis
Bronchorrhea
Rhinorrhea
Bronchospasm
Miosis
Hyperperistalsis
Bradycardia
Nicotinic Effects
Skeletal muscle fasciculations
Skeletal muscle weakness
Skeletal muscle paralysis
Central Nervous System Effects
Seizures
Coma
Central apnea

However, poisoning can also take place by absorption of the substance through the skin or eyes and by eating or drinking contaminated food or water (Table 29.14). Muscarinic signs and symptoms of organophosphate exposure include profuse exocrine secretions (tearing, rhinorrhea, bronchorrhea, salivation), gastrointestinal signs, and ophthalmic signs such as miosis. Exposure to larger doses results in stimulation of nicotinic receptors, which produces skeletal muscle weakness, fasciculations, and paralysis. Cardiovascular findings may include tachycardia or bradycardia, hypertension, or hypotension. CNS effects include cognitive impairment, convulsions, and coma. Acute respiratory failure is the primary cause of death and is mediated by bronchorrhea, bronchospasm, respiratory muscle and diaphragmatic weakness or paralysis, and inhibition of the medullary respiratory center.

Treatment of organophosphate overdose involves administration of three types of drugs: an anticholinergic drug to counteract the acute cholinergic crisis, an oxime drug to reactivate inhibited acetylcholinesterase, and an anticonvulsant drug to prevent or treat seizures (Table 29.15). Atropine in 2-mg doses repeated every 5 to 10 min as needed is the main antidote for this poisoning. The clinical endpoint of atropine therapy is ease of breathing without significant airway secretions. Pralidoxime

TABLE 29.15 Goals of Treatment of Organophosphate Poisoning

Reverse acute cholinergic crisis created by the poison
Atropine 2 mg IV every 5–10 min as needed until ventilation improves
Reactivate functioning of acetylcholinesterase
Pralidoxime 1–2 g IV
Prevent or treat seizures
Diazepam or midazolam as needed
Provide supportive care

IV, Intravenously.

is an oxime that complexes with the organophosphate, which results in removal of the organophosphate from the acetylcholinesterase enzyme and splitting of the organophosphate into rapidly metabolizable fragments. Removal of the organophosphate from acetylcholinesterase reactivates the enzyme, and its normal functions can be resumed. Benzodiazepines are the only effective anticonvulsants for treating patients with organophosphate exposure. All patients with severe intoxication by these compounds should be given diazepam or midazolam. Respiratory muscle weakness may require mechanical ventilation.

Carbon Monoxide Poisoning

Carbon monoxide (CO) poisoning is a common cause of morbidity and the leading cause of poisoning mortality in the United States. Exposure may be accidental (inhalation of fire-related smoke, motor vehicle exhaust, fumes from a poorly functioning heating system, tobacco smoke) or intentional.

Pathophysiology

CO is a colorless, odorless, nonirritating gas that is easily absorbed through the lungs. The amount of CO absorbed depends on minute ventilation, duration of exposure, and ambient CO and oxygen concentrations. CO toxicity appears to result from a combination of tissue hypoxia and direct CO-mediated cellular damage. CO competes with oxygen for binding to hemoglobin. The affinity of hemoglobin for CO is more than 200 times greater than its affinity for oxygen. The consequence of this competitive binding is a shift of the oxyhemoglobin dissociation curve to the left, which results in impaired release of oxygen to tissues (Fig. 29.5). However, the binding of CO to hemoglobin does not account for all the pathophysiologic consequences of CO poisoning. CO also disrupts oxidative metabolism, increases nitric oxide concentrations, causes brain lipid peroxidation, generates oxygen free radicals, and produces other metabolic changes that may result in neurologic and cardiac toxicity. CO binds more tightly to fetal hemoglobin than to adult hemoglobin, so infants are particularly vulnerable to its effects. Children, because of their higher metabolic rate and oxygen consumption, are also very susceptible to CO toxicity. CO exposure has uniquely deleterious effects in pregnant women because CO readily crosses the placenta; fetal carboxyhemoglobin (HbCO) concentration may exceed maternal HbCO concentration, and fetal elimination of CO is slower than that of the mother.

Signs and Symptoms

The initial signs and symptoms of CO exposure are nonspecific. Headache, nausea, vomiting, weakness, difficulty concentrating, and confusion are common. The highly oxygen-dependent organs—the brain and heart—show the major signs of injury. Tachycardia and tachypnea reflect cellular hypoxia. Angina pectoris, cardiac dysrhythmias, and pulmonary edema may result from the increased cardiac output necessitated by hypoxia. Syncope and seizures may result from cerebral hypoxia and cerebral vasodilation. Of note, the degree of systemic hypotension in CO poisoning correlates with the severity of CNS structural damage. The classic finding of cherry-red lips is not commonly seen.

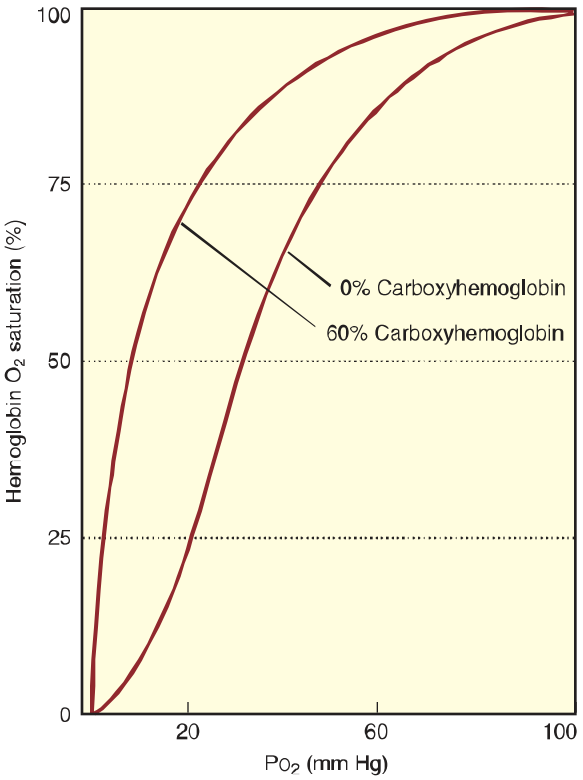

Fig. 29.5 Carboxyhemoglobin shifts the oxyhemoglobin dissociation curve to the left and changes it to a more hyperbolic shape. This results in decreased oxygen-carrying capacity and impaired release of oxygen at the tissue level. (Adapted from Ernst A, Zibrak JD. Carbon monoxide poisoning. *N Engl J Med.* 1998;339:1603–1608. Copyright 1998 Massachusetts Medical Society. All rights reserved.)

The effects of CO poisoning are not confined to the period immediately after exposure. Persistent or delayed neurologic effects may be seen. Delayed neuropsychiatric syndrome, which may include cognitive dysfunction, memory loss, seizures, personality changes, parkinsonism, dementia, mutism, blindness, and psychosis, may occur after apparent recovery from the acute phase of CO intoxication. No clinical findings or laboratory test results reliably predict which patients are at risk of delayed neuropsychiatric syndrome, but patients who are comatose at presentation, older patients, and those with prolonged exposure seem to be at greater risk.

Diagnosis

Serum HbCO concentrations should be obtained for patients suspected of CO exposure. Arterial blood sampling is not necessary because arterial and venous HbCO levels correlate well. Measurement requires a CO oximeter, which, by spectrophotometry, can detect and quantify all normal and abnormal hemoglobins. Routine blood gas analysis does not recognize the presence of abnormal hemoglobins, and pulse oximetry cannot distinguish HbCO from oxyhemoglobin. Oxygen saturation values measured by pulse oximetry may therefore be quite misleading.

Treatment

Treatment consists of removal of the individual from the source of CO production, immediate administration of supplemental

oxygen, and aggressive supportive care (airway management, blood pressure support, cardiovascular stabilization). Oxygen therapy shortens the elimination half-time of CO by competing at the binding sites on hemoglobin and improves tissue oxygenation. Oxygen administration is continued until HbCO concentrations have returned to normal. The half-life of HbCO is 4 to 6 hours when patients are breathing room air, 40 to 80 min when they are breathing 100% oxygen, and approximately 15 to 30 min when they are breathing hyperbaric oxygen. Hyperbaric oxygen therapy consists of delivery of 100% oxygen within a pressurized chamber, which results in a huge increase in the amount of oxygen dissolved in blood. Hyperbaric oxygen therapy accelerates elimination of CO and may decrease the frequency of the neurologic sequelae that can result from severe CO exposure. Hyperbaric oxygen therapy is controversial, is not universally available, and has some risks. However, it may be indicated in selected patients: those who are comatose or have neurologic abnormalities at presentation, those who have HbCO concentrations in excess of 40%, and those who are pregnant and have HbCO concentrations above 15%.

KEY POINTS

- Serotonin syndrome is a potentially life-threatening adverse drug reaction that results from overstimulation of central serotonin receptors. It can be caused by an excess of precursors, increased release, reduced reuptake, or reduced metabolism of serotonin. Many drugs are serotonergic (i.e., involved in these serotonin processes), including selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, monoamine oxidase inhibitors (MAOIs), lithium, drugs of abuse, and narcotic analgesics.
- In addition to the seizure and its neuropsychiatric effects, ECT produces significant cardiovascular effects. The typical cardiovascular response to the electrically induced seizure consists of 10 to 15 sec of parasympathetic stimulation producing bradycardia and a reduction in blood pressure. This is followed by sympathetic nervous system activation resulting in tachycardia and hypertension lasting several minutes.
- Hospitalization is an opportunity to identify and intervene on substance use disorders. Substance use disorders refers to a spectrum of substance use that increases the risk of health consequences and ranges from hazardous/risky use to severe substance use disorders, or addiction. Without employing universal screening strategies, clinicians are at risk to underrecognize substance use.
- Addiction is a treatable, chronic disease of the brain whose symptoms include compulsive use of substances and continued use of substances despite harms. Risk factors such as genetics, environment, and psychosocial factors such as trauma and adverse childhood experiences predispose individuals to addiction. Substance use disorder is the term used to describe the spectrum of substance use.
- Alcohol withdrawal syndrome can be complicated in people who have a history of prior complicated alcohol withdrawal. Alcohol use disorder responds well to medication treatments.
- Acute cocaine administration is known to cause coronary vasospasm, myocardial ischemia, myocardial infarction, and ventricular dysrhythmias, including ventricular fibrillation. Associated systemic hypertension and tachycardia further increase myocardial oxygen requirements at a time when oxygen delivery to the heart is decreased by the effects of cocaine on coronary blood flow. Cocaine use can cause myocardial ischemia and hypotension for as long as 6 weeks after discontinuance of the drug.
- Anesthesiologists comprise 5.5% of all physicians in the United States but are overrepresented in addiction treatment programs, enrolling at a rate approximately three times higher than that of any other physician group. In addition, anesthesiologists are at highest risk of relapse of all physician specialists.
- Fentanyl and sufentanil are the drugs most commonly abused by anesthesiologists. This drug choice is particularly evident among anesthesiologists younger than age 35. Alcohol abuse is seen primarily among older anesthesiologists, perhaps because the time to produce impairment is significantly longer than that observed with opiate addiction. It appears that opiates are the substances of choice for abuse early in an anesthesiologist's career.
- The primary goal of an intervention is to get a physician with a substance use disorder into a multidisciplinary medical evaluation process conducted by a team of experts at an experienced outpatient or residential treatment program. One-on-one intervention must be avoided. After an individual has been confronted and is awaiting final disposition of the case, it is important not to leave the individual alone, because newly identified addicted physicians are at increased risk of suicide following the initial confrontation.
- Acetaminophen overdose is the most common medicinal overdose reported to poison control centers in the United States. Patients typically have nausea and/or vomiting and abdominal pain. Acetaminophen hepatic toxicity is caused by a metabolite of acetaminophen that reacts with and destroys hepatocytes. Normally this metabolite constitutes only 5% of acetaminophen metabolic products and is inactivated by conjugation with endogenous glutathione. In an overdose the supply of glutathione becomes depleted, and the destructive metabolite is not detoxified.
- Nerve agents are organophosphate poisons that have been used in warfare and terrorist attacks. They inactivate acetylcholinesterase and create an acute, severe cholinergic crisis. Emergency management of this poisoning consists of administration of repeated large doses of atropine.
- Routine blood gas analysis does not recognize the presence of abnormal hemoglobins, and pulse oximetry cannot

distinguish carboxyhemoglobin from oxyhemoglobin. Therefore in the presence of carbon monoxide poisoning, these methods provide erroneous information.

- The effects of carbon monoxide are not confined to the period immediately following exposure. Delayed neuropsychiatric syndrome, which may include cognitive dysfunction, memory loss, seizures, personality changes, parkinsonism, dementia, mutism, blindness, and psychosis, may occur after apparent recovery from the acute phase of carbon monoxide intoxication. Patients who are comatose at presentation, older patients, and those with prolonged exposure seem to be at greater risk.

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30

Diseases of Aging

Julie K. McSwain

OUTLINE

INTRODUCTION

Compared to 100 years ago, people are living much longer. The US life expectancy for men in 1900 was 48 years and for women, 51 years. Currently the average life expectancy in the United States exceeds 75 years. The elderly, defined as those older than 65 years, constitute one of the fastest-growing segments of the population. In 2010, the US elderly population numbered 47 million, representing 17% of the total population. In 2018, there were an estimated 52 million US citizens 65 years and older, and by 2030 there will be approximately 80 million elderly (Fig. 30.1). This growth in the older population is a worldwide phenomenon. In the United States alone, there was a 34% growth in the US population age 65 years and older from 2010 to 2020, and by the year 2025 there are expected to be 15 million individuals aged 85 years. The social, economic, and political costs of these demographic changes are enormous.

Surgeries that were considered prohibitively high risk and rare in octogenarians two decades ago are now being performed routinely. Many elderly patients now undergo complex major cardiac, orthopedic, and other noncardiac surgery. With the changing demographics and advancement in surgical techniques, this trend is likely to grow.

Elderly patients utilize disproportionately more medical care than younger people. By some estimates, 35% of total US medical costs are spent on patients older than 65 years. Per capita healthcare costs are three times higher in patients older than 85 years versus those younger than 65 years. About 40% of all surgery and inpatient procedures are performed on elderly patients.

Though the impact of aging and its associated diseases has been recognized for a long time, optimal care of the elderly continues to evolve. Most anesthesia providers for adults are now involved in the care of geriatric patients and so can be considered "geriatric anesthesiologists." Thus it is imperative that an anesthesiologist know the impact of aging on physiology and pharmacology, the impact of comorbidities, and the composite effect of all these changes on perioperative outcomes. Elderly patients are not only "old" or "very old"; they are a unique phenotype comprising an aged biological system, multiple comorbid diseases, and a spectrum of geriatric syndromes. Preoperative assessment of the elderly patient must involve assessment of geriatric syndromes, functional status, frailty, cognition, nutritional status, and goals of care.

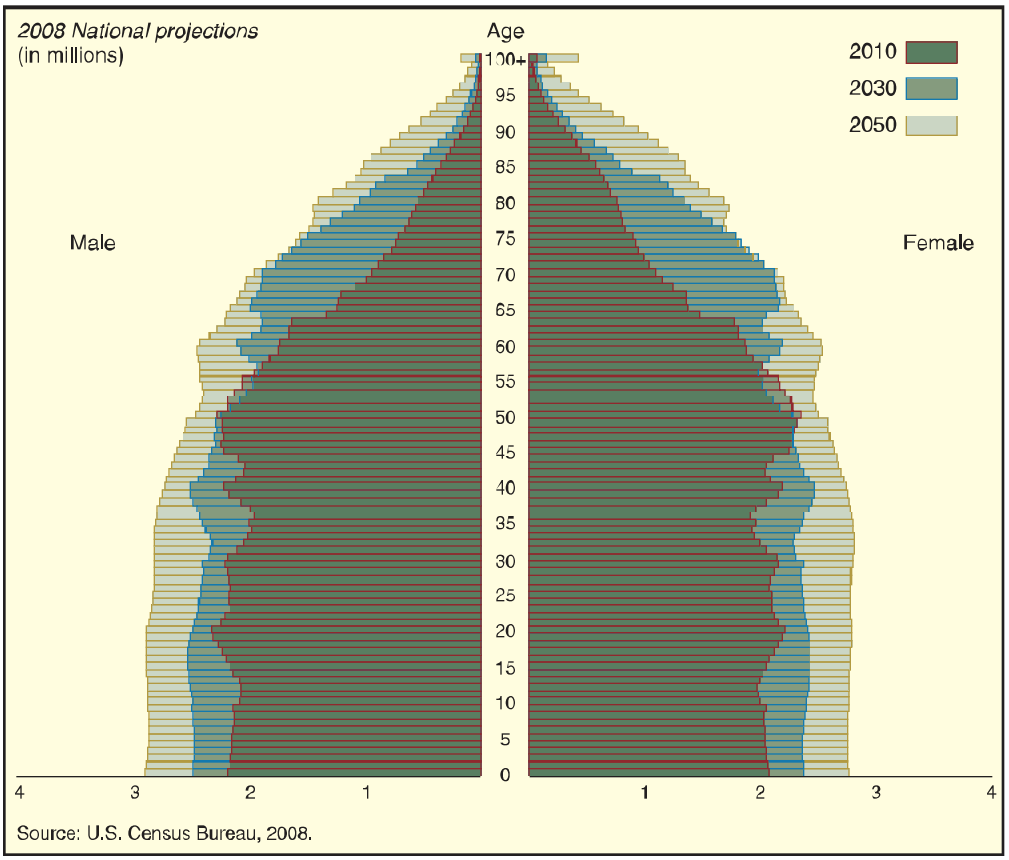

Fig. 30.1 Age and sex structure of the US population for 2010, 2030, and 2050 (2008 national projections in millions). (Source: US Census Bureau, 2008.)

BIOLOGY OF AGING

In the past few decades there has been significant research on the process of aging, the mechanisms that underlie aging, and potential interventions that could delay aging. Aging appears to be driven by progressive accumulation of a variety of random molecular defects that build up in cells and tissues. Aging is thus a continuous process, starting early and developing gradually, instead of being a distinct phase that begins in middle to later life. It is well recognized that all individuals do not age at the same rate. Five key elements seem to contribute to the individuality of the human aging process: genes, nutrition, lifestyle, environment, and chance.

There are two main evolutionary theories for biological aging: the mutation accumulation theory (gene mutations that did not impact reproduction accumulated over time that ultimately resulted in the aging phenotype) and the antagonistic pleiotropy theory of aging (genes that were beneficial in youth and thus favored by natural selection have deleterious effects in late life). Regardless of how aging developed over time, it is clear that aging and longevity are influenced to a degree by our genetic makeup, accounting for about 25% of the variance in the human life span. Multiple genes contribute to the aging phenotype, but there are no specific genes for aging.

There are many mechanisms that can lead to defects and aging, and it is highly likely that no single process is responsible for physiologic aging. The following aging mechanisms are considered the most important and may work synergistically:

Oxidative damage: Free radicals, reactive oxygen species, are by-products of oxygen use and energy metabolism. These free radicals can cause damage to chromosomal deoxyribonucleic acid (DNA) and subsequently impair gene function and damage mitochondrial DNA and telomeres.

DNA damage and repair: Age-related increases in somatic mutations and other forms of DNA damage are well recognized. They can produce permanent alterations of DNA sequences and hence function. A key enzyme involved in the repair of damaged DNA is poly(ADP-ribose) polymerase 1 (PARP-1), and its levels correlate positively with life span. Centenarians who have maintained generally good health have higher levels of PARP-1 than the general population. Telomeres are regions of repetitive nucleotide sequences found at the end of each chromosome. They protect the ends of the chromosome from deterioration and from fusion with nearby chromosomes. A growing body of evidence links telomere length to aging and mortality. With normal aging, telomeres shorten in several tissues, thus limiting the ability of these tissues to regenerate over time, ultimately leading to loss of function and cell death. Premature shortening of telomeres can occur and has been associated with certain diseases such as vascular dementia, psychological and physiologic stress, and

others. Telomere shortening is potentially one way by which environmental factors contribute to premature aging.

Mitochondrial senescence: Mitochondria are intricately involved in energy metabolism and generation of oxygen radicals. Just like somatic DNA, mitochondrial DNA also develops point mutations and deletions over time. An increased incidence of mutated mitochondrial DNA has been noted in aging brain tissue, muscle cells, and gut epithelium.

Malfunction of proteins: Damaged, misfolded, or malfunctioning proteins also accumulate over time and are seen in many age-related diseases such as Parkinson disease, Alzheimer disease, and senile cataracts. Though these faulty proteins should be cleared rapidly, their accumulation and aggregation over time become less efficient. Malfunctioning or accumulated proteins lead to loss of particular functions and ultimately to dysfunction of the entire cell.

Environmental factors: Aging is affected by environmental factors that interact with the genome in various ways. It has been recognized that a low-caloric diet leads to a longer life span. This phenomenon is explained by the disposable soma theory, which postulates that natural selection has led to those pathways that optimize utilization of metabolic resources (energy) among competing physiologic demands (growth, maintenance, reproduction). Insulin and insulin-like growth factor gene systems seem to play a crucial role in these processes. Activation of these genes alters the function of a variety of downstream stress response genes, genes encoding for a variety of antimicrobial proteins, and pathways involved in protein turnover.

The boundary between aging and disease pathogenesis is somewhat arbitrary. The same cellular and molecular functions that contribute to improved life span are also responsible for degenerative diseases such as osteoporosis, osteoarthritis, and dementia.

PHYSIOLOGIC EFFECTS OF AGING

Central Nervous System

Aging affects the brain, and cognitive decline with aging has been considered an unavoidable consequence of brain senescence. Though there are changes with aging, new evidence suggests that part of these changes is due to aging-related medical conditions. Brain function associated with the normal process of aging should be differentiated from specific changes due to neurodegenerative diseases.

All major cell types in the brain undergo structural changes with aging. These changes include neuronal cell death, dendritic retraction and expansion, synaptic loss and remodeling, and changes in glial cell (astrocyte and microglia) reactivity. There is an overall reduction in neuronal regenerative capacity. The mass of the brain decreases by approximately 15% with aging. This decrease is due to cell loss and shrinkage of cell volume. There is a compensatory increase in cerebrospinal fluid volume. However, all areas of the brain do not shrink at the same rate. The cerebellum, prefrontal cortex, and hippocampus demonstrate increased atrophy after middle age. In addition, white matter is lost at a greater rate than gray matter during the aging process and may contribute to age-related cognitive decline and increase risk for age-related brain disorders.

Changes in brain structure are not limited only to cell volume, but also affect synaptic connections. Neural connections play a critical role in brain function and are responsible for the neural plasticity of the brain. With aging, neural plasticity decreases, yet neuronal connectivity may increase.

Cellular signaling transduction pathways, cytokines, and growth factors that are involved in neuronal excitability and plasticity are affected by aging. There are significant changes in neurotransmitter signaling. Cholinergic signaling, which plays a crucial role in learning and memory, can be especially impaired in patients with Alzheimer disease. Presynaptic and postsynaptic dopaminergic neurotransmission can also be significantly affected by aging. In conjunction with thalamic contraction, there is impairment of dopamine signal transduction pathways. These pathways play a significant role in age-related deficits in motor control and may explain the susceptibility of the elderly to the extrapyramidal side effects of dopamine receptor antagonist drugs. Norepinephrine levels are increased in some parts of the aging brain, while levels of □$_2$-agonist receptors may decrease. Levels of ionic glutamate receptors and ¯-aminobutyric acid $(GABA)_A$ binding sites decrease with age. Neurovascular, endocrine, and immunologic changes are also noted in the brain with aging (Fig. 30.2). Aging brain has decreased cerebral blood flow due to a reduction in cerebral metabolic rate and is more susceptible to metabolic stress.

Significant cognitive dysfunction is related to aging and age-related diseases. The incidence of many chronic diseases increases proportionally with age, so it can be difficult to differentiate age-related cognitive dysfunction from disease-related cognitive dysfunction in any particular patient. Hypertension, diabetes mellitus, nutritional deficiency, chronic obstructive pulmonary disease, obstructive sleep apnea, thyroid dysfunction, alcoholism, depression, and medications (opioids, benzodiazepines, anticonvulsants, antipsychotics, antidepressants, antihistamines, anticholinergics, and central nervous system stimulants) can affect cognitive function. General intellectual functioning, attention, memory, and psychomotor function decline with age, but language and executive function remain more or less intact.

Cardiovascular System

Tissue elasticity decreases with age, whereas the proportion of collagen increases. Elastin becomes fragmented because of increased activity of matrix metalloproteinases, and collagen becomes increasingly cross linked. These changes produce increased stiffness in tissues, causing significant structural and physiologic changes in the cardiovascular system.

Two major structural effects occur in blood vessels: stiffening and atherosclerosis. The first is a natural change in the composition of blood vessel walls, with decreasing amounts of elastin and increasing amounts of collagen. The cumulative effects of free radicals and glycosylation of proteins add to the progressive stiffness and thickening of arteries, but the aortic lumen actually increases in diameter despite the arterial

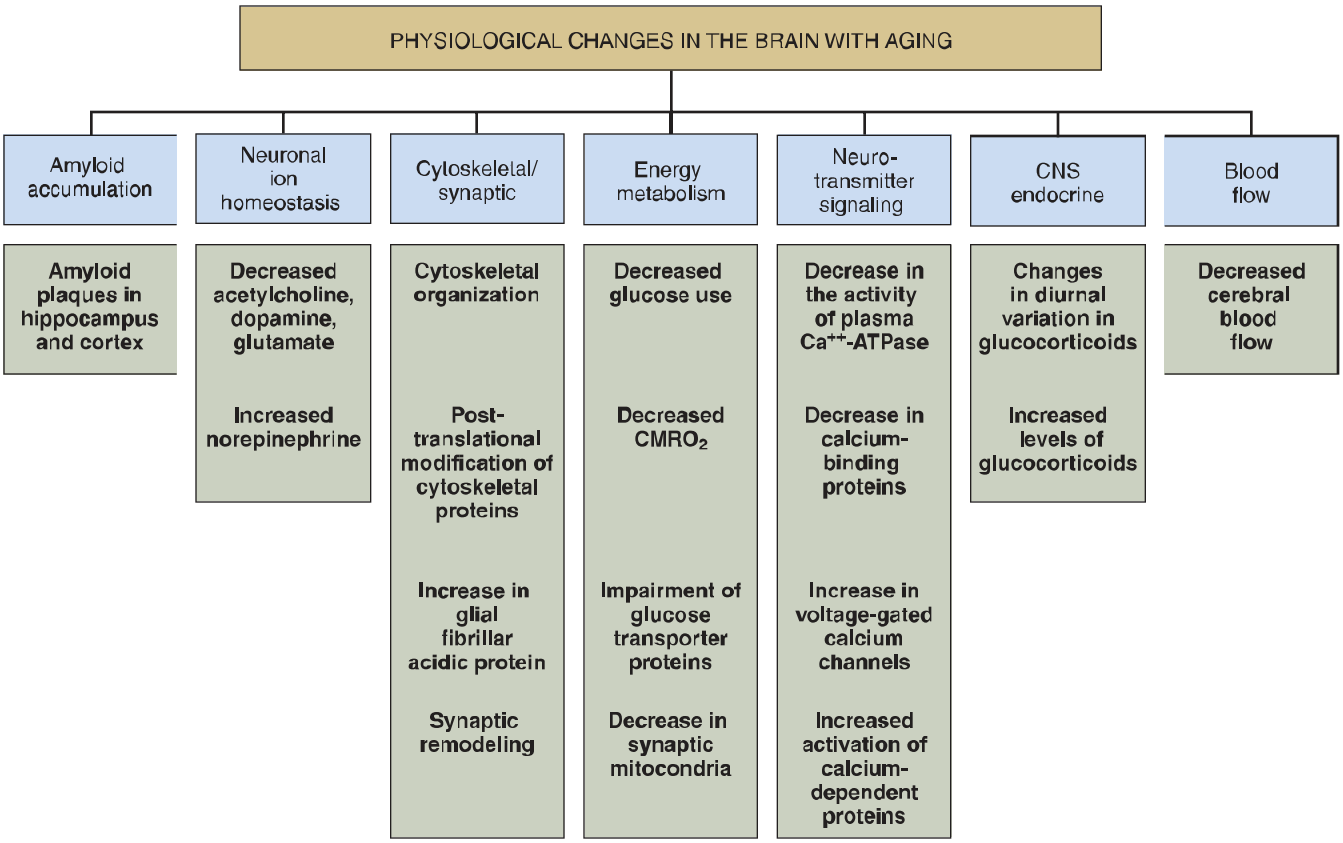

Fig. 30.2 Central nervous system changes with aging. *$CMRO_2$,* Cerebral metabolic rate; *CNS,* central nervous system.

stiffness/thickening. Atherosclerosis and arterial stiffening due to elastin/collagen changes occur simultaneously, but these processes are quite different. Atherosclerosis is a heterogeneous process that happens quite uniformly throughout the conduit arteries. The severity of blood turbulence and shear stress provide a nidus for the atherosclerotic process. Inflammation is the hallmark of atherosclerosis, with increased cholesterol as a cofactor. Atherosclerosis causes occlusion of arteries, whereas age-related changes typically cause dilatation. Functionally the arteries become less responsive to both vasoconstrictors and vasodilators owing to changes in the endothelium. Though levels of endothelin 1 (a potent vasoconstrictor) are increased, the effect of other vasoconstrictor chemicals such as norepinephrine, ephedrine, and phenylephrine is attenuated.

The consequence of stiff arteries is that the pulse wave of the ejected blood travels faster. Velocity increases twofold between the ages of 20 and 80, independent of blood pressure. Stiffer arteries also allow pressure to reflect from the periphery back to the heart quicker while the aortic valve is still open and the heart is ejecting, effectively increasing the afterload on the heart (Fig. 30.3). Thus systolic blood pressure is augmented. Data from the Framingham Heart Study show that systolic blood pressure increases by about 5 mm Hg per decade until the age of 60 and thereafter increases by 10 mm Hg per decade. Diastolic pressure remains unchanged.

These changes lead to alterations in ventricular-vascular coupling. The heart responds to the increased impedance by developing left ventricular hypertrophy. Left ventricular mass increases by 15% between age 30 and 70, with subsequent effects on systolic and diastolic function (Fig. 30.4). These chronic changes make the myocardium more prone to ischemia. Decreased oxygen supply due to an increase in left ventricular end-diastolic pressure and decreased aortic diastolic pressure occurs at the same time as oxygen demand increases owing to ventricular hypertrophy, increased left ventricular end-systolic pressure, increased aortic pressure, and increased duration of systole (Fig. 30.5).

The incidence of diastolic dysfunction increases with age, and this has been proven by detailed echocardiographic studies. Any systolic dysfunction in the elderly should be considered abnormal, especially if it is accompanied by a wall motion abnormality. Though the cardiac myocytes continue to multiply during life, their ability to keep pace with apoptosis decreases. Consequently there is a net loss of about half of cardiac myocytes during life. Older myocytes are stiffer and lack the ability for ischemic preconditioning. The incidence of heart failure increases significantly with age. With heart failure the ratio of β_1- to β_2-adrenergic receptors also changes. In persons without heart failure the left ventricle has 80% β_1-adrenergic receptors and 20% β_2-adrenergic receptors. In heart failure the ratio changes to 60% β_1 receptors and 40% β_2 receptors. This can have a significant impact on how adrenergic agonists and blockers impact ventricular function.

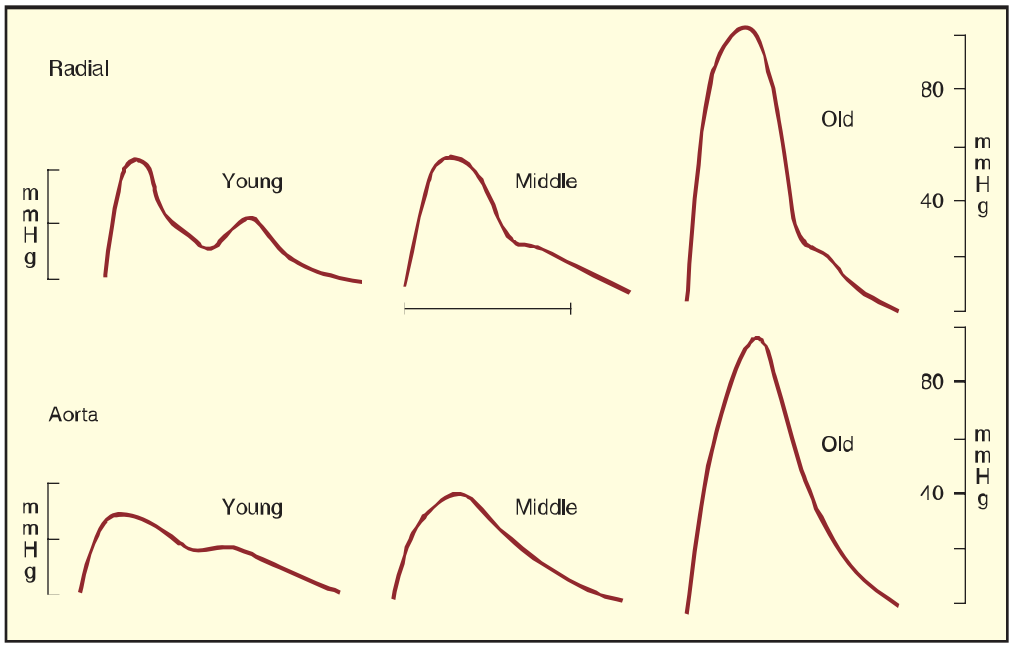

Fig. 30.3 Impact of vascular changes with aging on pulse waveforms of the ascending aorta and radial artery. Pulse pressure is increased almost fourfold in the ascending aorta and twofold in the upper limb. (Adapted from O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol.* 2007;50:1–13.)

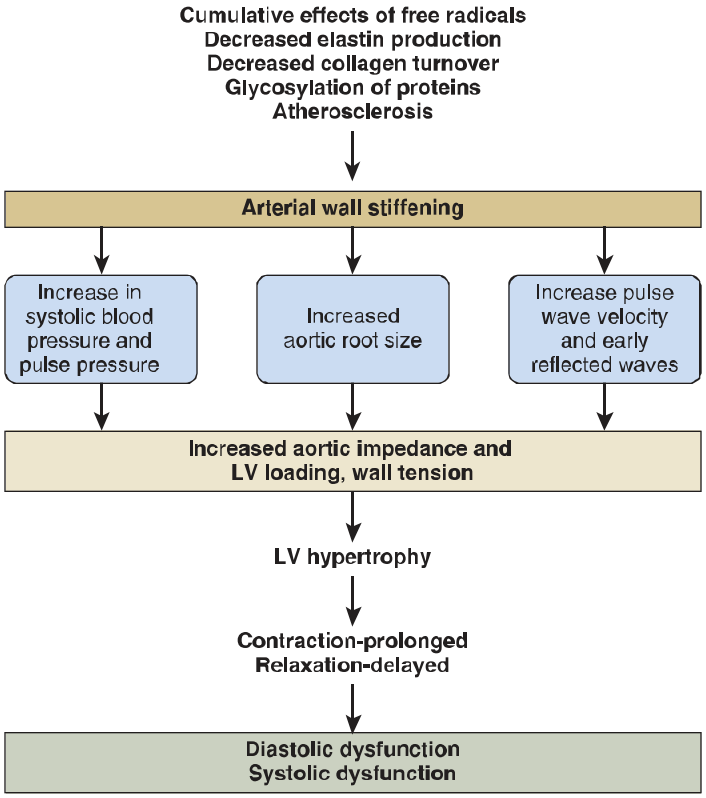

Fig. 30.4 Impact of vascular changes on myocardial function with aging. *LV,* Left ventricular.

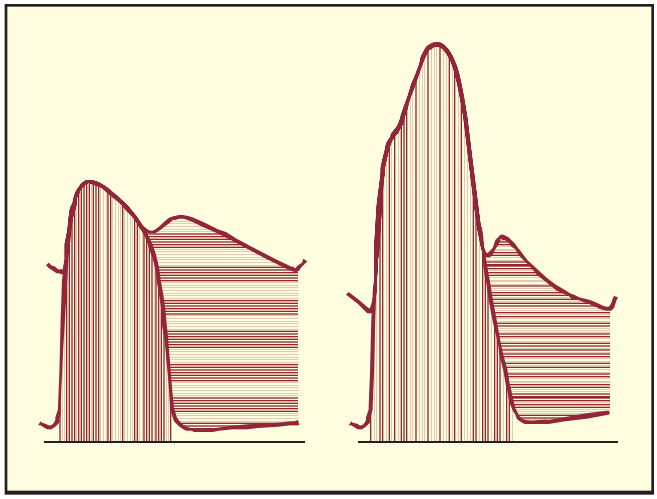

Fig. 30.5 Ascending aortic *(horizontally lined area)* and left ventricular *(vertically lined area)* pressure waves in young and old subjects, with the young subject on the left and the old subject on the right. In the older person, myocardial oxygen demands are increased by the increase in left ventricular (LV) and aortic systolic pressure and by the increased duration of systole. Myocardial oxygen supply is reduced by a shorter duration of diastole, lower aortic pressure during diastole, and increased LV pressure during diastole caused by LV dysfunction. (Adapted from O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol.* 2007;50:1–13.)

Ventricular septal thickness increases with age, as does thickness of the aortic and mitral valve leaflets. Annular dilatation is very common, and 90% of healthy octogenarians demonstrate some form of mild multivalvular regurgitation, which is typically central and associated with normal-appearing valve leaflets. Left atrial chamber size also increases. The incidence of aortic sclerosis and stenosis increases with age.

The electrical system of the heart declines with age. The number of pacemaker cells is reduced by about 90% by age 70. Prolongation of the PR interval, QRS duration, and QT interval

is noted. The incidence of dysrhythmias, especially atrial fibrillation, increases significantly. The resting heart rate slows, and there is a marked decrease in maximum heart rate in response to exercise. The response to atropine administration is half that of younger individuals. Decreased chronotropic, inotropic, and lusitropic responses to dobutamine have been noted in the elderly. Heart rate variability (i.e., variation in instantaneous heart rate and the R-R interval), which is considered a marker of physiologic reserve, is decreased.

Normal age-related changes in cardiovascular physiology include a decrease in peak heart rate, peak cardiac output, and peak ejection fraction. In addition, there are changes in autonomic tone and baroreceptor reflex activity. There is overall dampening of autonomic and baroreceptor activity with aging. This results in a slower resting heart rate and decreased ability to increase cardiac output via a change in heart rate. Compared to younger individuals, increases in cardiac output in the elderly are achieved by increasing end-diastolic volume rather than by increasing heart rate. This results in an increased reliance on atrial contraction for maintenance of cardiac output. Overall, the ability of the cardiovascular system to withstand stress is significantly decreased.

Respiratory System

Age-related physiologic changes in the respiratory system can be grouped into three broad categories: (1) mechanical changes, (2) changes in gas exchange, and (3) changes in sensing mechanisms. A progressive decrease in elasticity alters respiratory mechanics and alveolar architecture. The chest wall becomes stiffer as lung tissue loses its intrinsic elastic recoil. Thus chest wall compliance decreases while lung compliance increases. Total lung capacity remains the same, residual volume increases, and vital capacity decreases. Mechanical changes lead to increased work of breathing and make the elderly more prone to respiratory failure. Owing to a progressive decline in diaphragmatic strength and changes in the airway, expiratory flows such as FEV_1 (forced expiratory volume in the first second of expiration) and $FEF_{75\%}$ (forced expiratory flow at 75% of forced vital capacity) decrease (Fig. 30.6).

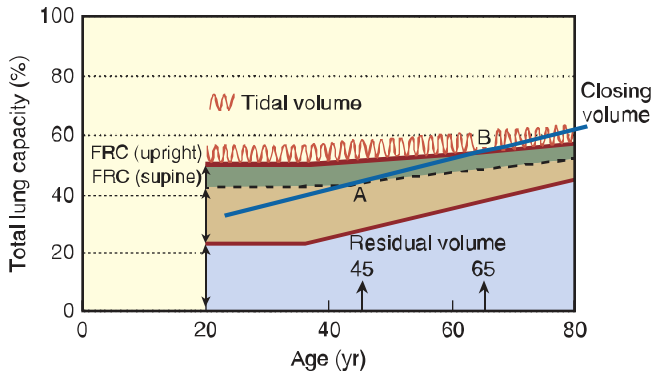

Fig. 30.6 Changes in lung volumes and capacities with aging. Residual volume and functional residual capacity *(FRC)* increase with age, whereas total lung capacity remains the same. Closing volume increases with age and exceeds FRC in the supine position at about age 45 and exceeds FRC in the upright position at about age 65. (Adapted from Corcoran TB, Hillyard S. Cardiopulmonary aspects of anaesthesia for the elderly. *Best Pract Res Clin Anaesthesiol.* 2011;25:329–354.)

Complex changes at the alveolar level cause a reduction in arterial oxygen tension with age. It is estimated that the arterial partial pressure of oxygen (Pao_2) decreases at an average rate of 0.35 mm Hg per year. Mean arterial oxygen tension on room air decreases from 95 mm Hg at age 20 to less than 70 mm Hg at age 80. These changes in arterial oxygenation are caused by an increase in ventilation/perfusion mismatching and to a lesser extent by intrapulmonary shunting. The reduction in elastic tissue in the lung interstitium results in emphysematous changes in lung/airway architecture. Therefore there is an increased tendency of airways to close (i.e., closing volume increases). Closing volume approaches tidal volume, so the elderly are more prone to atelectasis. Residual volume also increases as a proportion of total lung capacity. It is 20% at age 20 and 40% at age 70. Protective cough mechanisms may become attenuated, and both decrease the ability to clear secretions and increase the risk of aspiration. The endurance of the respiratory muscles decreases. Functionally there is reduced respiratory drive in response to hypoxia, hypercarbia, and a resistive load. Increased airway reactivity is also seen.

Renal System, Fluids, and Electrolytes

Various aspects of renal function decline with normal aging. The salient changes in renal function that accompany normal aging are as follows:

Renal vascular dysautonomy: The attenuation of autonomic renal vascular reflexes that are present to protect the kidney from hypotensive and hypertensive states

Senile hypofiltration: The progressive decline in the glomerular filtration rate (GFR) of about 1 mL/year after age 30 that is seen in about two-thirds of the elderly

Tubular dysfunction: Reduction in the maximal tubular capacity to reabsorb and excrete solutes, especially sodium

Medullary hypotonicity: The reduction in tonicity of the renal medulla, which causes a reduced antidiuretic hormone effect and thereby a reduction in water absorption. Elderly patients are unable to maximally concentrate or dilute urine

Tubular frailty: Renal tubular cells being more susceptible to hypoxic or nephrotoxicity injury and take longer to recover from acute tubular necrosis

The clinical consequences of all these changes can be profound. The aging kidney is more susceptible to injury, less able to accommodate hemodynamic changes, and not able to handle water and salt perturbations. A low GFR and diminished tubular function lead to reduced ability to concentrate urine, which means that the obligatory urinary volume to excrete waste products must increase. However, also owing to decreased GFR, the ability to excrete excess free water is diminished, making the elderly more prone to fluid overload, pulmonary edema, and development of hypoosmolar states (e.g., hyponatremia) if large amounts of hypoosmolar fluids are administered.

Aging also causes decreased sensitivity of volume and osmoreceptors, so the thirst response may be diminished and drinking behavior altered. Bladder dysfunction or incontinence can also alter drinking behavior to avoid embarrassing situations. Since many elderly patients have mobility problems or difficulties

with the activities of daily living (ADLs), difficult access to fluids further predisposes them to dehydration.

Gastrointestinal System

Aging significantly affects the motility of the oropharyngeal/upper esophageal area, colonic function, gastrointestinal immunity, and gastrointestinal drug metabolism. Liver size, blood flow, and perfusion normally decline by 30% to 40% between the 3rd and 10th decades. However, these changes do not have a significant impact on liver function. Liver function has to decrease by 70% to have clinically relevant effects. No significant abnormalities are noted on conventional liver function tests in the elderly.

Immune System

Significant changes in the immune system include both changes in the innate immune system (macrophages, neutrophils, natural killer cells, etc.) and in the adaptive immune systems. The bactericidal activity of immune cells is decreased. Increased levels of cytokines and chemokines have been noted, which is consistent with a low-grade chronic inflammatory process in the elderly. Age-related functional changes have also been noticed in T-cell and B-cell functions. These changes are thought to impact the ability of the elderly to fight infection and control cancers.

Endocrine Function

The endocrine glands tend to atrophy in the elderly and reduce hormone production. This frequently leads to impaired endocrine function, such as impaired glucose homeostasis. Deficiencies of insulin, thyroxine, growth hormone, renin, aldosterone, and testosterone are often present. Chronic electrolyte abnormalities, diabetes mellitus, hypothyroidism, impotence, and osteoporosis are common.

The resting metabolic rate declines approximately 1% per year after age 30, and total energy expenditure also goes down, probably secondary to a decline in lean body mass. However, in elderly persons with multiple morbidities and those affected by chronic illness, total energy expenditure increases. Sick individuals often expend most of their energy performing simple ADLs. Longitudinal studies have demonstrated that peak oxygen consumption declines progressively with aging, so the elderly are unable to cope with high oxygen demands.

Sarcopenia and Body Composition

There is a 10% to 15% decrease in intracellular fluid owing to loss of muscle mass. Total fat content decreases, but the percentage of fat per total body weight increases. Weight tends to decline with aging because of a significant reduction in lean body mass, which is predominantly composed of muscle and visceral organs. Muscle atrophy is greater in fast-twitch than in slow-twitch muscle fibers, presumably secondary to loss of motor neurons. Waist circumference increases throughout one's life span are due to increasing visceral fat. In some individuals, fat can also accumulate inside muscle tissue, affecting muscle quality and function. Fibroconnective tissue also builds up with aging, and it too can affect muscle quality and function. This loss of muscle mass and quality results in reduced muscle strength that ultimately affects functioning and mobility.

FRAILTY

Frailty is defined as a state of reduced physiologic reserve that is associated with increased susceptibility to disability. It is related to normal changes of aging, chronic disease, and inflammation and is characterized by failure of the body to respond to additional stresses such as surgery or infection. Aging, however, does not necessarily guarantee frailty; there are elderly patients who may not become frail just as there are patients under the age of 65 who may meet criteria for being frail. In addition, there is no gold standard for assessing frailty, although there are several well-studied and validated instruments such as the Clinical Frailty Scale, Edmonton Frail Scale, Risk Analysis Index, and Frailty Index. Frailty assessments can be used as a risk stratification tool to provide a more comprehensive informed consent and shared decision making, or they can be used as a more formal assessment to identify areas that may be modified preoperatively to potentially improve outcome. A proposed phenotype definition of frailty is characterized by weight loss, fatigue, impaired grip strength, low physical activity, slow gait speed, and, in some patients, cognitive decline. All these changes lead to a decreased reserve. Compared to their nonfrail counterparts, elderly patients who are frail are likely to decompensate more quickly and recover more slowly from pathologic or physiologic insults such as surgery. Frailty is more prevalent in the perioperative patient compared to the general population, and it is estimated that 25% to 40% of elderly perioperative patients are frail. Current evidence suggests that geriatric surgical patients who are frail have a two- to fourfold increase in mortality and postoperative complications as well as a fivefold increase in hospital discharge to places other than home.

GERIATRIC SYNDROMES

Geriatric syndromes encompass clinical conditions that are frequently encountered in older people. The pathophysiology of geriatric syndromes is multifactorial and can involve multiple unrelated organ systems. These syndromes have deleterious effects on independent functioning and quality of life. The list of geriatric syndromes includes incontinence, delirium, falls, pressure ulcers, sleep disorders, problems with eating or feeding, pain, and depressed mood. In addition, dementia and physical disability can also be considered geriatric syndromes. Geriatric syndromes are the phenotypic consequences of frailty. Virtually all geriatric syndromes are characterized by changes in four domains: (1) alteration in body composition, (2) gaps in energy supply and demand, (3) signaling disequilibrium, and (4) neurodegeneration. Only dementia and falls will be discussed here.

Dementia

The population of patients with dementia is growing. In 2020, the World Health Organization (WHO) reported dementia to affect an estimated 50 million people, 5% to 8% of the global

TABLE 30.1 Comparison of Different Central Nervous System Disorders

Diagnosis	Distinguishing Features	Symptoms	Course
Dementia	Memory impairment	Disorientation, agitation	Slow onset, progressive, chronic
Delirium	Fluctuating level of consciousness, decreased attention	Disorientation, visual hallucinations, agitation, apathy, withdrawal, memory and attention impairment	Acute; most cases remit with correction of underlying medical condition
Psychotic disorders	Deficit in reality testing	Social withdrawal, apathy	Slow onset with prodromal syndrome; chronic with exacerbations
Depression	Sadness, loss of interest and pleasure in usual activities	Disturbances of sleep, appetite, concentration; low energy; feelings of hopelessness and worthlessness; suicidal ideation	Single episode or recurrent episodes; may be chronic

population age 60 and over. They further project that this number will rise to 82 million in 2030 and 152 million in 2050. Thus a significant proportion of elderly perioperative patients are likely to have preexisting dementia. Intellectual decline is one of the early hallmarks of dementia. Major differences are seen in the elderly in terms of intellectual function compared to themselves in early adulthood. In any patient with a slowly progressive dementia, sudden changes in cognitive, behavioral, or health status may occur. Mental status is often a barometer of health in these patients, and abrupt changes necessitate a search for any additional problem that may be occurring (Table 30.1). Numerous population-based studies report decreased longevity in elderly individuals who experience cognitive decline. In fact, the WHO listed dementia as the seventh leading cause of death worldwide and the third leading cause of death in both Europe and the United States in 2019. *Diminishing cognitive performance over any time interval is predictive of an earlier death.* In addition, preexisting dementia in the surgical patient is a strong predictor of postoperative complications and greater hospital costs and is an independent predictor of 30-day mortality. Perhaps the most important challenge in treating dementia is identifying causes of reversible dementia, such as chronic drug intoxication, vitamin deficiencies, subdural hematoma, major depression, normal-pressure hydrocephalus, and hypothyroidism.

Unfortunately, most causes of dementia, including degenerative brain diseases such as Alzheimer disease and other common multi-infarct states, are incurable. This does not mean, however, that symptoms cannot be treated and ameliorated. Pharmacotherapy for dementia is tailored to control behavioral problems such as agitation, depression, and sleep disorders that may be present and to prevent further intellectual decline and neurodegeneration. These treatments may include vitamin E, N-methyl-D-aspartate (NMDA) antagonists, selective serotonin reuptake inhibitors (SSRIs), melatonin, and centrally acting acetylcholinesterase inhibitors.

For the anesthesiologist the challenges in caring for elderly patients with declining mental capacity are many. Perioperative interactions with the patient and family must take into account the patient's compromised ability to process general and medical information and capability to provide truly informed consent. Care for individuals with dementia typically requires multidisciplinary collaboration, including family and caregivers with written identification of healthcare power of attorney and advanced directives preoperatively. Documentation of baseline cognitive and neurologic function may become significant if postoperative alterations in mental function are encountered. If acute deterioration is suspected, a neurologic consultation is advised. While more research is needed to elucidate the best perioperative care for elderly patients with dementia, perioperative care should focus on evaluating and managing delirium, treating postoperative pain, and minimizing sleep disturbances.

Falls and Balance Disorders

Unstable gait and falls are a serious concern in older patients. Problems with balance and falls tend to be multifactorial. Poor muscle strength, neural damage in the basal ganglia and cerebellum, and peripheral neuropathy are all recognized risk factors for falls. The American Geriatric Society recommends asking all older adults about falls and gait instability. Patients with a history of multiple falls should undergo an evaluation of gait and balance to determine the precipitating factors.

PHARMACOKINETIC AND PHARMACODYNAMIC CHANGES WITH AGING

Elderly patients often suffer from multiple morbidities and are taking multiple medications. *Polypharmacy is common in the elderly.* The effects of drug interactions are substantially increased with advanced age. Older, sicker patients require less anesthesia. Their increased sensitivity to anesthetics has been attributed to loss of neuronal tissue or poorly defined changes in receptor functions. Progressive changes in functional connectivity in the aging brain and the varying effects of anesthetics provide other possible explanations for this increased sensitivity and may explain both anesthetic toxicity and the cognitive dysfunction associated with anesthesia in the elderly.

Management of Anesthesia

The pharmacokinetics of anesthetic drugs are affected by progressive physiologic changes that occur with aging. Total body water decreases by 10% to 15%, and this decrease causes a decrease in the measured central compartment volume. This can lead to an increase in initial plasma concentration following

rapid intravenous (IV) administration of an anesthetic drug. Body fat increases as muscle mass decreases, so lipid-soluble drugs (most IV anesthetics) have a large volume of distribution with the potential for prolonged clinical effects.

Changes in serum proteins include a decrease in plasma albumin and a slight increase in Ξ_1-acid glycoprotein. These changes could theoretically affect circulating free drug concentrations and the concentration of drug at the effect site. In practice, however, these protein changes do not appear to have a significant impact on geriatric anesthetic pharmacology. A greater concern is the need for adjustment of drug dosages based on a smaller lean body mass and weight in the elderly.

Drugs that are metabolized by microsomal cytochrome P450 enzymes may be affected. These changes result in a reduction in clearance of about 30% to 40%, which corresponds to the degree hepatic blood flow is reduced in the elderly. As renal function declines, drugs that are cleared by the kidneys should be administered judiciously. In particular, neuromuscular blockers that are excreted by the kidneys must be carefully dosed.

Inhalational Anesthetics

The minimum alveolar concentration (MAC) required to achieve adequate anesthetic depth progressively decreases with age. By some estimates, MAC values decrease by about 6% per decade after age 40 for volatile anesthetics and about 8% per decade for nitrous oxide. The exact mechanism for this is unknown. The effects of volatile anesthetics and nitrous oxide are additive. Thus an 80-year-old patient who gets 66% nitrous oxide will require only 0.3% sevoflurane to achieve 1 MAC anesthetic concentration (Fig. 30.7). The hemodynamic impact of excessive anesthetic administration is well recognized.

Propofol

The pharmacodynamics and pharmacokinetics of propofol are significantly altered with aging. Age-related changes have been found for both induction and infusion doses. This dosing adjustment may be nearly a 50% decrease. Elderly patients develop deeper anesthetic stages (as evidenced by electroencephalography [EEG]), need more time to reach deeper anesthetic stages, and require more time for recovery. They need less propofol for steady-state maintenance of a defined stage of hypnosis. The hemodynamic effects of propofol are much greater in the elderly. Interestingly there are gender differences in propofol pharmacokinetics. Propofol clearance is decreased much more in women than in men. Though the drug has been extensively studied, investigations have been limited to relatively healthy older patients. Current practice for anesthetic care of the very elderly is based on extrapolation of these data.

Etomidate

Etomidate is an anesthetic and amnestic but not an analgesic. It is often considered an ideal drug for the elderly because it causes less hemodynamic instability than propofol or thiopental. However, it has a smaller initial volume of distribution and reduced clearance in the elderly. A significant increase in sensitivity to this drug has also been shown. Like propofol, much lower induction doses are recommended in the elderly.

Thiopental

The central volume of distribution for thiopental decreases in the elderly, and the total dose of this drug will need to be reduced. An optimal dose in an 80-year-old patient is suggested to be 50% to 80% of the dose needed for an adult patient. Recovery after a bolus dose of thiopental is delayed in older patients because of the decreased central volume of distribution.

Midazolam

Elderly patients are significantly more sensitive to midazolam than younger patients, primarily because of pharmacodynamic differences. However, the exact mechanism of this pharmacodynamic difference is unknown. The duration of effect of midazolam may be much longer and can contribute to postoperative delirium (POD). Furthermore, midazolam is metabolized to the pharmacologically active metabolite hydroxymidazolam, which is excreted by the kidneys and may accumulate in patients with diminished renal function. A 75% reduction in dose from a 20-year-old to a 90-year-old has been recommended.

Opioids

Pharmacodynamic changes within the opioid receptor system have been noted with aging. Receptor density, receptor affinity, and binding may change. Though increased sensitivity to opioids is attributed to pharmacodynamic changes, age-related pharmacokinetic changes, especially on opioid metabolism, affect the choice of opioids to be used in the elderly. The liver metabolizes the opioids, and the kidneys excrete the metabolites. Metabolites of some opioids, including codeine, morphine, and meperidine, are pharmacologically active and contribute to both analgesia and many side effects. The primary risk of opioids is respiratory depression, the incidence of which is markedly increased with age.

Fentanyl. Fentanyl is a highly selective Ξ-receptor agonist. Age has a greater effect on fentanyl pharmacodynamics than on its pharmacokinetics. A 50% increase in the potency of fentanyl has been reported in octogenarians. Since elderly patients are much more sensitive to fentanyl, they should receive reduced IV doses.

Remifentanil. Remifentanil is an ultrashort-acting synthetic opioid and is metabolized by nonspecific tissue and plasma esterases. This makes it an ideal drug for use in the elderly because it has a very short half-life and is not dependent on liver and renal function for clearance. However, elderly patients are quite sensitive to remifentanil. The equilibrium constant is decreased by approximately 50% over the age range of 20 to 85 years. The onset and offset of remifentanil effect are also slower in elderly individuals. Elderly patients need only about half the bolus dose of younger patients to achieve the same effect. This is because of increased pharmacodynamic sensitivity rather than pharmacokinetic changes. Elderly patients require an infusion rate about one-third that of younger patients because of the combined impact of increased sensitivity and decreased clearance.

Meperidine. Meperidine is a relatively weak $\exists$ agonist with about 10% of the potency of morphine. It is metabolized to an active metabolite, normeperidine, which is excreted by the kidneys and has a very long half-life of 15 to 30 hours. Use of

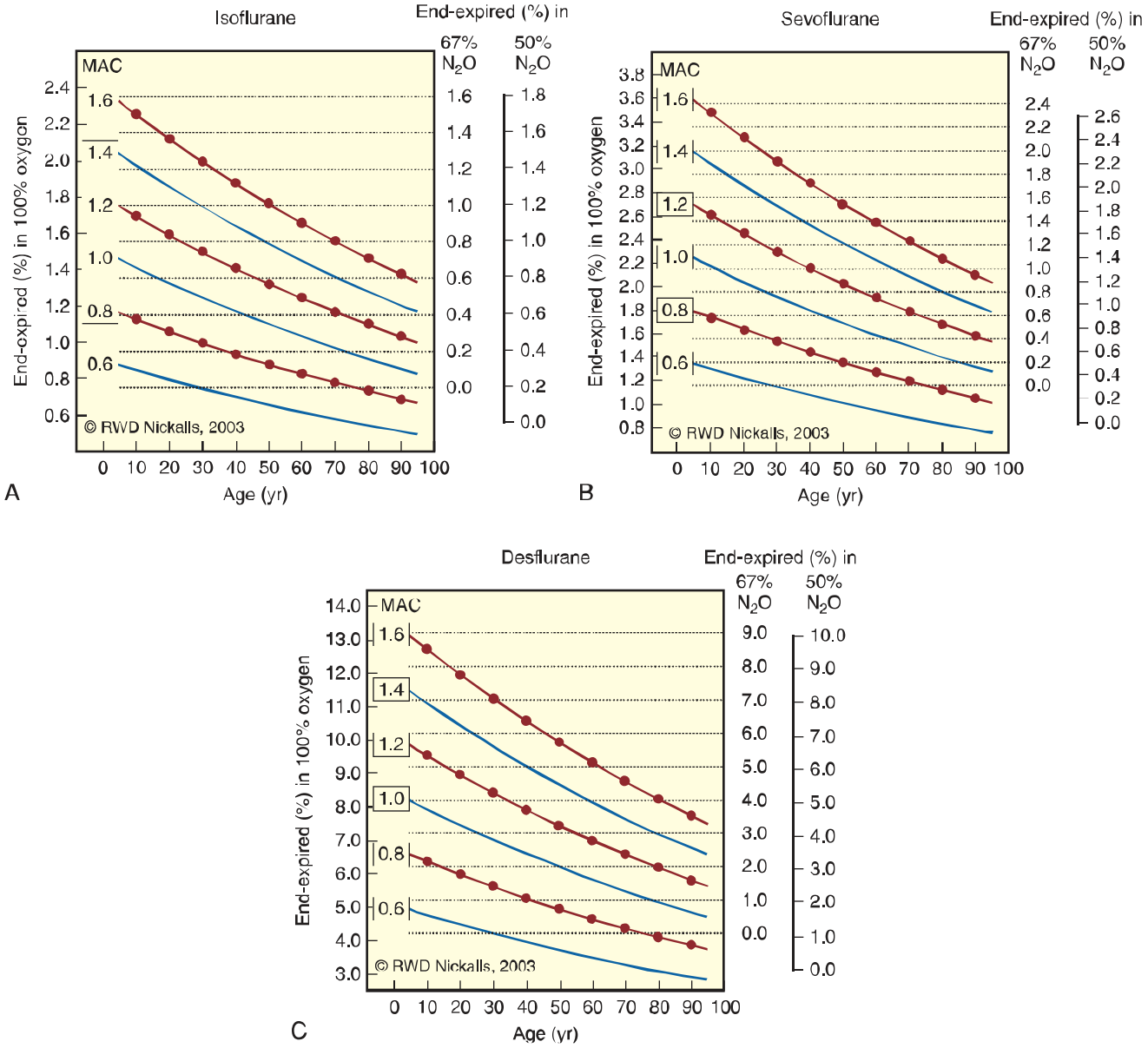

Fig. 30.7 Minimum alveolar concentration (MAC) charts for isoflurane (A), sevoflurane (B), and desflurane (C) (age 1 yr). (Adapted from Nickalls RW, Mapleson WW. Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane in man. *Br J Anaesth*. 2003;91:170–174.)

meperidine has been associated with development of POD in elderly patients, so its use is not recommended in older adults except in the very small doses needed to manage postoperative shivering.

Neuromuscular Blocking Drugs

The pharmacodynamics of neuromuscular blocking drugs are not significantly altered by age. The ED_{95} of neuromuscular blockers is essentially the same for young and old patients. In contrast, the pharmacokinetics of neuromuscular drugs are significantly altered with age. The onset to maximal block may be delayed, and metabolism by the liver and excretion by the kidneys can be significantly prolonged in elderly patients with hepatic and/or renal dysfunction. Recovery time from neuromuscular blockade could be increased by as much as 50%, and the impact of residual neuromuscular blockade on pharyngeal and pulmonary function can be significant in the elderly.

PERIOPERATIVE OUTCOMES AFTER CARDIAC AND NONCARDIAC SURGERY

Perioperative outcomes are dependent on many factors, the two most important of which are the surgical risk of the procedure and the number of defined clinical risk factors in the patient. As the number of clinical risk factors increases and the risk of the surgical procedure increases, the overall risk of a poor outcome also increases. Surgery performed in high-volume centers with specialized staff and extra resources may have better outcomes.

Based on their physiologic changes, it is expected that outcomes in the elderly would be worse than in their younger

counterparts. However, this has not been clearly shown. One reason for this unexpected observation is that the rate of decline of function varies significantly among individuals. The rate of decline is dependent on genetic factors, coexisting diseases, and environmental insults. Thus a "healthy" 80-year-old may be more physiologically robust than a 70-year-old with several comorbidities. Complicated surgery or procedures cannot be denied to elderly patients solely on the basis of age and the presence of any comorbidities. The functional level of the patient must also be considered.

The probability that an octogenarian will be completely healthy is remote. According to 2011 American Heart Association statistics, the prevalence of cardiovascular disease in patients older than 80 years is 78% to 85%. The incidences of hypertension (_ 65%), coronary artery disease (23–37%), and congestive heart failure (13–15%) are all higher (Fig. 30.8). Furthermore, the incidence of diabetes mellitus, renal insufficiency, atrial fibrillation, and chronic obstructive pulmonary disease increases significantly with aging.

Elderly patients do have significantly worse outcomes than their younger counterparts. This has been shown in national databases and individual studies. The operative mortality of octogenarians undergoing cardiac surgery is reported to be 6% to 11% compared with 3% to 4% in younger patients. Octogenarians have a significantly higher risk for any complication with cardiac surgery, including neurologic events, pneumonia, dysrhythmias, and wound infection (Fig. 30.9). Operative mortality is two to five times higher in octogenarians than in younger patients. This is also true for noncardiac surgery (Fig. 30.10).

A high rate of postoperative complications—as high as 60%—has been reported. In one study, pulmonary insufficiency or infection was one of the leading causes of postoperative morbidity. One-fifth of patients required prolonged (¬24 hours) mechanical ventilation. Atrial fibrillation and surgical wound infection are more frequent. The stroke rate is about twice that of younger patients. Neurocognitive dysfunction is very common after both cardiac and noncardiac surgery in the elderly. Delirium is common after major surgery, and the incidence of a long-term decline in cognitive function is also very common. This has been most clearly demonstrated after coronary artery bypass surgery. The incidence of cognitive dysfunction after noncardiac surgery is three to nine times more frequent than in the elderly who do not undergo surgery. Many of these complications account for increased hospital length of stay and increases in cost.

Functional recovery after cardiac and noncardiac surgery is not the norm. Some studies report that fewer than 50% of

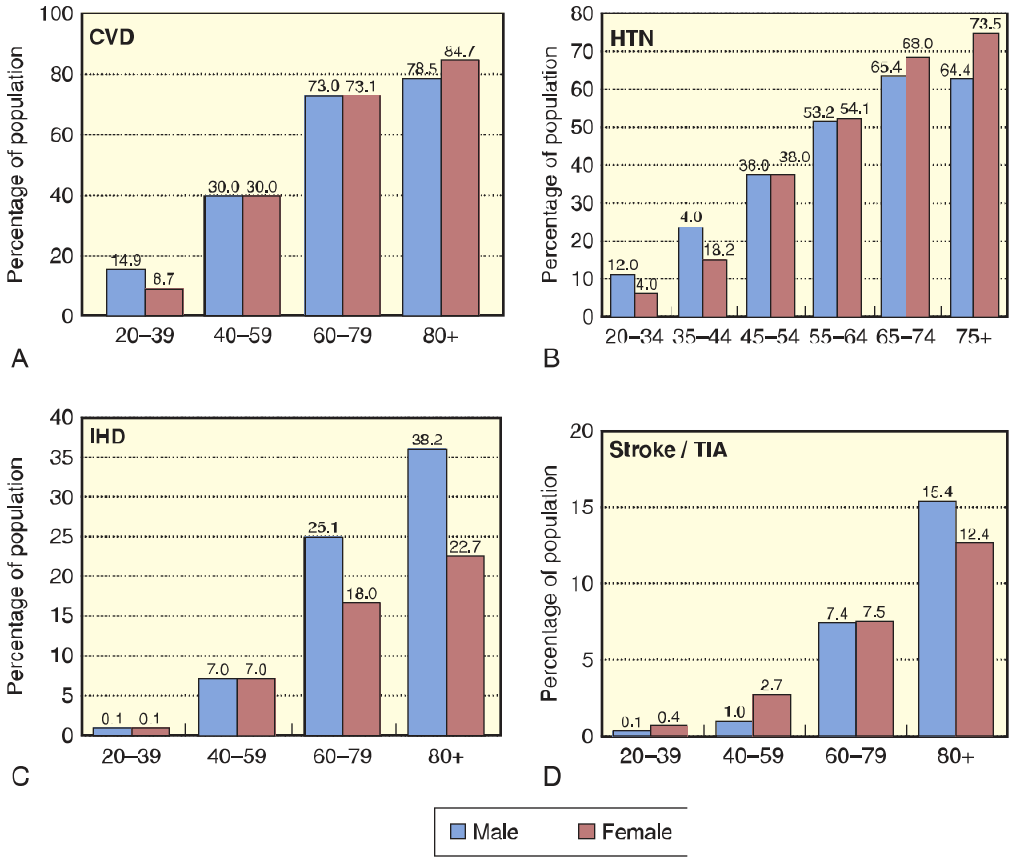

Fig. 30.8 Incidence of cardiovascular disease based on age and gender. A, Cardiovascular disease *(CVD)*. B, Hypertension *(HTN)*. C, Ischemic heart disease *(IHD)*. D, Stroke/transient ischemic attack *(TIA)*. (Data from Lloyd-Jones D, Adams RJ, Brown TM, et al. on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation*. 2010;121:e46–e215.)

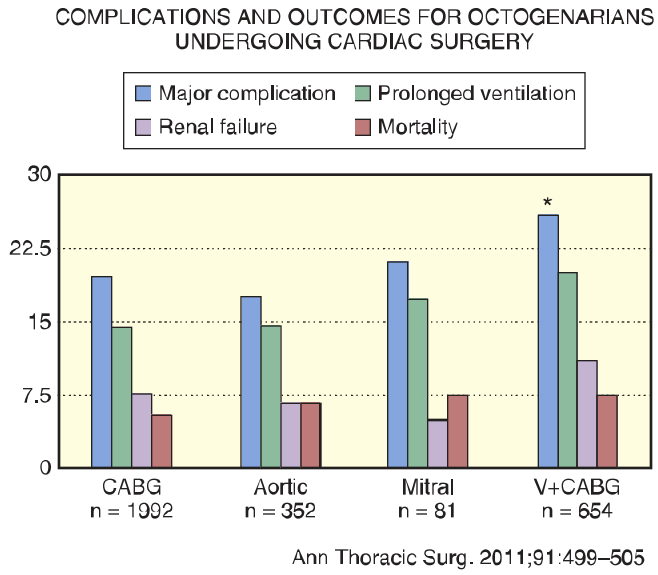

Fig. 30.9 Morbidity after cardiac surgery in octogenarians. *CABG*, Coronary artery bypass grafting; *V+CABG*, valve surgery in addition to CABG. (Data from Bhamidipati CM, LaPar DJ, Fonner Jr E, et al. Outcomes and cost of cardiac surgery in octogenarians is related to type of operation: a multi-institutional analysis. *Ann Thorac Surg.* 2011;91:499–505.)

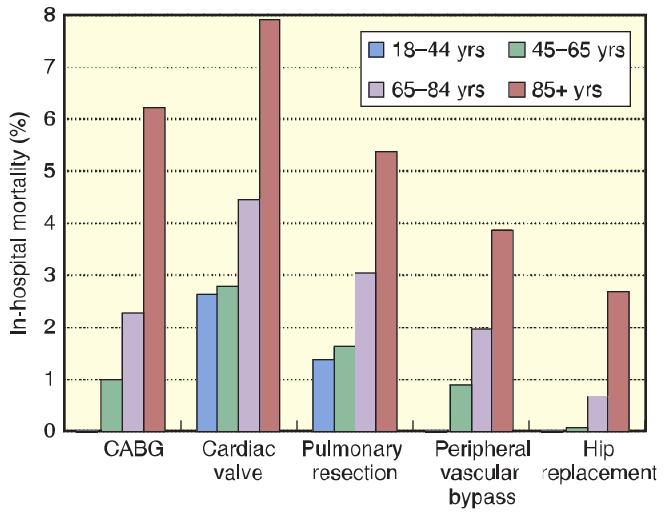

Fig. 30.10 Operative mortality by age for the year 2009. *CABG*, Coronary artery bypass grafting. (Data from Healthcare Cost and Utilization Project [HCUP]. Nationwide inpatient sample 2009. www.hcup-us.ahrq.gov.)

elderly patients are discharged back to their homes. Instead, many patients are discharged to long-term rehabilitation facilities or nursing homes.

PERIOPERATIVE CARE OF ELDERLY PATIENTS

Preoperative Assessment

It is well recognized that elderly patients have decreased reserve and hence are more prone to major adverse events. Comprehensive preoperative assessment is crucial in determining perioperative risk and optimizing care. Because of the complexity of geriatric patients, it is not uncommon that geriatric consultation is obtained preoperatively or that an elderly patient is comanaged with a geriatrician.

Traditional risk indices cannot predict outcomes in octogenarians. They do not take into account frailty, which signifies decreased functional capacity and increased perioperative risk in an elderly individual. Validated frailty instruments have been shown to predict outcomes in the elderly population and have a role in perioperative risk assessment. For example, adding the Frailty Index to the established Revised Cardiac Risk Index can improve risk prediction by 8% to 10% and can be of incremental value in cardiovascular risk assessment. Frailty assessments may also identify potentially modifiable risk factors such as polypharmacy, anemia, physical deconditioning, poor nutrition, and increased risk for POD. A comprehensive geriatric preoperative assessment must also include review of geriatric syndromes, nutritional status, assessment of functional status, baseline cognitive status, review of medications, and goals of care.

Nutrition and Anorexia

Normal aging is associated with a decline in food intake, which is more marked in men than in women. This is partly a result of a low level of physical activity, a decline in lean body mass, and a slow rate of protein turnover. Loss of taste sensation, reduced stomach compliance, and high levels of certain hormones also lead to a decrease in appetite. About a quarter of elderly individuals meet the criteria for malnutrition. Malnutrition or undernutrition is associated with multiple adverse health consequences, such as impaired muscle function, decreased bone mass, immune dysfunction, anemia, reduced cognitive function, poor wound healing, and increased risk of falling. In the perioperative setting poor nutrition is related to complications such as prolonged intubation and increased risk of pneumonia, infection, and 30-day mortality. If there is a concern regarding malnutrition due to alcohol consumption, vitamin B_{12} and folate levels should be measured. Patients with an unintentional weight loss of more than 10% to 15% over the last 6 months, a body mass index (BMI) below 18.5, or a serum albumin below 3 g/dL are considered to be at severe nutritional risk. Preoperative nutritional support should be provided to these patients. Though there is consensus that nutritional assessment is important, nutritional supplementation in the perioperative period has not been definitively shown to improve outcome.

Functional Status

Poor functional status has been identified as a risk factor for surgical site infection and postoperative complications. About one-fourth of patients older than age 65 have impairment in their basic ADLs: bathing, dressing, eating, transferring from bed to chair, continence, and toileting; or their instrumental (I) ADLs: transportation, shopping, cooking, using the telephone, managing money, taking medications, housecleaning, and laundry. Half of persons older than 85 years have impairment in their ADLs. Functional status can be assessed by performance times in up-and-go mobility tests and a review of ADLs and

TABLE 30.2 Tools for Functional Assessment in Older Patients

Measurement Instrument	Evaluation	Activities/Reference
Index of Independence in ADLs	Self-reported	Difficulty/need for help in bathing, dressing, toileting, transferring, continence, feeding
Instrumental ADLs	Self-reported	Difficulty using the telephone, using a car/public transportation, shopping, preparing meals, housework, managing medications, financial management
Functional Independence Measure	Consensus by multidisciplinary team	Motor (eating, grooming, bathing, dressing, toileting, managing bladder/bowels, transferring, walking, climbing stairs); cognitive (auditory comprehension, verbal expression, social interaction, problem solving, memory)
Barthel Index	Professionally evaluated	Independence or need for help in feeding, transferring from bed to chair and back, grooming, transferring to and from toilet, bathing, walking, climbing stairs, dressing, continence
Mobility Questionnaire	Self-reported	Severe difficulty walking 1/4 mile and/or climbing stairs
Short Physical Performance Battery	Objective performance based	Time required to walk 4 m, rise from a chair five times, maintain balance
Berg Balance Scale	Objective and professionally evaluated	Performance in 14 tasks related to balance
Walking Speed	Objective performance	Measure walking speed over a 4-m course
6-Minute Walk	Objective performance based	Distance covered in 6 min
Long-Distance Corridor Walk (400 m)	Objective performance based	Time to fast-walk 400 m

ADLs, Activities of daily living.
From Ferrucci L, Studenski S. Clinical problems of aging. In: Kasper DL, Fauci AS, Hauser SL, et al., eds. *Harrison's Principles of Internal Medicine*. 19th ed. New York: McGraw-Hill Education; 2015.

IADLs. Some tests require special training and performance by specific healthcare professionals, whereas others can be easily performed in a preoperative clinic (e.g., walking speed over a 4-m distance) (Table 30.2). Elderly patients with impaired mobility and increased dependency are at increased risk of postoperative complications. Common serious impairments in hearing and vision should also be elicited.

The concept of prehabilitation has become more prevalent for the elderly surgical patient and is often a part of an Enhanced Recovery after Surgery (ERAS) pathway at many institutions. Prehabilitation refers to the preoperative improvement of functional capacity, both physical and mental, with the goal of improving a patient's ability to withstand the physiologic stress of surgery. Many prehabilitation programs focus on optimizing nutrition, exercise, and psychological well-being for 4 to 8 weeks prior to surgery. Some studies found prehabilitation to improve postoperative pain and physical function and reduce hospital length of stay, but overall data are inconsistent in part due to the heterogeneity of prehabilitation programs, and very few studies specifically evaluated older patients.

Cognition

An older individual's cognitive capacity, decision-making capacity, and risk for POD should be assessed. For patients without a known history of dementia, a cognitive assessment tool such as the Mini-Cog test should be performed. The Mini-Cog is a three-item recall and clock-drawing test that efficiently screens for cognitive impairment; 1 point is awarded for each item recalled and 2 points for a normal-appearing clock. A score of 0 to 2 points indicates increased risk for cognitive impairment. This screening is the initial step in identifying patients who may lack the capacity to make medical decisions and are at high risk for POD. However, it should be noted that the Mini-Cog is not a diagnostic test for Alzheimer disease or other forms of dementia.

Medication Review

As noted earlier, polypharmacy is very common in the elderly. Over half of these patients take more than 5 medications weekly, and a fifth take more than 10. The risk of adverse events during a hospitalization increases significantly with the number of medications a patient is taking. Preoperative evaluation is an ideal opportunity to review medications. Anticholinergic medications should be discontinued if possible as they are associated with delirium and gait instability. Up to 25% of elderly patients may be using benzodiazepines chronically and may be at risk of a withdrawal syndrome in the postoperative period. It is prudent to taper off these drugs prior to surgery so they cannot contribute to postoperative confusion, gait instability, and delirium. By some estimates, over half of elderly patients also take over-the-counter herbal products. The American Society of Anesthesiologists (ASA) recommends that whenever possible, herbal products be discontinued at least 1 to 2 weeks prior to surgery. Garlic extract and ginkgo biloba increase the risk of perioperative bleeding. The Beer's criteria is a list of potentially inappropriate medications (PIMs) that should be avoided or used with caution in adults aged 65 years or older. Beer's criteria medications that are commonly administered by anesthesia providers during the perioperative period include benzodiazepines (midazolam), gabapentinoids,

diphenhydramine, phenothiazines (promethazine), anticholinergics (atropine, scopolamine), antipsychotics (haloperidol), corticosteroids, H_2-receptor antagonists, meperidine, and metoclopramide. The risks and benefits of these medications should be weighed carefully in the elderly to avoid potential postoperative complications such as excessive sedation, delirium, and gait instability. If these medications are deemed to have benefit that outweighs risk, dosage should be carefully considered.

Goals of Care

Preoperative assessment of an elderly patient is an excellent opportunity to discuss goals of care. This time provides the family and patient the opportunity to make important decisions, formalize decisions, express their wishes, and complete legal paperwork.

Preoperative Assessment of Patients Undergoing Urgent or Emergent Surgery

Many elderly patients present for urgent or emergent surgery after trauma, falls, hip fractures, intracranial bleeding, or intraabdominal/vascular emergencies. The urgency of the surgery may preclude detailed preoperative evaluation and optimization. Decisions need to be made regarding the value of waiting for medical problems to be optimized versus proceeding promptly to surgery. Basic evaluation of the cardiorespiratory system, looking for signs of acute heart failure, fat embolism, acute lung injury, and signs of dehydration, should be done. Increased oxygen requirements and low oxygen saturation may denote worsening left ventricular function, acute lung injury, aspiration, and/or pneumonia. Acute delirium may be evident even before the surgery and should be investigated (if possible) prior to surgery to rule out a new intracranial process. Patients coming for urgent or emergent surgery have worse outcomes than patients who come for elective surgery. Patients and their caregivers should be given realistic information regarding intraoperative risk and potential postoperative outcomes, including the need for mechanical ventilation, intensive care unit (ICU) admission, and a prolonged hospital stay.

Intraoperative Management

Monitoring

Age alone is not an indication for invasive monitoring. The impact of transesophageal echocardiography, pulmonary artery catheterization, or noninvasive cardiac output monitors has yet to be defined in the elderly population, but the decision to use these monitors should be based on their potential benefits and risks, the potential for considerable blood loss or large fluid shifts during surgery, the patient's ASA physical status, the presence of concurrent illnesses, and the planned surgery.

Anesthetic Management

Choosing an anesthetic plan for an elderly patient requires consideration of many details. Several retrospective and prospective studies have failed to show a difference in outcome or a clear benefit for regional or neuraxial anesthesia versus general anesthesia. These studies could not identify any meaningful difference in mortality and morbidity except for a clearly reduced incidence of deep vein thrombosis with regional anesthesia. There is some evidence that use of regional anesthesia may decrease intraoperative blood loss in certain subsets of surgical patients. However, regional anesthesia is not suitable for all surgery.

Anesthetic requirements are reduced significantly in the elderly. The MAC of sevoflurane in an octogenarian is 30% lower than that of a younger person (see Fig. 30.7). IV anesthetics have more pronounced hemodynamic effects, and smaller doses are required to achieve the same anesthetic depth. Dose of an induction drug and opioids should be decreased by at least 25%. *Benzodiazepines should be avoided whenever possible.* Meperidine should not be used in the elderly. It is prudent to use cisatracurium in patients with renal and/or liver dysfunction.

The elderly have decreased skin elasticity and reduced skin and soft tissue perfusion, which increases the risk of skin breakdown or ulcerations. The presence of osteoarthritis and osteoporosis also poses a risk of injury. Bony prominences must be protected and padded.

Elderly patients are often dehydrated. Because of decreased left ventricular compliance and limited β-adrenergic receptor responsiveness, these patients are more prone to develop hypotension when hypovolemic, and congestive heart failure when hypervolemic. A thorough assessment of intravascular volume status is essential before induction of anesthesia.

Measures to conserve body heat and decrease the risk of hypothermia should be implemented. Prolonged elimination of anesthetic drugs and slower postoperative awakening can occur as a result of intraoperative heat loss. Elderly patients can respond to hypothermia by shivering during the early postoperative period. Shivering results in a greatly increased oxygen demand, which is a special concern in patients with coronary disease or in those with compromised cardiovascular reserve.

Fluid Therapy/Blood Transfusion

Fluid therapy should not be considered routine. It should be given as much importance as administration of any drug. Owing to atherosclerosis, stiff ventricles, reduced β-receptor response, diastolic dysfunction, and coronary artery disease, elderly patients do not tolerate hypovolemia or hypervolemia. Hypovolemia leads to severe hypotension and organ hypoperfusion; overhydration can lead to congestive heart failure. Intraoperative use of goal-directed fluid therapy may assist the anesthesia provider in optimizing fluid administration for the elderly patient.

Blood component therapy should also be used judiciously. There is some evidence suggesting that higher hemoglobin and hematocrit values may be more desirable in elderly patients.

Postoperative Management

Postoperative Delirium and Cognitive Dysfunction

Neurocognitive dysfunction is very common in the elderly after both cardiac and noncardiac surgery. Delirium affects 15% to 55% of hospitalized older patients. It is characterized by (1) a rapid decline in the level of consciousness, with difficulty

focusing, shifting, or sustaining attention; and (2) a cognitive change (e.g., incoherent speech, memory gaps, disorientation, hallucination) not explained by preexisting dementia and/or a medical history suggestive of preexisting cognitive impairment, frailty, and comorbidity. The mechanism of POD remains elusive, but it has been hypothesized that the stress of surgery and its associated inflammatory response result in leukocyte migration into the central nervous system, where they play an active role in the pathophysiology of POD. Most patients with POD experience a complete recovery, but this disorder is far from benign. Hospitalized patients with delirium have up to a 10-fold higher risk of developing other medical complications and have longer hospital stays, increased medical costs, an increased need for long-term care, and a higher 1-year mortality rate.

The strongest predisposing factor for POD is preexisting dementia. Other factors that can contribute to delirium include dehydration, alcohol consumption (or withdrawal), psychoactive drugs, visual impairment, and hearing deprivation. Stressful conditions that can precipitate delirium include surgery, anesthesia, persistent pain, sleep deprivation, immobilization, hypoxia, malnutrition, metabolic and electrolyte derangements, and treatment with opioids and anticholinergic agents. Even though it is a common condition, there are no known substantive prevention measures, including medications. In addition, there are no medications that have been definitively proven to shorten the duration of delirium once it occurs in non-ICU patients. Early identification, supportive measures, and symptomatic treatment are the rule. Multiple professional societies have recently published guidelines and expert consensus statements on the prevention of POD, including the American Geriatrics Society, American College of Surgeons, American Society for Enhanced Recovery, Perioperative Neurotoxicity Working Group, European Society of Anaesthesiology, and ASA Perioperative Brain Heath Initiative. While there are some small differences between societal recommendations, in general all recommend preoperative screening for delirium with a validated screening tool, avoiding or minimizing medications associated with POD (Beer's criteria), optimizing pain control using multimodal strategies, and utilizing multicomponent nonpharmacologic pathways to minimize delirium. While there is no gold standard for a multicomponent delirium prevention program, the majority include certain elements in the postoperative period such as sleep enhancement, reorientation, return of cognitive aids (hearing devices, glasses), early mobilization, pain management, medication reconciliation, and nutrition optimization. Many of these components can be implemented with little cost and risk to the patient.

Postoperative Pain Control

Management of acute postoperative pain is challenging in the elderly, especially in patients with baseline cognitive dysfunction. The American Geriatric Society has developed comprehensive guidelines for the management of acute postoperative pain. Though not based on strong levels of evidence, they provide an adequate framework for pain management in the elderly. Many elderly patients may also suffer from chronic pain. Acute procedural pain should be differentiated from chronic pain or pain due to complications of a procedure (e.g., new pain, increased intensity of pain, pain not relieved by previously effective strategies), and treatment should be directed accordingly. Conducting a pain history before a procedure can help discriminate procedural from chronic pain.

The principles of pain management in the elderly are the same as for a younger population, but the tools for assessing pain must be adapted to compensate for the cognitive and sensory impairments in the elderly. Adaptations for auditory impairments include positioning oneself clearly in view of the patient; speaking in a slow, normal tone of voice; reducing extraneous noise; and (if appropriate) ensuring the patient has a functioning hearing aid. Adequate time to process information and respond to questions must be allowed. Adaptations for visual impairment include using simple lettering (at least 14-point font size), adequate line spacing, and nonglare paper and making sure the patient has eyeglasses.

The cognitive status of the older adult impacts the approach to pain assessment, patient and family education, and pain treatment options. A baseline assessment of cognitive status provides the basis for evaluating changes in cognitive status throughout an episode of illness. Older adults with mild to moderate cognitive impairment are often able to rate pain using self-reporting instruments, and an individual patient's ability to do so should be assessed. It may be necessary to try several assessment tools to evaluate which one can be used most easily by the cognitively impaired individual. Even many severely impaired persons can respond to simple questioning about the presence of pain and may be able to use a simple rating scale. Scales that are the simplest and most usable for cognitively impaired older adults include verbal descriptor scales, pain thermometers, and pain scales with faces.

Elderly adults who cannot report pain must be assessed for the presence of factors that cause pain. Whenever an older adult with cognitive impairment shows a change in mental status, pain should be considered a potential etiology. Potential sources of pain include a distended bladder, the incision, infection, inflammation, fracture, positioning, urinary tract infection, and constipation. Treating the underlying cause of pain using etiology-specific interventions is important. Observing behavior when the patient is engaged in activity (e.g., transfers, ambulation, repositioning) can provide clues to the level of pain the patient may be experiencing. Assessing pain by only observing a patient at rest can be misleading. Nonverbal cognitively impaired patients need to be observed closely for essential information on which to make a judgment regarding the presence of pain. Failure to assess and treat pain in the elderly, and specifically in cognitively impaired individuals, is often due to the mistaken belief by healthcare providers that the perception of pain is decreased in individuals with cognitive impairment.

Some drugs that treat pain should be avoided or used with caution in the elderly, and Beer's criteria should be referenced. The use of meperidine is not recommended in older individuals. The use of transdermal fentanyl is not recommended for acute pain management in opioid-naïve older adults because of its potential for delirium and respiratory depression. Agonist-antagonist opioids should be avoided in older adults because their

side effects can be pronounced. Butorphanol and pentazocine produce psychotomimetic effects and may lead to delirium. Pentazocine causes hallucinations, dysphoria, delirium, and agitation in older adults and has been shown to be no more effective in controlling pain than aspirin or acetaminophen. Analgesics with a long, highly variable half-life (e.g., opioids such as methadone and levorphanol) should also be avoided. Drugs with a long half-life can readily accumulate in older adults and result in toxicity (i.e., respiratory depression, sedation).

Care of the Elderly in the ICU

It is not uncommon to have elderly patients transferred to the ICU because of the need for mechanical ventilation or postoperative hemodynamic monitoring after major surgery. Postoperative care of elderly patients is governed by the same goals as their intraoperative care. The presence of comorbidities and the patient's tolerance of the intraoperative course help determine the intensity of postoperative monitoring. For sedation, dexmedetomidine is a better drug than benzodiazepines because it is associated with less delirium and earlier recovery.

The care of a geriatric patient in the ICU can be very challenging. Dealing with social, ethical, and end-of-life issues can be particularly daunting. To achieve the best possible outcomes, physicians need to be mindful of the sensitivities and wishes of the patient and provide a realistic prognosis to family members and caregivers.

KEY POINTS

- Aging appears to be driven by progressive accumulation of a variety of random molecular defects that build up in cells and tissues. Aging is a continuous process, starting early and developing gradually, rather than a distinct phase that begins in middle to later life. It is well recognized that individuals do not all age at the same rate. Five key elements seem to contribute to the individuality of the human aging process: genes, nutrition, lifestyle, environment, and chance.
- The boundary between aging and disease pathogenesis is somewhat arbitrary. The same cellular and molecular functions that contribute to improved life span are also responsible for degenerative diseases such as osteoporosis, osteoarthritis, and dementia.
- All major cell types in the brain undergo structural changes with aging. These changes include neuronal cell death, dendritic retraction and expansion, synaptic loss and remodeling, and changes in glial cell (astrocyte and microglia) reactivity. The mass of the brain decreases by about 15% with aging. This decrease is due to cell loss and shrinkage of cell volume. There is a compensatory increase in cerebrospinal fluid volume.
- The incidence of many chronic diseases increases proportionally with age. Hypertension, diabetes mellitus, nutritional deficiency, chronic obstructive pulmonary disease, obstructive sleep apnea, thyroid dysfunction, alcoholism, depression, and medications (opioids, benzodiazepines, anticonvulsants, antipsychotics, antidepressants, antihistamines, decongestants, central nervous system stimulants) can affect cognitive function.
- Two major structural effects occur in blood vessels. The first is the natural change in the composition of blood vessel walls, with decreasing amounts of elastin and increasing amounts of collagen; the vessels become stiff and thickened. The second is the effect of atherosclerosis.
- The incidence of diastolic dysfunction increases with age. Any systolic dysfunction in the elderly should be considered abnormal, especially if it is accompanied by a wall motion abnormality.
- Closing volume approaches tidal volume in the elderly so they are more prone to atelectasis.
- The aging kidney is more susceptible to injury, less able to accommodate hemodynamic changes, and not able to handle significant changes in water and salt balance.
- Frailty is defined as a state of reduced physiologic reserve associated with an increased susceptibility to disability. It is characterized by failure of the body to respond to additional stresses such as surgery or infection. Patients who are frail have a significant increase in morbidity, mortality, and discharge to places other than home.
- The list of geriatric syndromes includes incontinence, delirium, falls, pressure ulcers, sleep disorders, problems with eating or feeding, pain, and depressed mood.
- Perioperative outcomes are dependent on many factors, the two most important of which are the surgical risk of the procedure and the number of defined clinical risk factors in a patient.
- Neurocognitive dysfunction is very common after both cardiac and noncardiac surgery in the elderly. Delirium is very common after major surgery; multicomponent nonpharmacologic pathways may help to minimize delirium.
- Anesthetic requirements are reduced significantly in the elderly.
- Elderly adults who cannot report pain must be assessed for the presence of factors that cause pain. Whenever an older adult with cognitive impairment shows a change in mental status, pain should be considered a potential etiology.

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31

Pediatric Diseases

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OUTLINE

UNIQUE CONSIDERATIONS IN PEDIATRIC PATIENTS

When it comes to anesthetic care, children are not merely small adults. Many considerations come into play beyond underlying medical conditions: the child's age, developmental stage (physically and psychologically), physiology, social circumstances, and family factors all play a significant role.

Anesthesia-Induced Developmental Neurotoxicity

The topic of anesthesia-induced developmental neurotoxicity has garnered widespread attention in recent years. Mounting evidence from animal studies over the past 2 decades has consistently shown increased and accelerated neuroapoptosis upon exposure to virtually every known anesthetic agent. It is unclear whether the observed acute neuroapoptosis leads to permanent brain cell loss and how or if the degree of immediate neuronal injury correlates with subsequent neurocognitive sequelae. While inconclusive, results from studies to date generally suggest that repeated or prolonged anesthetic exposure at a young age (<3 years) may be associated with subsequent behavioral and learning difficulties. The data led to a black box warning on anesthetic agents in 2018. Recent results from a large international, multicenter, randomized controlled trial suggests a single exposure of short duration appears to have little consequence. Further high-quality evidence is needed before changes in practice can be justified. At present, no change in current practice is recommended for lifesaving and/or truly emergent

or urgent procedures requiring anesthesia. However, anesthesiologists may consider delaying elective surgeries until after age 3 years when possible.

Anxiety and Behavioral Health

Anxiety is a normal and expected response to anticipation of surgery and anesthesia. In fact, anxiety is sometimes the only indication for sedation or anesthesia for nonpainful diagnostic procedures. An appreciation of circumstances and patient factors that contribute to preanesthetic anxiety is important in designing an approach that minimizes apprehension and potential psychological trauma.

Reasons for perianesthetic anxiety vary by age group. Separation anxiety becomes prominent around 8 to 10 months of age while fears of body disfigurement, loss of control, and death arise in older children. An understanding of the different categories of fears is essential in selecting the age-appropriate approach. Strategies for mitigating perianesthetic anxiety include but are not limited to medical play, distraction with toys/electronic devices, make-believe, storytelling, and pharmacologic agents.

Other psychological or behavioral concerns may influence perioperative management. Children affected by autism spectrum disorder (ASD) may struggle in the perioperative environment due to sensory sensitivities. Coordination with the child's parent to determine the best course of action to mitigate anxiety and provide the least threatening experience possible for the child is essential: Each child with ASD has unique needs, and a single approach will not suffice for all. Other psychiatric concerns such as stress-related disorders (e.g., posttraumatic stress disorder), mood disorders, and disruptive behavior disorders (e.g., oppositional defiant disorder) may be present and need to be considered in order to individualize care.

Anatomy and Physiology

Body Size and Thermoregulation

Neonates and infants are vulnerable to perioperative hypothermia. Body heat is lost more rapidly in this age group than in older children or adults, owing to the ratio of large body surface area to body weight/volume, minimal subcutaneous fat, and a decreased ability to produce heat. Neonates are not able to shiver; they generate heat via nonshivering thermogenesis mediated by brown fat metabolism.

It is very difficult to reestablish normothermia once hypothermia ensues in newborns and infants. Prevention of hypothermia is essential. Strategies include minimizing exposure of skin (swaddling, hats, etc.), room warming, heat lamps, forced-air blankets, fluid warming, humidifiers in the anesthesia circuit, and minimizing fresh gas flows. Potential complications associated with intraoperative hypothermia include surgical wound infections, negative nitrogen balance, delayed wound healing, delayed postoperative anesthetic recovery, impaired coagulation, and prolonged hospitalization.

Airway

The airway of a term newborn differs in several ways from that of an adult. Newborns have a proportionally larger head and tongue, a larynx that is situated higher in the neck, a short and mobile epiglottis, and vocal cords whose anterior commissure is slanted inferiorly. Airway obstruction occurs more readily owing to the larger tongue size relative to the oral cavity. Infants are obligate nose breathers due to this anatomy: choanal atresia causes significant difficulties with breathing and feeding. The cricoid cartilage (as opposed to the vocal cords in adults) is the narrowest portion of the larynx in pediatric patients. As in adults, angulation of the right mainstem bronchus favors right endobronchial intubation if the tracheal tube is inserted beyond the carina. The importance of the smaller absolute dimensions of the upper and lower airways in newborns and infants cannot be overemphasized: One millimeter of airway edema in a 4-mm infant airway reduces cross-sectional area by 75% and increases resistance to airflow by a factor of 16. The relative size of the head and tongue decreases as the child ages, and the position of the larynx in the neck moves to the lower position as seen in adults during early childhood.

Respiratory System

Significant physiologic differences exist between young children and adults. Oxygen consumption (VO_2) is much greater on a per kilogram basis in children compared to adults, owing to the difference in the ratio of surface area to volume. In addition, the high compliance of lung parenchyma and chest wall in newborns and infants predisposes to alveolar collapse, with resultant V/Q mismatching and hypoxemia.

Cardiovascular System

Pulmonary vascular resistance (PVR) gradually decreases over the first several months of life, but the pulmonary vasculature remains reactive; PVR can increase dramatically under conditions of acidosis, hypoxemia, and hypercarbia. The foramen ovale and ductus arteriosus can reopen under these circumstances, with reversion to fetal circulatory patterns resulting in significantly decreased pulmonary blood flow and profound hypoxemia. Anatomic closure of the foramen ovale occurs between 3 months and 1 year of age, although 20% to 30% of adults have a probe-patent foramen ovale. Functional closure of the ductus arteriosus normally occurs 10 to 15 hours after birth, with anatomic closure taking place in 4 to 6 weeks. Ductus arteriosus constriction occurs in response to increased arterial oxygenation that develops after birth. Nevertheless, the ductus arteriosus may reopen during periods of arterial hypoxemia.

Heart rate is the main determinant of cardiac output and systemic blood pressure in neonates and young infants. Due to a relative decrease in contractile elements, contractility of the neonatal myocardium is decreased compared to that in older children and adults. Stroke volume is relatively fixed due to a paucity of elastic elements. The Frank-Starling mechanism is not operational under most circumstances. As such, increases in cardiac output in the newborn are dependent on increases in heart rate for the most part.

Fluids and Renal Physiology

Total body water content and extracellular fluid (ECF) volume are increased proportionately in neonates. The ECF volume is equivalent to approximately 40% of body weight in neonates,

compared with 20% in adults. By 18 to 24 months of age, the proportion of ECF volume relative to body weight is similar to that in adults. In addition to fluid replacement, newborns and young infants may also require glucose supplementation. Maintenance glucose requirement for newborns is 6 to 8 mg/kg/min. Term newborns are capable of maintaining normoglycemia for up to 10 hours with no exogenous glucose administration. Careful monitoring, with likely need for glucose replacement, is necessary for neonates born to diabetic mothers.

Perioperative fluid administration for pediatric patients can be divided into several components:

1. Replacement of fluid deficits from fasting
2. Maintenance fluid requirement
3. Replacement of blood loss
4. Replacement of evaporative losses

Fluid maintenance and replacement of deficits are based on the Holliday-Segar formula for caloric expenditure of children of different sizes. Caloric expenditure based on weight and water requirement is approximately 1 mL/kcal expended per day. This is the basis for the 4:2:1 rule (Table 31.1). Blood loss is generally replaced 3:1 for each milliliter of blood loss with isotonic crystalloid, and evaporative loss replenishments are guided by estimations based on type of procedure and associated area of surgical exposure (Table 31.2).

The glomerular filtration rate is greatly decreased in term newborns but increases nearly fourfold by 3 to 5 weeks. Newborns are obligate sodium losers and cannot concentrate urine as effectively as adults. Therefore adequate exogenous sodium and water must be provided during the perioperative period. Conversely, newborns excrete volume loads more slowly than adults and are more susceptible to fluid overload. Decreased renal function can also delay excretion of drugs dependent on renal clearance for elimination.

TABLE 31.1 Holliday-Segar Formula for Caloric Expenditure

Weight	Caloric Expenditure	Water Requirement	Fluid Maintenance[a]
0–10 kg	100 kcal/kg/day	100 mL/kg/day	4 mL/kg/h (for first 10 kg)
10–20 kg	50 kcal/kg/day	50 mL/kg/day	2 mL/kg/h (for second 10 kg)
>20 kg	20 kcal/kg/day	20 mL/kg/day	1 mL/kg/h (for each additional kg above 20 kg)

[a]Fluid maintenance rates are additive. For example, a 25-kg child requires 4 mL/kg/h for the first 10 kg (40 mL/h) plus 2 mL/kg/h for the second 10 kg (20 mL/h) plus 1 mL/kg/h for each additional kg above 20 kg (5 mL/h), totaling 65 mL/h (40 + 20 + 5) as the hourly fluid maintenance rate.

TABLE 31.2 Intraoperative Fluid Therapy for Pediatric Patients

	NORMAL SALINE OR LACTATED RINGER SOLUTION (ML/KG/H)		
Procedure	Maintenance	Replacement	Total
Minor surgery (e.g., herniorrhaphy)	4	2	6
Moderate surgery (e.g., pyloromyotomy)	4	4	8
Extensive surgery (e.g., bowel resection)	4	6	10

Hepatic System

At term, the liver has significant glycogen stores that can be converted to glucose for use by the neonate. The newborn's glycogen stores, on a per kilogram basis, are at least equal to the stores in most adults. Hepatic capacity for biotransformation and metabolism of drugs, however, is diminished until several months of age.

Hematologic System

The hematologic system undergoes significant changes after birth. In fetal life the lower P_{50} of fetal hemoglobin (Hb) allows the fetus to extract O_2 from maternal Hb. In the first 2 months of life, as fetal Hb is replaced by adult Hb, P_{50} increases from 19 mm Hg to 22 mm Hg and then eventually to the typical adult level of 26 mm Hg. In addition to the change in Hb type (fetal to adult), Hb concentration changes as well. Physiologic anemia occurs between 2 and 3 months of age. In view of the decreased cardiovascular reserve of neonates and the leftward shift of the oxyhemoglobin dissociation curve, it may be useful to maintain the neonate's hematocrit (Hct) closer to 40% than 30%, as is often accepted for older children. Typical blood cell values are delineated in Table 31.3.

There is no need for routine preoperative Hb determination in healthy children for surgeries not expected to produce significant blood loss. Preoperative Hb measurement may be prudent in symptomatic children ahead of major surgery or ahead of lesser procedures necessary within the window of physiologic anemia. Based on estimated blood volume (Table 31.4),

TABLE 31.3 Hematologic Values in Infancy and Childhood

Age	Hemoglobin (g/dL)	Hematocrit (%)	Leukocytes (1000/mm³)
Cord blood	14–20	45–65	9–30
Newborn	13–20	42–66	5–20
3 months	10–14	31–41	6–18
6 months to 12 years	11–15	33–42	6–15
Young adult male	14–18	42–52	5–10
Young adult female	12–16	37–47	5–10

TABLE 31.4 Estimated Blood Volumes for Neonates, Infants, and Children

Age Group	Estimated Blood Volume (mL/kg)
Premature neonate	90–100
Term neonate	80–90
Infants	75–80
Children >1 year	70–75

TABLE 31.5 Estimation of Maximal Allowable Blood Loss[a]

A 3-kg term neonate is scheduled for intraabdominal surgery. The preoperative Hct is 50%. What is the maximum allowable blood loss (MABL) to maintain the Hct at 40%?

$MABL = EBV \times [(Hct_{high} - Hct_{low})/Hct_{average}]$

$EBV = 3\ kg \times 85\ mL/kg = 255\ mL$

$Hct_{high} - Hct_{low} = 50\% - 40\% = 10\%$

$Hct_{average} = (50\% + 40\%)/2 = 45\%$

$MABL = 255\ mL \times [(50\% - 40\%)/45\%] = 56.1\ mL$

EBV, Estimated blood volume; *Hct*, hematocrit.
[a]These calculations are only guidelines and do not consider the potential impact of fluid infusion therapy on the measured Hct.

calculation of the maximal allowable blood loss is useful to guide transfusion therapy (Table 31.5).

Pharmacology

Pharmacologic responses to drugs may differ in pediatric patients and adults. They manifest as differences in anesthetic requirements, response to muscle relaxants, and pharmacokinetics.

Anesthetic Requirements

Full-term neonates require lower concentrations of volatile anesthetics than infants aged 1 to 6 months. Furthermore, the minimum alveolar concentration (MAC) in preterm neonates decreases with decreasing gestational age. MAC steadily increases until age 2 to 3 months, but after 3 months the MAC steadily declines with age, although there are slight increases at puberty. Sevoflurane is unique among the currently used volatile anesthetics. The MAC of sevoflurane in neonates and infants remains constant.

Despite immature neuromuscular junctions, greater total body water content, and immature muscle composition in young infants, the dosage of nondepolarizing neuromuscular blocking agents is not changed on a per kilogram basis compared to adults. Duration of action of these drugs may be prolonged; the use of train-of-four monitoring is critical to determine depth of blockade. Antagonism of neuromuscular blockade is generally unaffected in infants, but requirements for anticholinergics may be decreased owing to longer clearance times than in adults. Sugammadex is becoming frequently used in pediatric patients; however, careful consideration of associated risks of bradycardia, anaphylaxis, recurarization, and interference with contraception is warranted and may require additional patient counseling. Neonates and infants require more succinylcholine on a per kilogram basis than do older children to produce similar degrees of neuromuscular blockade; this is due to the increased ECF and larger volume of distribution characteristic of this age group.

Pharmacokinetics

Pharmacokinetics differ in neonates and infants compared with adults. For example, uptake of inhaled anesthetics is more rapid in infants than in older children or adults because of the infant's high alveolar ventilation relative to functional residual capacity. More rapid uptake may unmask negative inotropic effects of volatile anesthetics, resulting in an increased incidence of hypotension in neonates and infants upon inhalational induction of anesthesia.

An immature blood-brain barrier and decreased ability to metabolize drugs could increase the sensitivity of neonates to the effects of hypnotics. As a result, neonates might require lower doses of intravenous (IV) induction agents. On the other hand, older children and adolescents generally require a higher dose of IV induction agents compared to adults (up to 3 mg/kg of propofol in children and teenagers compared to 1.5–2 mg/kg for adults).

Decreased hepatic and renal clearance of drugs, which is characteristic of neonates, can produce prolonged drug effects. Clearance rates increase to adult levels by age 5 to 6 months, and during early childhood may even exceed adult rates. Protein binding of many drugs is decreased in infants, which could result in high circulating concentrations of unbound and pharmacologically active drugs.

Pediatric Cardiac Arrest During Anesthesia

The majority of children tolerate general anesthesia without incident. However, cardiac arrests do occasionally occur. Respiratory events are by far the most common cause of pediatric cardiac arrest. Many arrests also result from either the critical health condition of the patient (especially complex congenital heart disease) or surgically related complications. The incidence of anesthesia-related cardiac arrest reported in infants is 15:10,000, with a range of 9.2 to 19:10,000. Overall, children experience anesthesia-related cardiac arrest at a rate of 3.3:10,000 anesthetics. The incidence of anesthesia-related cardiac arrest reported for all pediatric age groups is 1.8:10,000.

Causes of Cardiac Arrest

More than 50% of arrests occur among infants. Patients with congenital heart disease are at significantly higher risk of perioperative cardiac arrest while undergoing noncardiac procedures. High American Society of Anesthesiologists (ASA) physical status and emergency status have been shown to be independent negative predictors of survival from perioperative cardiac arrest. Accidental IV injection of local anesthetic and local anesthetic systemic toxicity are also common causes.

Management

Management of a perioperative cardiac arrest depends on its cause. Initial management is guided by the same principles used for any pediatric cardiac arrest. Certification in pediatric advanced life support (PALS) is recommended for anesthesiologists regularly caring for infants and children. The reader is referred to the latest PALS algorithm published by the American Heart Association (https://cpr.heart.org/en/resuscitation-science/cpr-and-ecc-guidelines/algorithms). An underlying respiratory cause of cardiac arrest should always be sought. The overall outcome for children following anesthesia-related cardiac arrest is much better than for in-hospital nonanesthesia-related arrests with respect to survival and development of new neurologic deficits.

THE PRETERM NEWBORN

Definition

As defined by the Committee on Fetus and Newborn of the American Academy of Pediatrics, preterm newborns are classified based on gestational age rather than birth weight as in the past. Preterm morbidity also correlates better with gestational age than with birth weight. A preterm newborn is one born before 37 weeks of gestation. Table 31.6 illustrates the traditional classification of preterm newborns by weight and the related approximate gestational age. The term ELGAN (extremely low-gestational-age newborn) refers to a preterm newborn delivered before 28 weeks of gestation regardless of birth weight. ELGANs have immaturity of all organ systems and represent the most vulnerable of all pediatric patients, with the highest morbidity and mortality. Age terminology for preterm neonates and infants is defined in Table 31.7.

Newborns are classified as small, appropriate, or large for gestational age based on normal values established for weight at various gestational stages.

Respiratory Distress Syndrome

Lack of surfactant leads to development of neonatal respiratory distress syndrome (RDS). The incidence is inversely proportional to the gestational age and birth weight. Sufficient surfactant is present in most fetuses by 35 weeks of gestation; however, 5% of newborns diagnosed with RDS are born at term.

Signs and Symptoms

RDS is usually apparent within minutes of birth; it is evidenced by tachypnea, prominent grunting, intercostal and subcostal retractions, and nasal flaring. Grunting reflects the newborn's effort to mitigate alveolar collapse. Cyanosis and dyspnea progressively worsen. If untreated, apnea and irregular respirations, signs of impending respiratory failure, develop. The clinical course, chest radiograph, and blood gas analysis help establish the clinical diagnosis of RDS.

TABLE 31.6 Classification of Preterm Newborns

Weight-Based Category[a]	Birth Weight (g)	Estimated Gestational Age (weeks)
LBW	<2500	31–35
VLBW	1000 to <1500	26–30
ELBW	<1000	<26

[a]*ELBW*, Extremely low birth weight; *LBW*, low birth weight; *VLBW*, very low birth weight. VLBW and ELBW newborns are considered micropremies.

TABLE 31.7 Age Terminology for Preterm Newborns and Infants

Term	Definition
Gestational age (GA)	First day of LMP to birth in weeks
Chronologic age (CA)	Time since birth in weeks or months
Postmenstrual age	GA + CA in weeks or months
Corrected postconceptual age	CA − (40 − GA) in weeks or months

LMP, Last menstrual period.

Treatment

Surfactant is administered to preterm newborns either immediately in the delivery room or later as a rescue treatment. It increases lung compliance and stabilizes the alveoli at end exhalation. Surfactant administration decreases the need for high concentrations of inspired oxygen, ventilatory support, and high ventilatory pressures. Unfortunately it has not decreased the incidence of subsequent chronic lung disease or bronchopulmonary dysplasia (BPD). Current evidence also supports nasal continuous positive airway pressure (NCPAP) as the optimal treatment for newborns with RDS. It is proven to reduce the risk of death and BPD. Other strategies such as noninvasive positive pressure ventilation and high-flow nasal cannula are useful in special situations. Caffeine is also a mainstay of RDS treatment.

Management of Anesthesia

During anesthesia the arterial oxygen saturation should be maintained near its preoperative levels. An arterial catheter (ideally in a preductal artery) is useful to monitor oxygenation, avoid hyperoxia, and prevent respiratory and metabolic acidosis during the intraoperative and postoperative periods. Pneumothorax from barotrauma is an ever-present danger and should be considered if there is sudden cardiorespiratory decompensation. Maintaining the Hct near 40% helps optimize systemic oxygen delivery. Excessive hydration should be avoided; fluid resuscitation using smaller total volumes of colloids such as 5% albumin (10–20 mL/kg increments) should be considered over crystalloids.

Bronchopulmonary Dysplasia

BPD is a form of chronic lung disease of infancy. As mentioned, the incidence of chronic lung disease in ex–preterm newborns has not decreased despite widespread use of surfactant in the treatment of RDS.

Signs and Symptoms

BPD is a clinical diagnosis defined as oxygen dependence at 36 weeks of postconceptual age (PCA) or oxygen requirement (to maintain Pao_2 >50 mm Hg) beyond 28 days of life in infants with birth weights under 1500 g. Pulmonary dysfunction in patients with BPD is most pronounced during the first year of life. Infants with mild BPD may eventually become asymptomatic, but airway hyperreactivity frequently persists into adulthood.

Treatment

Maintenance of adequate oxygenation (Pao_2 >55 mm Hg and Spo_2 >94%) is necessary to prevent or treat cor pulmonale and to promote growth of lung tissue and remodeling of the pulmonary vascular bed. Reactive airway bronchoconstriction is

treated with bronchodilating agents. Diuretic administration is often needed to treat interstitial fluid retention and pulmonary edema to improve gas exchange.

Management of Anesthesia

Preoperative assessment of the child with BPD should focus on any recent respiratory decompensation and need for intervention. Ongoing drug therapy (bronchodilators, diuretics) as well as baseline oxygen saturations provide valuable clues to the severity of BPD. In children with a history of mechanical ventilation, an endotracheal tube (ETT) one to a half-size smaller than that predicted for age should be used because subglottic stenosis may be present. Tracheomalacia and bronchomalacia may also present as sequelae of past prolonged intubation. Airway hyperreactivity is likely; thus a deep plane of anesthesia, often including neuromuscular blockade, must be established prior to airway instrumentation. Indeed, children with active or prior BPD can be assumed to have lifelong airway hyperreactivity and should be treated similarly to those with asthma. Oftentimes increased peak inspiratory pressures (PIPs) are required, reflecting decreased pulmonary compliance. Adequate oxygen should be delivered to maintain a Pao_2 of 50 to 70 mm Hg. Patients with metabolic alkalosis from furosemide therapy may exhibit a compensatory retention of CO_2. Fluid should be administered judiciously to avoid pulmonary edema.

Laryngomalacia and Bronchomalacia

Laryngomalacia is a congenital or acquired condition of excessive flaccidity of the laryngeal structures, especially the epiglottis and arytenoids. It can result from lack of normal neural control of laryngeal muscles or from pressure on the laryngeal cartilage, leading to inadequate laryngeal rigidity and structural collapse with normal respiratory efforts. Laryngomalacia accounts for more than 70% of persistent stridor in neonates and young infants.

Bronchomalacia is seen in infants who have had a prolonged course in the neonatal intensive care unit (NICU). Risk factors include long periods of mechanical ventilation, poor nutrition, intercurrent infections, and other impediments to normal growth and development. The cartilage of the major airways is weakened; when affected infants bear down, these airways can collapse partially or completely. Infants with bronchomalacia generally also have a component of BPD. These two conditions together can lead to significant respiratory difficulties. Even a mild viral respiratory infection may worsen the situation sufficiently to require hospitalization.

Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a retinal disorder of pathologic vasculogenesis affecting preterm infants. It is a leading cause of childhood blindness and considerable visual morbidity worldwide. The risk of retinopathy is inversely related to birth weight and gestational age, occurring in up to 70% of premature infants weighing less than 1000 g at birth.

Signs and Symptoms

Approximately 80% to 90% of mild cases of ROP undergo spontaneous regression with little or no residual visual disability. However, infants with ROP have an increased risk of developing visual and retinal problems later in life, including myopia, amblyopia, strabismus, glaucoma, retinal tear, and retinal detachment.

Treatment

Laser photocoagulation of the peripheral retina is the mainstay of ROP treatment. Central vision is preserved at the expense of variable peripheral visual field loss. Scleral cryotherapy and lens-sparing vitrectomy have also been used with success.

Management of Anesthesia

When dealing with an infant with ROP there are challenges of limiting hyperoxia while avoiding hypoxemia. Currently there are no established guidelines for specific intraoperative goals of oxygen saturation for preterm infants presenting for surgery.

The optimal intraoperative oxygen saturation for these patients has yet to be determined, so it remains prudent to limit oxygen supplementation for preterm infants with or without ROP, especially in those less than 32 weeks of PCA. Supplemental oxygen should be used judiciously based on the patient's clinical needs. Many advocate for maintaining a stable intermediate range of oxygenation (89–94%).

Apnea of Prematurity

Apnea of prematurity (AOP) is a result of the immaturity of the respiratory control centers in the newborn brainstem. The severity of AOP is inversely proportional to the gestational age of the newborn at birth.

Signs and Symptoms

Affected newborns exhibit both primary (central) apnea, in which there is simply a lack of effort to breathe in the absence of any obstruction, and obstructive apnea. Mixed episodes of central and obstructive apnea are also seen. The CO_2 response of infants with AOP is decreased compared to infants without AOP. Diagnosis of AOP is made on clinical grounds, and the criteria are somewhat variable. The diagnosis is made if an infant exhibits apnea longer than 15 to 20 seconds, apnea associated with heart rates below 80 to 100 beats per minute, or apnea associated with significant decreases in oxygen saturation.

Treatment

Treatment of AOP is begun once other causes of apnea (e.g., infection, central nervous system [CNS] disorder) have been eliminated. Some cases of AOP are associated with anemia and resolve with treatment. Other nonpharmacologic treatments include nasal CPAP and, in very severe cases, mechanical ventilation. Methylxanthines are the mainstay of drug therapy for AOP. These central stimulants increase the sensitivity of the respiratory centers to CO_2. Various forms of methylxanthines are used, with caffeine being the most common.

Postanesthetic Apnea

Postanesthetic apnea has many similarities with AOP. Preterm newborns who are at risk for AOP based on their corrected PCA

are also at increased risk for developing postanesthetic apnea. The incidence is inversely related to PCA. Regional anesthesia without the addition of systemic sedatives and opioids may decrease the risk for postanesthetic apnea in at-risk infants. Regardless, it is recommended to keep formerly premature infants whose PCA is less than 50 to 60 weeks for overnight observation after anesthesia. Term infants over 44 weeks PCA may qualify for outpatient surgery.

Hypoglycemia

Hypoglycemia is the most common metabolic problem occurring in newborns and young infants, with many different causes (Table 31.8). Inadequate glycogen stores and immature gluconeogenesis are important risk factors. The incidence of symptomatic hypoglycemia is highest in those born small for gestational age (SGA).

Signs and Symptoms

Serum glucose levels are rarely below 35 to 40 mg/dL in the first 24 hours of life or below 45 mg/dL thereafter. CNS or systemic signs of hypoglycemia such as agitation, seizures, apnea, lethargy, or mottling and pallor will usually be observed when serum glucose concentrations fall below 30 to 40 mg/dL in term infants during the first 72 hours and less than 40 mg/dL thereafter.

TABLE 31.8 Causes of Neonatal Hypoglycemia

Maternal Factors

Intrapartum administration of glucose
Drug treatment
1. β-adrenergic antagonists (terbutaline, propranolol)
2. Oral hypoglycemic agents
3. Salicylates

Maternal diabetes/gestational diabetes

Neonatal Factors

Depleted glycogen stores
1. Asphyxia
2. Perinatal stress

Increased glucose utilization (metabolic demands)
1. Sepsis
2. Polycythemia
3. Hypothermia
4. Respiratory distress syndrome
5. Congenital heart disease

Limited glycogen stores
1. Intrauterine growth retardation
2. Prematurity

Hyperinsulinism/endocrine disorders
1. Infants of diabetic mothers
2. Erythroblastosis fetalis, fetal hydrops
3. Insulinomas
4. Beckwith-Wiedemann syndrome
5. Panhypopituitarism

Decreased glycogenolysis/gluconeogenesis/utilization of alternate fuels
1. Inborn errors of metabolism
2. Adrenal insufficiency

Treatment

Infants with symptoms other than seizures should receive an IV bolus of 2 mL/kg (200 mg/kg) of 10% dextrose. If the infant is experiencing convulsions, an IV bolus of 4 mL/kg of 10% dextrose is indicated. Following bolus administration, a 10% dextrose infusion should be continued at 8 mg/kg/min and titrated to maintain the serum glucose above 40 to 50 mg/dL.

Hypocalcemia

Those at particular risk of hypocalcemia are neonates born prematurely or with low birth weight, particularly neonates with intrauterine growth retardation, neonates of insulin-dependent diabetic mothers, and neonates with birth asphyxia associated with prolonged and difficult deliveries. Late neonatal hypocalcemia occurring 5 to 10 days after birth is usually due to ingestion of cow's milk, which contains high levels of phosphorous; it is not seen in breast-fed infants as human breast milk has a lower phosphate content.

Signs and Symptoms

The clinical manifestations of hypocalcemia include irritability, seizures, and lethargy; hypocalcemic tetany is very uncommon. Under anesthesia, hypocalcemia will manifest as hypotension and depressed cardiac performance. Treatment with IV calcium should be considered in newborns presenting with hypotension without an obvious cause. It is important to evaluate both total and ionized calcium.

Treatment

Management of hypocalcemia involves correction of hypocalcemia as well as hypomagnesemia and any other metabolic or acid-base abnormalities. Intravenous calcium dosage is based on the amount of elemental calcium administered. The starting dose is 10 to 20 mg/kg of elemental calcium. Calcium gluconate 10% provides 9 mg/mL of elemental calcium, and calcium chloride provides 27.2 mg/mL of elemental calcium. These doses have been shown to increase ionized calcium, blood pressure, and cardiac contractility.

Bradycardia and even asystole have been reported with rapid IV administration of calcium. As such, IV calcium should be given over 5 to 10 minutes with electrocardiographic (ECG) monitoring. If calcium is given via an umbilical venous line, the tip should be confirmed to be in the inferior vena cava and not too near the right atrium; administration of calcium too close to the heart can result in dysrhythmias.

SURGICAL DISEASES OF THE NEWBORN

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is a defect in the diaphragm that is associated with a variable amount of intraabdominal organ extrusion into the thoracic cavity. It has an incidence between 1:2500 and 1:3000 live births. Concomitant anomalies are seen in approximately 50% of CDH cases. Some associated congenital syndromes include Beckwith-Wiedemann, CHARGE (coloboma, heart defects, atresia of the choanae, retardation [intellectual disability], genital anomalies, and ear anomalies), and trisomies 21 and 18.

Signs and Symptoms

Prenatal diagnosis of CDH has increased from approximately 10% in 1985 to nearly 60% in present day. The most common findings include displacement of the heart and gastrointestinal segments into the thorax. Most newborns present in the first few hours of life with respiratory distress (from mild dyspnea to cyanosis) and apparent dextrocardia in left-sided lesions. Typical physical findings include a scaphoid abdomen and a barrel-shaped chest with decreased breath sounds, distant or rightward displaced heart sounds, and bowel sounds in the chest. A chest radiograph typically shows a bowel gas pattern in the chest and a mediastinal shift.

Pulmonary parenchymal and vascular hypoplasia increase PVR. This causes right-to-left shunting of blood through the ductus arteriosus, with persistence of fetal circulatory patterns. Persistent pulmonary hypertension (HTN) of the newborn ensues, and if uncorrected, permanent pulmonary HTN follows.

Treatment

Care of a newborn with a severe CDH starts immediately in the delivery room. Prompt endotracheal intubation and placement of a naso/orogastric tube for decompression of the stomach are recommended for most cases to minimize lung and even heart compression. Once considered a surgical emergency, the current approach aims at medical stabilization before surgical repair.

Specific goals of preoperative medical management include achievement of a preductal oxygen saturation of at least 90% and correction of metabolic acidosis. Crystalloid fluid and blood products are administered to maintain intravascular volume and red blood cell mass. Adequate sedation is administered in an effort to minimize increases in PVR. Mechanical ventilation should be accomplished with the lowest settings possible (goal, PIP <25 cm H_2O), allowing for moderate permissive hypercarbia in an effort to minimize ventilator-induced lung injury. Surgery should be delayed until PVR has decreased and ventilation can be maintained with low PIPs and reasonable supplemental oxygen requirement. If pulmonary HTN persists or recurs, trials of inhaled nitric oxide and high-frequency oscillatory ventilation are initiated; extracorporeal membrane oxygenation (ECMO) may also be considered. In the case of severe pulmonary hypoplasia, an ex-utero intrapartum treatment (EXIT) procedure may be planned.

Management of Anesthesia

Endotracheal intubation should be carried out with avoidance of gastric distention. Avoiding positive pressure mask ventilation, the patient should undergo a rapid-sequence induction of anesthesia followed by tracheal intubation. "Awake" intubation should only be considered when no alternative is possible; it results in a sudden increase in PVR with agitation and ingestion of air with crying, thereby increasing risks of right-to-left shunting and lung compression, respectively. In addition to routine monitors, two pulse oximeters (pre- and postductal locations) are useful to monitor the degree of shunting. A preductal arterial cannulation (right radial) is recommended for monitoring systemic blood pressure, acid-base status, and other blood analyses. Venous access should be avoided in the lower extremities in case venous return is impaired from compression of the inferior vena cava following reduction of the hernia.

Anesthesia can be maintained with intravenous agents (e.g., opioids, ketamine, dexmedetomidine, benzodiazepines), a nondepolarizing muscle relaxant, and (if tolerated) low concentrations of inhaled anesthetics. Nitrous oxide should be avoided. In the case of EXIT procedure, extensive planning and coordination with all involved parties (surgical team, obstetric team, pediatric and obstetric anesthesia teams as well as the operating room [OR] nursing/technical staff and NICU team) is necessary to ensure safety of both mother and newborn.

Repair of CDH via thoracoscopic approach is becoming more common, but open repair is still the most common. Newborns with CDH have, almost by definition, pulmonary dysfunction that limits the patient's ability to tolerate thoracoscopy and associated CO_2 insufflation and one-lung ventilation. The primary advantages of thoracoscopic repair are smaller surgical incisions, less postoperative pain, and decreased risk of long-term thoracic and rib deformities. However, thoracoscopic repairs tend to be longer in duration and are very challenging for the anesthesiologist, since compromise of cardiorespiratory functions may be even more significant than that seen with open repairs. The two most obvious challenges are lung compression and significant hypercarbia from CO_2 insufflation, further worsening ventilation with resultant respiratory acidosis that increases PVR.

In the open surgical technique, reduction of the diaphragmatic hernia is accomplished through either a left subcostal abdominal incision or a thoracotomy incision. Depending upon the size of the defect, prosthetic material may be used to close the diaphragm. Throughout the intraoperative course, airway pressures should be monitored and maintained below 25 to 30 cm H_2O to minimize the risk of barotrauma and pneumothorax. After reduction of the herniated contents, an attempt to inflate the hypoplastic lung is *not* recommended; it is unlikely to expand, and excessive positive airway pressures may damage the contralateral lung. In addition to lung hypoplasia, these neonates are likely to have an underdeveloped abdominal cavity. Hernia reduction can cause increased intraabdominal pressure, with cephalad displacement of the diaphragm, decreased functional residual capacity, and compression of the inferior vena cava. To prevent excessively tight abdominal surgical closures in infants with large defects, it is often necessary to create a ventral hernia (which can be repaired later) and close the skin or place a silastic pouch.

Postoperative Management

Postoperative management of neonates with CDH presents significant challenges. The long-term outcome of these patients is ultimately determined by the degree of pulmonary hypoplasia. There is no effective treatment for pulmonary hypoplasia.

Esophageal Atresia and Tracheoesophageal Fistula

Esophageal atresia (EA) is the most frequent congenital anomaly of the esophagus, with an approximate incidence of 1 in

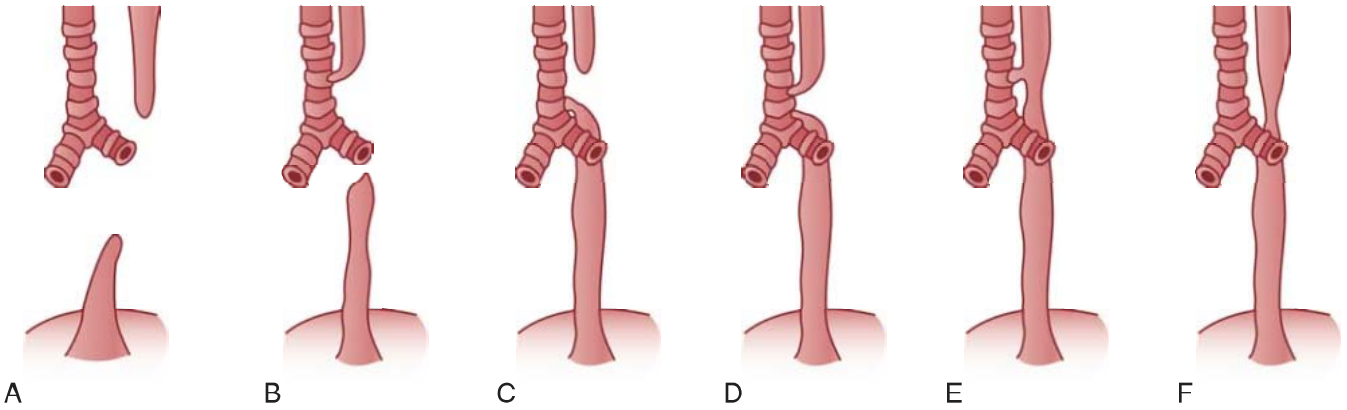

Fig. 31.1 Gross classification of congenital anomalies of the trachea and esophagus. (A) Esophageal atresia (EA) without fistula. (B) EA with proximal fistula. (C) EA with distal fistula. (D) EA with proximal and distal fistulas. (E) Tracheoesophageal fistula with no EA. (F) Esophageal stenosis. (With permission from Holzman RS, Mancuso TJ, Polaner DM. *A Practical Approach to Pediatric Anesthesia*. ed 1. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:387, fig. 18.5.)

4000 neonates (Fig. 31.1). More than 90% have an associated tracheoesophageal fistula (TEF). The most common form of EA/TEF (type C) represents 90% of all cases and presents as a blind upper esophageal pouch and a distal esophagus that connects to the trachea via a fistula tract, typically on the posterior aspect near the carina.

More than 25% of infants with EA have other congenital anomalies, most often with the VATER (vertebral defects, imperforate anus, tracheoesophageal fistula, and renal dysplasia) or VACTERL (VATER with cardiac and limb anomalies) associations. TEF and EA are also commonly seen in some chromosomal abnormalities such as trisomies 13, 18, and 21. Approximately 20% of neonates with EA have major congenital heart defects, and 30% to 40% are born preterm.

Signs and Symptoms

EA should be suspected if maternal polyhydramnios is present. It is usually diagnosed soon after birth when an oral catheter cannot be passed into the stomach or when the neonate exhibits cyanosis, coughing, and choking during oral feedings. Plain radiographs of the chest and abdomen will reveal coiling of a nasogastric tube in the esophageal pouch and possibly an air-filled stomach in the presence of a coexisting TEF. In contrast, pure EA may present as an airless scaphoid abdomen. Infants with an isolated TEF without EA may elude diagnosis until later in life when they may present with recurrent pneumonias and refractory bronchospasm.

Treatment

Initial therapeutic measures include maintaining a patent airway and preventing aspiration of secretions. The infant is fed nothing by mouth, given IV fluids, and placed in a head-up position to minimize regurgitation of gastric secretions through the fistula. Continuous suctioning of the proximal esophageal segment prevents aspiration of oropharyngeal secretions. Endotracheal intubation is avoided if possible because of the potential to worsen distention of the stomach, which can lead to gastric rupture. One-lung ventilation may be necessary until the stomach can be decompressed.

Primary repair without initial gastrostomy is routine. Repair of a TEF is urgent. A thorough evaluation for associated anomalies, particularly congenital heart disease, should be undertaken preoperatively. If the newborn is too unstable for a complete primary repair, a staged approach with an initial gastrostomy under local anesthesia may be all the neonate can safely tolerate.

Management of Anesthesia

Minimally sedated fiberoptic intubation with preservation of spontaneous respiration allows for optimal positioning of the ETT while minimizing the risk of ventilatory impairment associated with gastric distention due to positive pressure ventilation and passage of gases through the fistula. Awake intubation is not recommended unless there is no alternative. Induction of anesthesia can also be done via the inhalational or IV route. Regardless, spontaneous respiration should be maintained as much as possible, with positive pressure ventilatory maneuvers kept to the lowest possible inspiratory pressures. Use of muscle relaxant should be avoided or at least delayed until decompressive gastrostomy is accomplished. Proper placement of the ETT is critical; it should be above the carina but below the TEF. The ETT must be above the carina because the right lung is compressed during thoracotomy. The ETT may also be subject to obstruction with secretions during surgical manipulation or displacement into the fistula; great vigilance must be exercised to ensure adequate ventilation and delivery of volatile anesthetics. Low-dose volatile anesthetics in conjunction with air/O_2/opiate are usually well tolerated if the neonate is adequately hydrated. In addition to routine monitors, an arterial catheter is useful for blood gas monitoring. Ligation of the TEF and primary esophageal anastomosis is usually performed via a right thoracotomy. Thoracoscopic approach is also becoming more common.

Omphalocele and Gastroschisis

Omphalocele and gastroschisis are defects of the anterior abdominal wall that permit external herniation of the abdominal

TABLE 31.9 Comparison of Omphalocele and Gastroschisis

	Omphalocele	Gastroschisis
Gender distribution	Male > female	Male = female
Preterm birth	30%	60%
Location	Within umbilical cord	Periumbilical cord (right)
Sac	Present	Absent
Associated anomalies	>50% (cardiovascular 20%)	Rare
Surgical intervention	Not urgent	Urgent
Prognostic factors	Associated anomalies	Condition of bowel

Adapted from Christison-Lagay ER, Kelleher CM, Langer JC. Neonatal abdominal wall defects. *Semin Fetal Neonatal Med.* 2011;16:164–172, table 1.

viscera. They are the most common congenital abdominal wall defects, with important differences between them (Table 31.9).

Signs and Symptoms

Omphalocele. Omphalocele manifests as external herniation of abdominal viscera through the base of the umbilical cord. By definition the defect is larger than 4 cm. A defect smaller than 4 cm is termed an *umbilical hernia*. The abdominal contents are contained within a sac formed by the peritoneal membrane internally and the amniotic membrane externally, without overlying skin. Most cases involve only intestinal herniation, with herniation of liver and intestine occurring half as frequently. Over 50% of cases are associated with other congenital structural or chromosomal anomalies. Approximately 30% of neonates with omphaloceles are born preterm. Cardiac defects and prematurity are the major causes of mortality.

Gastroschisis. Gastroschisis manifests as external herniation of abdominal viscera through a small (usually <5 cm) defect in the anterior abdominal wall. In most cases the defect occurs laterally, just to the right of the normally inserted umbilical cord. Unlike an omphalocele, a hernia sac is absent, and the exposed viscera is in direct contact with amniotic fluid.

In most cases, only intestines are herniated. Gastroschisis is rarely associated with other congenital anomalies except for intestinal atresia, which occurs in 10% of cases.

Treatment

Gastroschisis requires urgent surgical intervention to limit evaporative and thermal losses. Upon delivery, the exposed viscera is at once covered in warm saline-soaked gauze, with careful positioning of the newborn to prevent kinking of the mesentery. Options for surgical management include traditional primary closure, staged closure with prefabricated silos, and more recently sutureless or plastic closure repair, where the umbilical cord itself is used to cover the abdominal wall defect, which is then allowed to close with epithelialization and granulation over time. The introduction of these sutureless techniques can often avoid intubation and anesthesia in some patients (smaller, uncomplicated defects).

Decompressing the stomach with an oro/nasogastric tube decreases risks of regurgitation, aspiration pneumonia, and further bowel distention. Broad-spectrum antibiotic prophylaxis is initiated along with fluid resuscitation to replace evaporative losses (150–300 mL/kg/day). As there is considerable protein loss and third-space fluid translocation, protein-containing solutions (5% albumin) should constitute approximately 25% of the replacement fluids. A urinary catheter should be placed to monitor a goal of 1 to 2 mL/kg/hr of urine output.

Initial medical management of omphalocele is similar to that of gastroschisis. Surgical intervention is essential but not urgent; the hernia sac provides some protection against evaporative and thermal losses. The high incidence of coexisting congenital anomalies warrants a thorough preoperative evaluation of the major organ systems, especially the heart. Although primary closure is desirable, it is not possible in most cases, owing to the large defect size and the unacceptable increase in intraabdominal pressure with one-stage reduction. Abdominal compartment syndrome can ensue with respiratory compromise, decreased venous return, poor organ perfusion, anuria, profound acidosis, and bowel necrosis. If primary closure is deemed not feasible, the viscera should be covered with a prosthetic silo and then slowly reduced over a period of days to weeks.

Management of Anesthesia

Important aspects of anesthetic management for omphalocele and gastroschisis closure include preservation of normothermia and fluid resuscitation. Intubation is best achieved with a rapid-sequence induction. The ETT should allow for ventilation with PIP greater than 20 cm H_2O. Primary closure may require higher PIPs, at least in the initial postoperative period. Repair of a large defect will require maximal muscle relaxation intraoperatively and during the initial postoperative period. Nitrous oxide is avoided because of its potential to hinder hernia reduction from potential bowel distention. Given the underdeveloped abdominal cavity, tight surgical abdominal closure can result in compression of the inferior vena cava and decreased diaphragmatic excursion. Monitoring airway pressures is helpful for detecting changes in pulmonary compliance during abdominal closure. Primary closure is not recommended if inspiratory pressures are above 25 to 30 cm H_2O or if intravesical or intragastric pressures are above 20 cm H_2O. Changes in ventilatory parameters and oxygen requirement can help the surgeon decide on treatment strategy. High ventilatory pressures and excessive Fio_2 are indications for postponing immediate abdominal closure.

Evidence of unacceptably high intraabdominal pressure requires removal of fascial sutures and closure of only the skin or addition of a prosthesis such as a silo, which consists of a silastic or Teflon mesh that is sutured to the fascia of the defect. After the silo is in place, the herniated viscera is gradually returned to the peritoneal cavity over successive days and can often be done at the bedside without anesthesia. Final closure is typically done in the OR.

Colonic and Anorectal Anomalies

Hirschsprung disease, or congenital aganglionic megacolon, is the most common cause of lower intestinal obstruction in

full-term neonates. The incidence is approximately 1:5000 live births, with a pronounced male predominance and no marked association with other anomalies. Other anorectal anomalies occur at the same rate. Up to 75% of patients with anorectal malformations have other congenital anomalies such as spinal and vertebral defects, and congenital cardiac lesions.

Signs and Symptoms

Hirschsprung disease may present at birth as neonatal bowel obstruction or later in childhood as chronic constipation or enterocolitis. Eighty percent of cases are diagnosed during the neonatal period, with a clinical picture of delayed passage of meconium, irritability, bilious vomiting, failure to thrive, and abdominal distention. Definitive diagnosis is obtained via a full-thickness rectal biopsy.

Anorectal malformations are apparent upon examination of the perineum. Delayed passage of meconium may also occur. Male infants with imperforate anus usually require emergent diverting colostomy to relieve the obstruction. In females, the presence of a rectovaginal (rectovestibular) fistula may allow for passage of stool.

Treatment

For Hirschsprung disease, the pull-through procedure is the definitive treatment and involves removal of the aganglionic segment followed by reanastomosis of normally innervated bowels, with preservation of anal sphincter function. Laparoscopic-assisted transanal pull-through procedures reportedly allow for earlier resumption of enteral feeding, better cosmetic result, less analgesic requirement, and faster time to discharge. Primary pull-through is preferable, but some patients may require an initial decompressive colostomy before definitive repair can take place. The outcome for patients with surgically treated Hirschsprung disease is reasonably good. Most patients attain fecal continence. For patients with retained or acquired aganglionosis, complications such as severe strictures, dysfunctional bowel, and intestinal neuronal dysplasia may occur, thus requiring additional surgical treatment.

Preliminary treatment for high anorectal lesions is a diverting colostomy followed by a posterior sagittal surgical repair. Low lesions such as perineal fistulas may be repaired during the neonatal period without an initial diverting colostomy. The majority of patients with perineal fistula and rectal atresia can attain full urinary and fecal incontinence after definitive repairs. More severe sacral malformations have significant reconstructive challenges and are associated with a lower rate of full bowel and bladder control.

Management of Anesthesia

In elective cases, general anesthesia may be induced via the inhalational or IV route. A rapid-sequence induction is appropriate in cases with abdominal distention or enterocolitis. Extra care should be taken with positioning, since these operations can be quite lengthy. A lithotomy position is required for anorectal pull-through procedures that involve both abdominal and perineal incisions. Intravenous catheters should be placed in the upper extremities as the lower extremities are typically included in the surgical field. Patients may require an initial IV bolus of 10 to 20 mL/kg of crystalloid to offset the volume deficit resulting from bowel preparation and fasting. In cases where electrical muscle stimulation is required to identify structures, neuromuscular blocking agents should be avoided.

Extubation at the end of surgery is routine. In the absence of regional or neuraxial analgesia, IV opioids along with adjuncts such as acetaminophen and ketorolac are the mainstay of postoperative analgesia. Postoperative fluid requirement may be greater than maintenance in the first 24 hours.

Infantile Hypertrophic Pyloric Stenosis

Infantile hypertrophic pyloric stenosis (IHPS) is the most common cause of intestinal obstruction in infancy. It occurs in 2 to 4 per 1000 live births and is more common in males than females (4:1), in first-born males, in white infants, and in infants born prematurely.

Signs and Symptoms

IHPS occurs as a result of marked hypertrophy of the circular and longitudinal muscle layers of the pylorus, leading to near-complete obstruction of the gastric outlet. Affected infants typically present with nonbilious forceful or projectile vomiting occurring immediately after feeds. It most commonly occurs between the ages of 3 and 5 weeks and up to 12 weeks; although much less common, it can present earlier or later in life (up to age 6 months). The classic metabolic derangements consist of hypochloremia, hypokalemia, and metabolic alkalosis resulting from loss of hydrogen, chloride, and potassium ions in gastric contents. The severity of dehydration can be assessed by skin turgor, mucous membranes, anterior fontanelle, urine output (number of wet diapers), and resting vital signs. Degree of serum hypochloremia correlates with severity of fluid and electrolyte loss.

On physical exam, presence of the olive sign is pathognomonic and is detected in 50% to 90% of affected infants. It can be palpated as a firm mass at the lateral edge of the rectus abdominis muscle in the right upper quadrant. Diagnosis is confirmed by abdominal ultrasonography.

Treatment

IHPS is a medical urgency, not a surgical one. Correction of hydration status and metabolic derangement is of first priority. Severely dehydrated infants should receive an initial IV bolus (20 mL/kg) of isotonic (0.9%) normal saline. Further resuscitation is given as 5% dextrose in 0.22% to 0.45% NaCl at up to 1.5 to 2 times the maintenance rate. Potassium chloride 10 to 40 mEq/L can be added based on laboratory data when adequate urine output is demonstrated. Fluid resuscitation should be guided by measurement of serum electrolyte concentrations. Once the patient is deemed medically stable, surgical correction can take place.

The traditional open Ramstedt pyloromyotomy is a relatively simple procedure with minimal operative mortality (<0.5%). A longitudinal incision is made in the hypertrophic pylorus and bluntly dissected down to the level of the submucosa. Minimally invasive laparoscopic pyloromyotomy has become the dominant approach in most centers.

Management of Anesthesia

All patients with pyloric stenosis should be regarded as having a full stomach and are at high risk of pulmonary aspiration of gastric contents. The stomach should be emptied as completely as possible with a large-bore orogastric catheter before induction of anesthesia; this may require several passes, including with the infant supine and in right and left lateral decubitus positions to ensure maximal stomach emptying. The airway should be secured by rapid-sequence induction and intubation. Muscle relaxation may be needed for surgical exposure. After tracheal intubation, an orogastric tube is reinserted and left in place during surgery so that air can be insufflated into the stomach to test for mucosal perforation after pyloromyotomy.

Analgesia with IV or suppository acetaminophen should be strongly considered in addition to local anesthesia infiltration at the incision site(s) administered by the surgeon. Regional techniques such as transversus abdominis plane (TAP) block and rectus sheath block have gained popularity in some centers to provide superior postoperative analgesia. Opioids should be avoided due to risk of postoperative apnea.

Extubation is the norm for otherwise healthy patients. However, these infants can experience increased postanesthetic respiratory depression. Therefore infants should have continuous cardiorespiratory monitoring for several hours postoperatively.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is characterized by varying degrees of mucosal or transmural necrosis of the intestine, most frequently involving the terminal ileum and proximal colon. It is the most common neonatal medical and surgical emergency. The overall incidence is 1 to 3:1000 live births, with 90% of cases seen in preterm neonates. The incidence and case fatality rate are inversely related to gestational age and birth weight.

Signs and Symptoms

Sudden feeding intolerance with gastric distention is often the first clue. Other early signs and symptoms include recurrent apnea, lethargy, temperature instability, and glucose instability. More specific clinical manifestations of NEC are abdominal distention, high gastric residuals after feeding, evidence of malabsorption, and bloody or mucoid diarrhea. Metabolic acidosis is very common secondary to generalized peritonitis and hypovolemia. Diagnosis is based on clinical findings and confirmed with abdominal radiography. Pneumatosis intestinalis (gas bubbles in the small intestinal wall) is the hallmark of NEC. Portal venous gas and intraperitoneal free air may also be seen, the latter indicating intestinal perforation.

Treatment

Treatment is based on severity of NEC and its associated symptoms. Medical treatment consisting of empirical broad-spectrum antibiotics and supportive measures is initiated in all cases. Enteral feeding is held until clinical conditions improve, with parenteral nutrition and resuscitative fluid replacement tailored individually. The existing umbilical arterial catheter should be removed to avoid compromise of mesenteric blood flow. NEC carries high mortality, especially when medical management fails, in which case mortality approaches 25%. Some may require significant or repeat bowel resections, predisposing them to short gut syndrome as well as complications from long-term parenteral nutrition.

Management of Anesthesia

Up to 50% of infants with NEC require surgical intervention. These patients typically have significant cardiovascular instability. Intraoperative care is often more a resuscitation effort than an anesthetic. Aggressive fluid and blood-product resuscitation should take place before induction of anesthesia. If not already intubated, induction should proceed with full stomach precautions. The ETT should allow for ventilation with PIPs above 20 cm H_2O because high intraabdominal pressures and decreased pulmonary compliance are likely to be encountered.

Maintenance of anesthesia is generally limited to short-acting IV opioids (fentanyl) as tolerated and muscle relaxation. Additional IV hypnotics such as ketamine and benzodiazepines can be considered. Volatile anesthetics are poorly tolerated in this population. Vigilant replacement of blood, evaporative, and third-space fluid loss is essential. Of note, rapid fluid administration to preterm neonates may cause intracranial hemorrhage or reopening of the ductus arteriosus. Blood and platelet products should be made readily available, as should vasopressors. A peripheral artery catheter is recommended to monitor systemic blood pressure, arterial blood gases, and other laboratory data to guide fluid and blood product resuscitation. Most patients will require parenteral nutrition, necessitating placement of centrally or peripherally inserted central venous catheters. Postoperative mechanical ventilation is usually required due to abdominal distention and coexisting RDS. Given the high incidence of septicemia, neuraxial analgesia is not recommended. Postoperative pain is usually managed with IV opioids, often as continuous infusions in the NICU.

Biliary Atresia

Biliary atresia is characterized by progressive and relentless obliteration of the extrahepatic bile tree, with resultant bile flow obstruction in the neonatal period. It has an overall incidence of 1:15,000 live births in Europe and North America but is much higher in east Asian countries (e.g., 1:5000 in Taiwan).

Signs and Symptoms

Biliary atresia typically presents in the early weeks after birth with persistent jaundice, dark urine, and acholic stool. Hepatomegaly and splenomegaly can both be seen, but the latter is usually a late sign. Any term infant presenting with jaundice for more than 14 days should be evaluated for underlying hepatobiliary disease. Specifically, conjugated hyperbilirubinemia is usually indicative of biliary pathologies. If left untreated, liver cirrhosis ensues, and death occurs by age 2 years. Initial diagnostic evaluation includes laboratory testing and ultrasonography. Endoscopic retrograde cholangiopancreatography and even magnetic resonance cholangiopancreatography are occasionally performed. Diagnosis is confirmed by liver biopsy.

Treatment

The Kasai procedure (hepatoportoenterostomy) and liver transplantation are the cornerstones of treatment for biliary atresia. The Kasai procedure involves excision of the porta hepatis to expose microscopic ductular continuity that allows for bile flow and is best performed by 8 weeks of age (Fig. 31.2). Although hepatoportoenterostomy can achieve complete resolution of jaundice and restoration of hepatic metabolic and synthetic functions, progressive inflammation of the hepatobiliary tree typically leads to recurrence of bile flow obstruction. Up to 50% of patients who have undergone the Kasai procedure will require liver transplantation by age 2 years.

Management of Anesthesia

Preoperative evaluation and correction of coagulopathy is important. A rapid-sequence induction is indicated if there is significant ascites. Adequate venous access is vital with a low threshold for central venous catheter placement. A peripheral arterial catheter is strongly recommended.

Anesthesia can be maintained with low doses of inhaled agents along with opioids and muscle relaxants. Nitrous oxide should be avoided. Blood loss can be moderate to severe; evaporative fluid loss is invariably significant. Postoperative care should continue in an ICU setting. If blood and evaporative

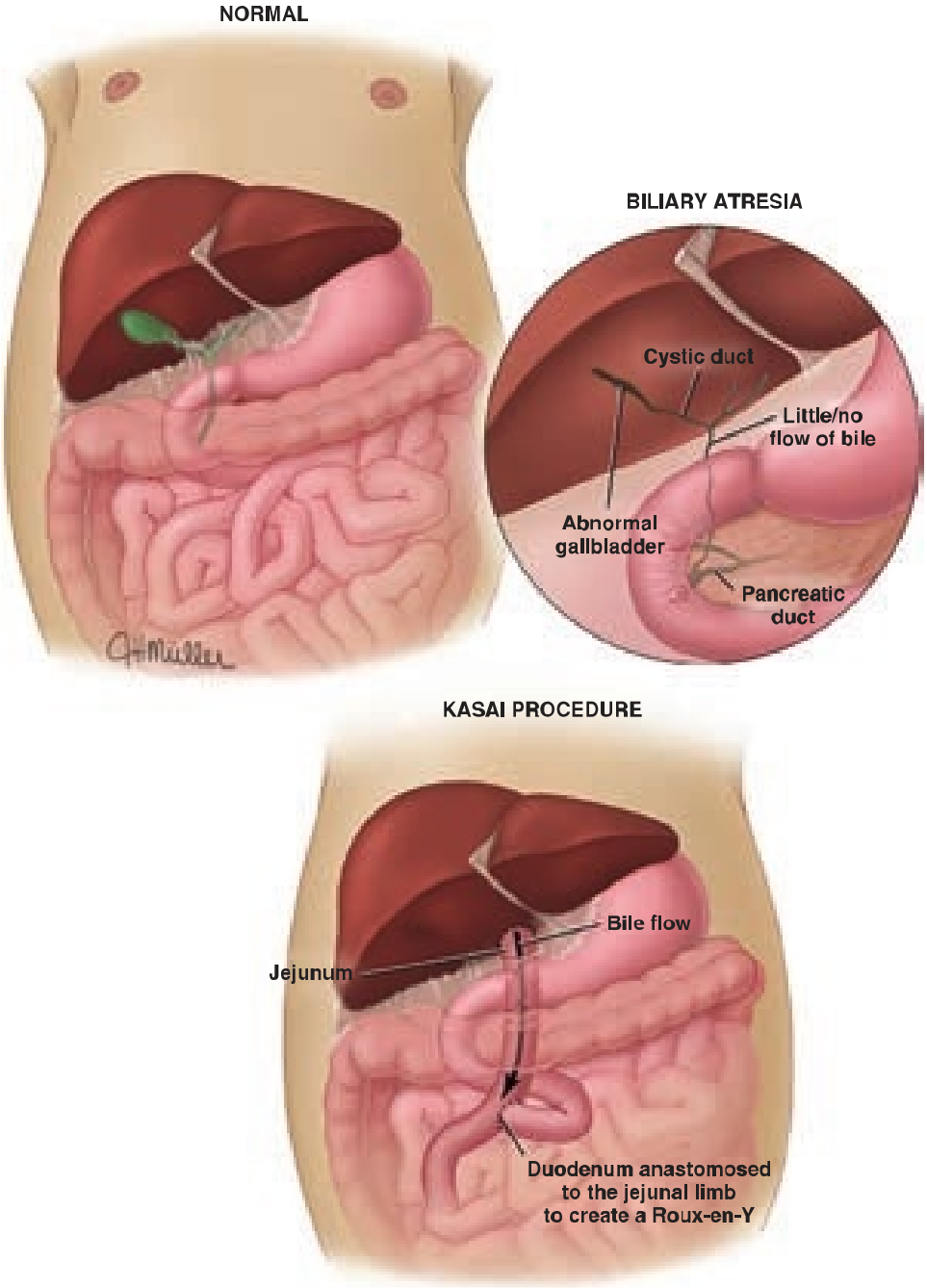

Fig. 31.2 Kasai hepatoportoenterostomy. (Reproduced with permission from Erlichman J, Loomes KM. Biliary atresia. http://www.uptodate.com/contents/biliary atresia. Copyright © 2015 UpToDate, Inc.)

losses were small, combined with a stable hemodynamic profile, consideration can be given to early extubation after the Kasai procedure. In many cases, postoperative mechanical ventilation is appropriate.

CENTRAL NERVOUS SYSTEM DISORDERS

Cerebral Palsy

Cerebral palsy (CP) is a heterogeneous group of nonprogressive disorders with kinetic and postural abnormalities. Etiologies may differ, but the representative phenotype of motor dysfunction results from abnormalities that occurred in the developing brain. Being a nonprogressive disorder of the CNS, CP is also termed *static encephalopathy*. Clinical expression will vary over the course of the child's lifetime with postnatal brain development. Seizure activity and additional disturbances of sensation, perception, cognition, and behavior are common.

Signs and Symptoms

CP is classified based on the resting tone, extremities involved, and presence of kinetic abnormalities. Spastic types of CP are the most common. Affected individuals manifest initial hypotonia (usually from age 6 months to 1 year) that later changes into spasticity. True hypotonic CP is rare. Gross motor delay is nearly universal and is commonly associated with delays in other milestones (fine motor, language, social interaction). Intelligence can range from normal to being severely impaired.

Truncal (postural) tone is often affected, with resultant spinal curvature deformities such as scoliosis. There is a high incidence of gastroesophageal reflux; bulbar and oromotor dysfunction can lead to recurrent aspiration events. Spasticity-induced contractures may require medical therapy or surgical intervention. Dysfunctional voiding and even neurogenic bladder are seen in 30% to 60% of cases. Seizure disorder is common.

Diagnosis is mostly based on a constellation of clinical findings over the course of months as symptoms surface with brain maturation. There should also be a thorough investigation of the prenatal, perinatal, postnatal, and intrapartum maternal history.

Management of Anesthesia

Patients with CP can present for a variety of surgical procedures ranging from brief dental restoration to complex posterior spinal fusion. There is no single best anesthetic plan as each patient will have different CP-related concerns; almost any anesthetic technique can be used. CP is not associated with malignant hyperthermia. Succinylcholine is not contraindicated but should be used with discretion. In general, children with CP require a lower MAC of volatile anesthetics and often experience delayed emergence. Low pharyngeal tone and a high incidence of gastroesophageal reflux call for a low threshold for endotracheal intubation to protect against aspiration, even for brief procedures. Muscle relaxants should be used with caution as recovery from neuromuscular blockade is typically prolonged. Positioning can be difficult due to contractures. For those with seizure disorders, drug-drug interactions (e.g., cytochrome P450 induction by antiepileptics) and epileptogenic effects of some anesthetic agents (etomidate, ketamine) must be kept in mind. Redosing regimen of anticonvulsants should be carefully followed throughout the perioperative period to maintain therapeutic drug levels.

Postoperative pain management can be challenging, especially for children who are noncommunicative or verbally delayed. Diazepam is an important adjunct for spasticity-related pain. Regional and epidural analgesia are ideal in providing superior pain control while limiting systemic exposure to drugs with respiratory depressant effects.

Hydrocephalus

Hydrocephalus is a disorder of cerebrospinal fluid (CSF) accumulation that results in ventricular dilatation due to increased intracranial pressure (ICP). Accumulation of CSF is due to an imbalance between CSF production and absorption. Hydrocephalus has many causes and can be congenital or acquired.

Signs and Symptoms

Hydrocephalus can be acute, subacute, or chronic. The rate of CSF accumulation and the compliance of the CNS determine the clinical presentation; in general, symptoms are nonspecific. If hydrocephalus occurs before the closure of cranial sutures (between 18 and 24 months of age), the rise in ICP is generally mitigated by expansion of the intracranial space. Once cranial sutures have closed, rapid increase in ICP can occur.

In neonates and infants, hydrocephalus most often manifests as macrocephaly. The anterior fontanelle can be full or bulging and scalp veins may be prominent secondary to increased venous pressure. Headaches along with nausea and vomiting result from stretching of the meninges and intracranial vessels. Infants are initially irritable, followed by progressive lethargy with increasing ICP.

Any newborn or infant with an enlarged head should be evaluated for hydrocephalus. Serial head circumference measurement is an easy and effective means of monitoring hydrocephalus. Most infants can be managed conservatively if head circumference increases at a slow and steady rate, unless accompanied by clinical symptoms. A rapid increase in head size usually requires surgical intervention even if the child is largely asymptomatic. Diagnosis is confirmed with neuroimaging.

Treatment

Medical therapy mainly consists of diuretic treatment (e.g., furosemide and acetazolamide decrease CSF production), although this remains controversial in children. Serial lumbar punctures have also been tried but only as a temporizing measure. The majority of children require surgical treatment either in the form of shunt placement or shuntless endoscopic third ventriculostomy (ETV). The former consists of placing a catheter into the lateral ventricle that is connected to a one-way valve shunt system that drains into the peritoneal space, right atrium, or more rarely the pleural space. Shunt malfunction occurs most frequently in the first year of placement (≈ 40% failure rate). ETV is most successful in children older than 1 year.

Management of Anesthesia

The most important anesthetic considerations of hydrocephalus relate to the presence and severity of increased ICP. Changes in position (head down, head flexion), behavior (crying), and physiologic derangement (hypercarbia) can all raise ICP. As such, the child should be kept in a head-up position with as few agitating maneuvers as possible. A delicate balance must be struck between promoting calmness with pharmacologic means and minimizing the risk of hypoventilation. A careful preoperative assessment consisting of history, current clinical symptoms, and physical examination usually provides the most useful information about the severity of ICP and its impact on the child's neurologic status.

Inhalational induction may be acceptable in the child without clinical and/or radiographic evidence of severe intracranial hypertension. Volatile agents are potent cerebral vasodilators and increase ICP. This can be attenuated by preinduction hyperventilation, but this is not an easily accomplished or feasible task in most children. Children with significantly elevated ICP are usually lethargic, which permits easier awake IV catheter placement. With the exception of ketamine, virtually all IV anesthetic agents lower ICP and generally preserve cerebral perfusion pressure (CPP) better than volatile agents. Ketamine is contraindicated as it can precipitate sudden increase in ICP and rapid neurologic decompensation. The neurophysiologic effects of dexmedetomidine, an α_2 agonist, are not as well understood. Succinylcholine may be used if necessary; it can increase cerebral blood flow and ICP, but the effects are transient and can be attenuated by premedication with a defasciculating dose of nondepolarizing muscle relaxant.

Continuation of muscle relaxation is necessary to prevent patient movement during surgical access to the intracranial ventricles. Normocapnia should be maintained for patients with normal ICP, whereas mild hypocapnia is helpful to prevent further increases in ICP; severe hypocapnia can precipitate cerebral ischemia. Invasive blood pressure monitoring is not needed in most cases but may be useful to help guide anesthetic management that optimizes CPP, particularly if an ICP monitor is in place (CPP = mean arterial pressure [MAP] − ICP).

Finally, positional changes can have serious consequences. Extreme positioning of the head (flexion, lateral rotation) can cause further displacement of any structural abnormality (e.g., Chiari malformation) and impair venous drainage, leading to increased ICP.

Spina Bifida

Spina bifida is the most common form of neural tube defect (Fig. 31.3), characterized by a cleft in the spinal column; this

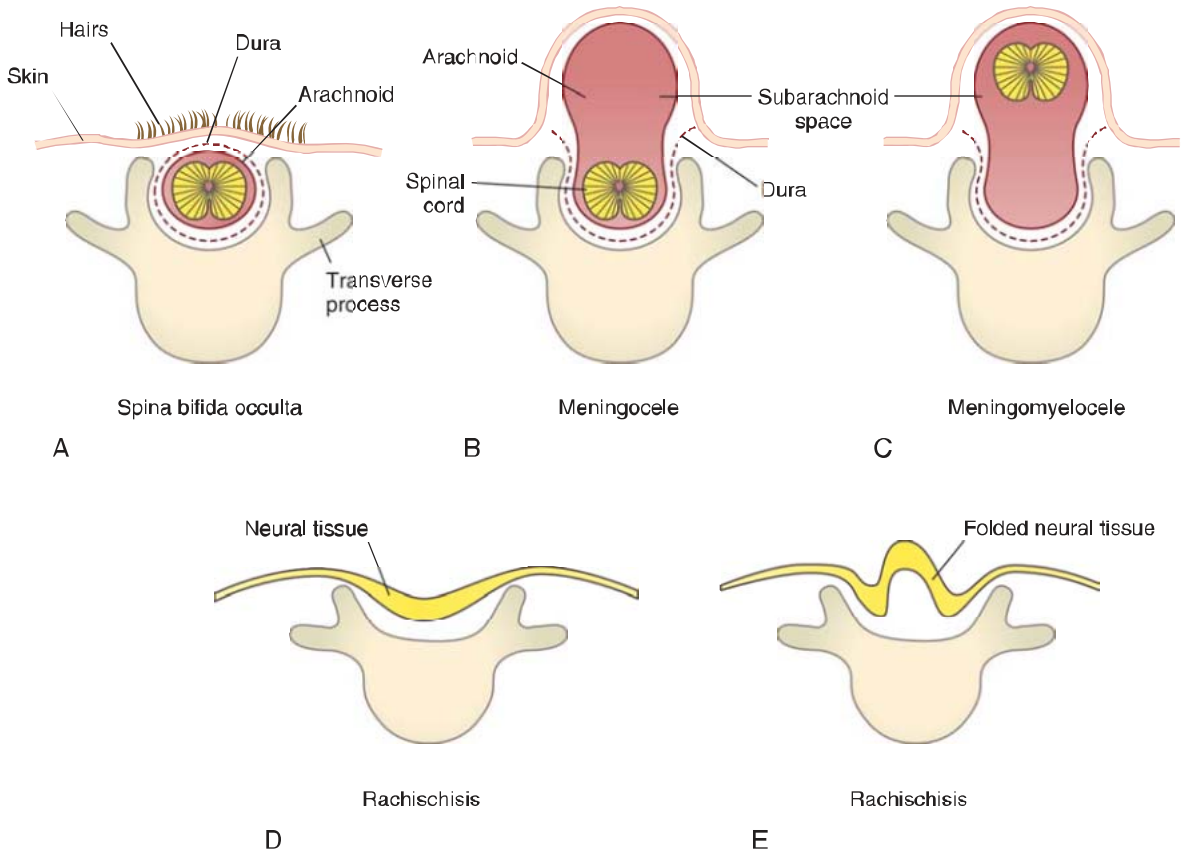

Fig. 31.3 Neural tube defects. (A) Spina bifida occulta—a bony defect only, covered by skin or skin with hair. (B) Meningocele—protrusion of a fluid-filled sac only (no neural tissue present). (C) Meningomyelocele—protrusion of a fluid-filled sac plus neural tissue. (D, E) Rachischisis—defects characterized by an open neural tube. (With permission from Holzman RS, Mancuso TJ, Polaner DM. *A Practical Approach to Pediatric Anesthesia*. ed 1. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:203, fig. 12.7.)

results from abnormal fusion of one or more vertebral posterior arches. This cleft can be covered by normal appearing skin, resulting in a hidden defect (spina bifida occulta) without involvement of the underlying neural structures. Meninges can herniate through the spinal cleft, creating a CSF-filled sac (meningocele) with or without skin covering. More often, both the spinal cord and meninges herniate (myelomeningocele) through the spinal cleft, forming a defect that lacks skin and sometimes dural covering.

Signs and Symptoms

Clinical presentation varies widely and depends on the neural elements involved and severity of the defect. Spina bifida occulta, as its name implies, is sometimes discovered only incidentally because normal skin hides the defect and the mild spinal cleft is without apparent neurologic deficits. In most cases, however, the overlying skin displays an abnormal lesion such as a dimple, hair patch, dermal sinus tract, hemangioma, or lipoma, the presence of which should alert the clinician of possible underlying spinal column and/or cord anomalies (e.g., tethered cord).

Meningoceles are normally diagnosed prenatally by fetal ultrasound or at birth by the presence of a dorsal spine mass. By definition only the meninges are affected, without nerve tissue involvement. As such, these patients display little if any neurologic deficits and are not at noticeable risk for developing long-term neurologic sequelae. Once the meningocele is discovered, expeditious surgical repair is needed to prevent sac injury, infection, and CSF leak. Although nerves are not involved, there can be nerve root entrapment by fibrous bands in the sac. Thus nerve injury is a potential problem during surgical sac ligation.

Myelomeningocele is the most common type of spina bifida, with extrusion of the spinal cord into the herniated meningeal sac; oftentimes the spinal cord ends in the sac, with the spinal canal exposed in a splayed-open fashion known as the neural placode. Children born with a myelomeningocele have varying degrees of motor and sensory deficits as well as bowel and bladder dysfunction. Any damage to the cord and spinal nerves evident at birth is usually irreversible. Over 90% of children with a myelomeningocele also have a Chiari II malformation (also known as Arnold-Chiari malformation), which consists of caudal displacement of the cerebellar vermis, fourth ventricle, and the medulla down through the foramen magnum into the cervical spinal canal. Hydrocephalus and other developmental brain abnormalities are also common. Additionally, myelomeningoceles are associated with a high incidence of cardiac, esophageal, intestinal, renal, urogenital, and orthopedic anomalies.

Treatment

Meticulous care at birth is needed to prevent sac rupture and damage to the spinal cord. The defect should be covered with saline-soaked sponges, with lateral or prone positioning of the newborn to prevent compression. Nonlatex gloves should be worn to avoid latex sensitization. Surgical closure usually takes place within 24 to 48 hours of birth. Compared to postnatal repair, intrauterine repair of myelomeningocele has been associated with a lower rate of shunt surgery for hydrocephalus and a lower rate of death at 12 months of postnatal age. Prenatal surgery, however, is only offered at a few centers and is associated with preterm birth and maternal morbidity. The majority of children with myelomeningocele have lifelong motor and sensory neurologic impairment as well as fecal and urinary incontinence.

Management of Anesthesia

Positioning is one of the first critical steps in the perioperative care of the child with spina bifida. Maintaining the patient in the prone or lateral decubitus position is essential to avoid sac and nerve injury, particularly for myelomeningoceles. In some cases, the patient may be elevated on soft rolls or a donut-shaped gel support to avoid compression of the defect, allowing for endotracheal intubation in the supine position. Some defects may be too large to risk supine positioning, and the anesthesiologist must always be prepared for a potentially difficult intubation with lateral positioning. Prone positioning is required for surgical repair. Meticulous attention must be paid to avoid compression injury to the eyes, brachial plexus, and any ventral defects such as bladder exstrophy, as well as compression of the inferior vena cava that can lead to impaired venous return.

A comprehensive preoperative assessment is necessary to identify specific anesthetic risks; myelomeningoceles are often associated with other congenital anomalies. Although an Arnold-Chiari malformation is present in almost all cases of myelomeningocele, clinically significant increase in ICP is rare. Respiratory insufficiency and apnea (due to potential brainstem compression) are also important perioperative concerns. Neuromonitoring is usually carried out to guide surgical repair. An anesthetic plan that minimizes signal interference is important. Blood and evaporative fluid loss can be significant. This is especially true for large defects that require extensive skin undermining for closure.

Craniosynostosis

Craniosynostosis is defined as premature closure of one or more cranial sutures. At birth, the cranium consists of floating bone plates that allow for rapid postnatal brain growth, requiring a proportionate increase in the intracranial space. Four major sutures separate these bone plates: (1) the metopic suture separates the frontal bones, (2) the sagittal suture separates the parietal bones, (3) the coronal suture separates the frontal from the parietal bones, and (4) the lambdoid suture separates the parietal bones from the occipital bone (Fig. 31.4). One or more sutures can be affected, and over 50% of cases involve the sagittal suture. Single-suture craniosynostosis is usually an isolated finding, whereas multiple-suture closure is often associated with other skull base suture abnormalities.

Signs and Symptoms

Craniosynostosis is usually evident at birth or during the first 2 years of life when rapid brain growth takes place. Increase in ICP occurs when brain growth continues against a nonexpanding calvarium. As such, increased ICP is not usually seen in secondary craniosynostosis, where there is little to no brain

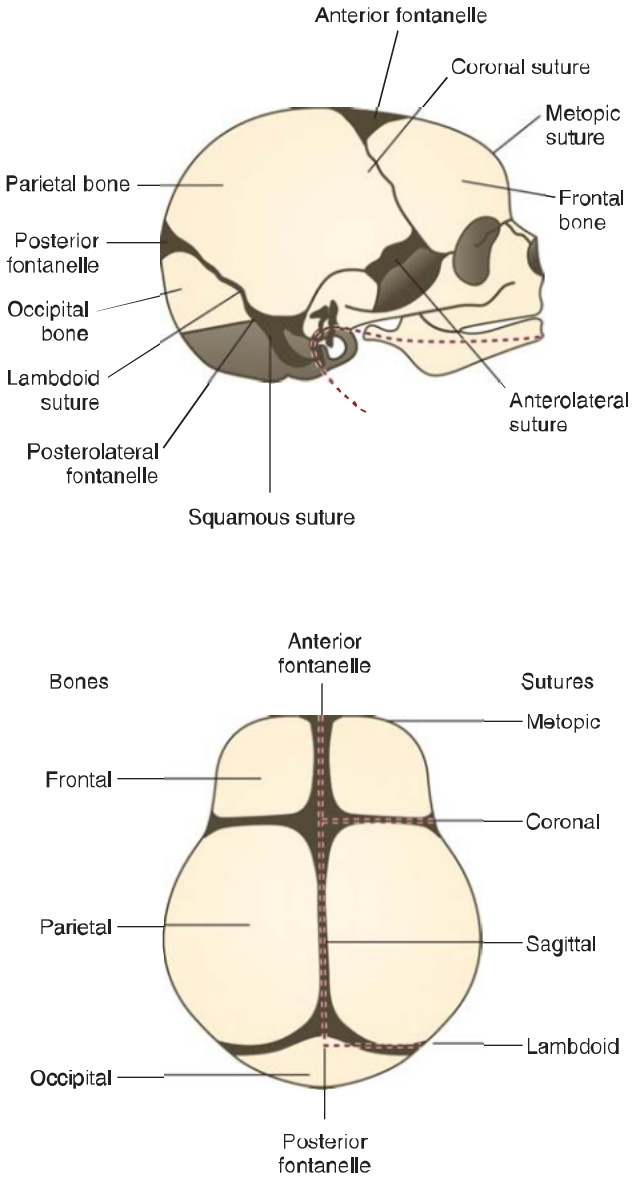

Fig. 31.4 Cranial sutures and fontanelles. (With permission from Holzman RS, Mancuso TJ, Polaner DM. *A Practical Approach to Pediatric Anesthesia*. ed 1. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:225, fig. 14.2.)

growth. Craniosynostosis involving one or even two sutures is not generally associated with increased ICP because the brain can still expand in at least one other direction. Premature closure of multiple sutures frequently leads to increased ICP; children may present with lethargy, nausea, vomiting, and papilledema.

Nonsyndromic craniosynostosis (only one or two sutures affected) may pose only cosmetic concerns with no physiologic sequelae. However, the physical deformity can adversely impact the child's psychological and social development if left untreated. Multiple-suture craniosynostosis is often associated with some degree of intellectual delay as well as hydrocephalus.

Treatment

Surgical repair can be done endoscopically (strip craniectomy or suturectomy) or may involve extensive calvarial reconstruction, depending on the deformity. Timing of repair is surgeon dependent and can vary between early and late infancy. Regardless, surgical correction is preferably done before 1 year of age to take advantage of a malleable skull, optimize potential for reossification, and decrease the risk of neurologic damage, since this time period confers the greatest neural plasticity. Early intervention is also necessary to provide room for rapid brain growth during the first 2 years of life.

Management of Anesthesia

Anesthetic management is tailored to any coexiting congenital anomalies and potential intracranial hypertension. Syndromic craniosynostosis often have other craniofacial abnormalities (midface and mandibular hypoplasia) that can make airway management extremely challenging; difficult airway equipment must be available accordingly.

Controlled ventilation should be set to maintain normocarbia unless hypocarbia is needed to minimize preexisting intracranial hypertension. Large-bore IV access is necessary, and insertion of an intraarterial catheter is preferred. Even with endoscopic procedures, excessive blood loss can occur. Significant blood loss is usually the norm in open cranial vault reconstructive procedures (as high as one-half to one blood volume). Blood products must be immediately available before skin incision. Cell salvage should be done, even for small infants, because relevant cell saver reservoir sizes (as small as 25 mL) are now available. Use of antifibrinolytics such as aminocaproic acid and tranexamic acid are effective in reducing intraoperative blood loss and decreasing transfusion requirements.

Other major intraoperative concerns include hypothermia, hypovolemia, and venous air embolism (VAE). Some practitioners elect to place a central venous catheter to evacuate air from the right atrium should a large VAE occur. However, the small-sized catheter used in infants does not permit rapid air evacuation. Precordial Doppler has a high sensitivity for detecting VAE before hemodynamic changes are evident. Nitrous oxide should be avoided.

Significant periorbital and facial edema can occur and may preclude immediate extubation. Unless there are concomitant craniofacial anomalies, however, most infants can be considered for immediate extubation if the edema is limited to the upper half of the face. In general, postoperative care in the ICU is preferred.

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a group of hereditary motor neuron disorders characterized by progressive skeletal muscle weakness and atrophy due to degeneration of anterior horn cells in the spinal cord as well as motor nuclei in the lower brainstem. It most commonly involves mutations of the *SMN1* gene (survival motor neuron 1, chromosome 5q) with an autosomal recessive inheritance pattern, whereby motor neuron mRNA synthesis is disrupted. It has an incidence between 4 and 10 per 100,000 live births and is the most common cause of infant mortality involving a single gene mutation. Diagnosis is made by molecular genetic testing.

TABLE 31.10 Spinal Muscular Dystrophy Subtypes

Type	Age of Onset	Motor Milestones[a]	Prevalence	Life Expectancy[b]
0	Prenatal	• None achieved • Fetal hypokinesia	Uncommon	1–6 months (with immediate respiratory support)
1 (Werdnig-Hoffmann disease)	<6 months	• Early flaccid paralysis • Never sits unassisted	Most common (60%)	2 years
2 (Dubowitz disease)	6–18 months	• Sits unassisted but loses milestone with progression • Never walks	10%	20 years and beyond
3 (Kugelberg-Welander disease, juvenile form)	> 18 months	• Achieves independent mobility • Disease progression leads to impaired mobility and even wheelchair dependence	20%	Normal life span
4 (adult onset)	20–30 years	• All milestones achieved and usually maintained	Uncommon	Normal life span

[a]Disease findings represent a continuum of clinical severity with no clear separation between subtypes in many cases.
[b]Life expectancy is improving with current respiratory care standards, corrective orthopedic options, as well as introduction of disease-modifying therapy.

Signs and Symptoms

There are five subtypes of SMA based on age of onset and clinical severity (Table 31.10). The hallmarks of SMA are symmetric proximal muscle weakness (lower limbs affected more than upper limbs), hyporeflexia or areflexia, and a variable degree of progressive restrictive lung dysfunction. Cognitive development and sensory function are preserved. Congenital heart defects can be seen in subtype 0, but the myocardium is generally spared in SMA. Arrhythmias have been reported in subtypes 1 to 3, but it is not clear if there is a direct causal relationship. SMA is not associated with dilated cardiomyopathy as can be seen in other genetic disorders of hypotonia. In the more severe forms, bulbar muscle weakness leads to poor suck and impaired swallowing, leading to failure to thrive and an increased risk of aspiration. Common orthopedic complications include scoliosis and joint contractures; mandibular ankylosis can also occur.

Treatment

The mainstay of treatment consists of multidisciplinary supportive measures aimed at preserving and optimizing three major components: nutrition, respiratory function, and orthopedic status. In recent years disease-modifying treatments have become available.

Nusinersen (Spinraza; US Food and Drug Administration [FDA] approval in 2016) can be used in all SMA subtypes associated with chromosome 5q mutations. It is an antisense oligonucleotide that modulates splicing of the *SMN2* gene, a native homologue to *SMN1*, to increase production of the survival motor neuron protein, which is deficient in SMA. Patients treated with nusinersen are reported to have improvement in motor milestones. Nusinersen is administered intrathecally, with four loading doses followed by maintenance injections every 4 months.

Onasemnogene abeparvovec (Zolgensma) is a gene replacement therapy using an adeno-associated recombinant viral vector containing functional *SMN1* gene encoding normal survival motor neuron protein to replace the in situ defective copy in motor neurons. It was FDA approved in May 2019 for use in children less than 2 years of age, administered as a single intravenous injection. Acute liver injury is the most common and serious side effect.

Both treatments are recommended for those who are not yet ventilator dependent. Treatment costs are extraordinarily high (Spinraza at $125,000 per injection, Zolgensma at over $2 million for a one-time administration). Long-term outcome data are still needed.

Management of Anesthesia

All types of anesthetic techniques have been used in patients with SMA with no clear benefit of one over another. Each patient needs a tailored approach based on preoperative risk factors centered mainly on pulmonary status, aspiration risk, and potential airway difficulty. Preoperative pulmonary evaluation is mandatory in those with moderate to severe SMA. Due to hypotonia, risk of aspiration is high and should be mitigated (i.e., gastric feeding tube vented prior to modified rapid sequence induction). Intubation may be difficult due to microstomia, temporomandibular joint ankylosis, and/or cervical spine immobility. Though cardiac morbidity is not a clinical hallmark of SMA, baseline physical debilitation should prompt preoperative cardiac evaluation especially ahead of lengthier and more extensive surgical procedures. Neuraxial and regional anesthesia and analgesia have been used safely without exacerbation of SMA symptoms. Increased sensitivity to nondepolarizing muscle relaxants has been observed. Succinylcholine should be avoided as for other neuromuscular disorders involving muscle degeneration and atrophy. Opioids should be used judiciously, particularly in those with significant pulmonary dysfunction. However, sensation is preserved in SMA, and pain management remains an important part of anesthetic care. Postoperative pulmonary needs may include but are not limited to pulmonary hygiene care, cough assist device, noninvasive and invasive ventilatory support, and need for intensive care monitoring and recovery.

Patients are presenting for intrathecal nusinersen injections with increasing frequency. Depending on institutional experience

and patient factors (e.g., degree of anxiety, severity of kyphoscoliosis), injections can be accomplished in the clinic setting without sedation, or in the perioperative setting with local anesthesia combined with mild sedation, or inhaled and/or intravenous general anesthesia.

CRANIOFACIAL ANOMALIES

Orofacial Clefts

Orofacial clefts are a heterogeneous group of tissue approximation defects manifesting as cleft lip, cleft lip and palate, and cleft palate. Nasal cleft is also possible. These defects can occur in isolation or in association with a congenital syndrome.

Cleft palate results from partial or complete failure of the apposition and fusion of the palatal shelves that normally occurs between 8 and 12 weeks of gestation. Complete cleft palate involves cleft defects of the uvula, soft palate, and hard palate. In some cases the hard palate defect may be covered by a mucous membrane that may extend to partially cover the soft palate cleft as well; this is termed *submucous cleft palate.*

Signs and Symptoms

Newborns with orofacial clefts should have immediate evaluation and early referral to a craniofacial specialist. The child may be at risk for aspiration and airway obstruction, particularly if additional craniofacial anomalies are present. Feeding difficulty is universal because the cleft defect prevents the generation of adequate negative pressure necessary for sucking. As such, failure to thrive is a common problem in these children. Special feeding bottles and nipples are used to facilitate a more effective and energy-efficient feeding process. A multidisciplinary team consisting of physicians, dentist, nutritionist, and speech therapist is recommended to address the physical and psychological concerns that arise in different developmental stages of childhood.

Cleft palates are associated with a higher incidence of otitis media because abnormal palatal muscle insertion impairs middle ear drainage. Myringotomy with ear tube placement is generally performed at a lower threshold in these children.

Treatment

Cleft lip repair is typically performed between 6 and 12 weeks of age to restore normal feeding, whereas cleft palate repair is done later, between 9 and 14 months. Timing of cleft palate repair is aimed at preventing further speech abnormalities and at minimizing facial growth distortion (as can occur if repair is done too early). Children with a history of orofacial cleft repair may present for surgery in later childhood for treatment of velopalatal insufficiency, dental anomalies, and cosmetic issues related to scarring.

Management of Anesthesia

Children with cleft lip or palate can undergo inhalational or IV induction of anesthesia. Concurrent cleft lip and palate defects as well as syndromic orofacial clefts may portend a difficult intubation. If a laryngeal mask airway (LMA) is used, its placement must be done carefully to prevent disruption of previous cleft palate repairs.

Preformed oral right-angle endotracheal (RAE) tubes are preferred for their low profile and better fit with the retractor used during surgery. Meticulous attention must be paid to securing the ETT because frequent surgical manipulations predispose to unintentional extubation. Cleft repair may also be done in positions that increase the risk of unplanned extubation (e.g., Rose position, where the patient's head is pulled over the edge of the operating table and placed in the surgeon's lap).

Significant edema of the tongue, palate, and pharyngeal tissues can occur from compression by the mouth retractor and may preclude immediate extubation. Placement of a nasopharyngeal airway by the surgeon in patients with known difficult airway, obstructive sleep apnea (OSA), or anticipated difficult extubation may be helpful in some cases. Use of oral airway is to be avoided, as is vigorous oropharyngeal suctioning.

Pain control must be balanced with the risk of respiratory depression. IV or rectal acetaminophen as well as regional anesthesia (infraorbital blocks) should be considered.

Mandibular Hypoplasia

Hypoplasia of the mandible is a common congenital anomaly. The majority occur as part of a congenital syndrome; nonsyndromic isolates are rare. Airway compromise is universal; the constricted mandibular space displaces the tongue posteriorly to cause airway obstruction.

Pierre-Robin Sequence

Pierre-Robin sequence (PRS), previously Pierre-Robin syndrome, consists of the triad of micrognathia (small mandible) or retrognathia (posterior displacement of mandible), glossoptosis, and airway obstruction. Cleft palate is present in the majority of cases. PRS can be syndromic or nonsyndromic. Associated congenital disorders include Stickler syndrome, velocardiofacial syndrome, hemifacial microsomia, and fetal alcohol syndrome.

Affected newborns present with varying degrees of airway obstruction and feeding difficulties. Intervention is aimed at restoring airway patency and can range from maneuvers as simple as lateral or prone positioning to surgical interventions such as tongue-lip adhesion, mandibular distraction osteogenesis, and tracheostomy. In the absence of intrinsic skeletal growth deficiency, airway obstruction usually improves over time with mandibular growth.

Hemifacial Microsomia

Hemifacial microsomia (HFM) is the one of the most common congenital facial anomalies (second only to cleft lip and palate). It is a facial asymmetry disorder affecting unilateral bone, muscle, and soft tissue structures. HFM typically affects the lower half of the face and is associated with prominent hypoplasia of the malar-maxillary-mandibular complex, with variable involvement of the ear, temporomandibular joint, and orbit, as well as the cervical spine. Goldenhar syndrome (oculoauricular-vertebral syndrome [OAV]) can be considered the most severe form of syndromic HFM, characterized by colobomas and vertebral anomalies in addition to facial asymmetry.

Treacher Collins Syndrome

Treacher Collins syndrome (TCS), also known as mandibulofacial dysostosis (defective ossification or formation of bone), is a rare autosomal dominant disorder of craniofacial anomaly with variable expression. TCS facies features downward-sloping palpebral fissures, diminutive or absent cheekbones, a normal-sized nose that may appear large with background hypoplasia, malformed pinnae, ear tags, abnormal external auditory canal, and receding chin. Occasionally, choanal atresia may be present. Intelligence is usually not affected unless hearing loss is not promptly addressed. A small percentage of patients with TCS may have coexisting congenital heart disease.

Immediate concerns revolve around establishing airway patency; tracheostomy may be necessary at birth. Swallowing difficulties lead to failure to thrive, and early gastrostomy is frequently needed for feeding. These children typically require multiple craniofacial and dental corrective surgeries throughout their childhood and adolescence.

Management of Anesthesia

Anesthetic concerns for patients with mandibular hypoplasia relate mainly to airway management. Concomitant congenital anomalies, especially cardiac lesions, must also be considered.

Patients with mandibular hypoplasia, especially in association with TCS and HFM, are not only difficult to intubate but may be nearly impossible to mask ventilate. When anesthesia can be safely induced, preservation of spontaneous respiration is critical before the airway is secured. Awake supraglottic airway placement followed by inhalation induction is a common induction strategy. Intubating supraglottic airway devices such as the Air-Q now exist in pediatric sizes that accommodate most neonates and infants. If utilizing fiberoptic bronchoscopy for intubation, maneuvers to pull the tongue forward are helpful, since glossoptosis is a major component of airway obstruction. Direct laryngoscopy is generally difficult and unsuccessful and is *not* recommended. Alternative means for visualizing the vocal cords (e.g., fiberoscope, video laryngoscope, optical laryngoscope) must be immediately available and set up for use from the outset: attempts to perform direct laryngoscopy may compound patient morbidity. Some surgical treatment approaches may require nasotracheal intubation.

Drugs with respiratory depressant effects should be used sparingly. Nonopioid analgesic adjuncts and local anesthetic should be considered whenever possible. Timing of extubation is as important as initial airway management, since there may be significant postsurgical edema.

Midface Hypoplasia

Midface hypoplasia involves underdevelopment of the eye sockets, cheekbones, and upper jaw. Growth deficiency of the midface gives the characteristic concave appearance with wideset eyes (hypertelorism), proptosis, flattened nasal bridge, and large underbite. As a result of crowding of midfacial structures, these patients often experience dental malocclusion and obstructive sleep apnea; proptosis increases the risk of keratoconjunctivitis.

Apert Syndrome

Apert syndrome is a rare inherited disorder (autosomal dominant) characterized by acrocephalosyndactyly. The cranium, midface, and bones and soft tissues of the hands and feet are affected. The result is a combination of craniosynostosis, midface hypoplasia, and symmetric syndactyly of the extremities, with cutaneous and bony fusion. Turribrachycephaly (towering skull deformity), hypertelorism, and lowset ears are also prominent features.

Most patients with Apert syndrome experience some degree of airway obstruction due to small nasopharyngeal and oropharyngeal dimensions, particularly if choanal atresia and tracheal stenosis are present. Obstructive sleep apnea is common and must be addressed early to avoid development of cor pulmonale. Eye complaints include proptosis (with risk of corneal injury), amblyopia, strabismus, and optic nerve atrophy.

Crouzon Syndrome

Crouzon syndrome shares many clinical features with Apert syndrome, but the viscera and extremities are spared. Also known as craniofacial dysostosis (malformation of the face and skull bones), it is a hereditary disorder (autosomal dominant) characterized by craniosynostosis, midface hypoplasia, mandibular prognathism, and shallow eye sockets with hypertelorism and proptosis. As a result of frequent premature fusion of the coronal sutures, brachycephaly (short and broad head) is usually seen. Intellectual delay is not an intrinsic part of Crouzon syndrome but may occur secondary to increased ICP and hearing impairment. Conductive hearing loss is common due to ear canal abnormalities (atresia or stenosis). Airway obstructive problems are similar to those seen in Apert syndrome.

Management of Anesthesia

Patients with midface hypoplasia typically present for midface advancement procedures, adenotonsillectomy, and cranial vault reconstruction if craniosynostosis is present. Some may require tracheostomy at an early age to establish airway patency.

Both mask ventilation and tracheal intubation may be extremely difficult, especially if there are cervical spine abnormalities that limit neck extension. A plan for difficult airway management must be prepared thoughtfully.

Special attention must be paid to avoid injury to the proptotic eyes. A history of headache, vomiting, and somnolence should raise suspicion of increased ICP. Lastly, IV access may be extremely difficult in patients with Apert syndrome, depending on the severity of syndactyly.

UPPER AIRWAY DISORDERS

Acute Epiglottitis (Supraglottitis)

Historically the most common cause of epiglottitis infection was *Haemophilus influenzae* type B (HIB). This infection is now much less common in developed countries, owing to HIB immunization in children. Vaccination has shifted the median age of presentation from 3 years to between 6 and 12 years. Epiglottitis can also occur in other age groups, including adults.

Although much less common, epiglottitis may occur as a result of trauma/injury. Acute epiglottitis, also termed *supraglottitis*, is a life-threatening infection of the epiglottis and adjacent supraglottic structures. Specifically, it is a cellulitis of the stratified squamous epithelium of these structures, including the lingual surface of the epiglottis, the aryepiglottic folds, and the arytenoids. Occasionally the uvula is also affected. Subglottic structures are generally spared.

Signs and Symptoms

The classic presentation is a toxic-appearing, agitated child with a high fever and the "4 Ds" (dysphagia, dysphonia, dyspnea, and drooling), history of severe sore throat, and muffled voice. Typical upper respiratory infection (URI) symptoms such as rhinorrhea and cough are usually absent. A croupy cough may rarely be present and may confuse the clinical picture with laryngotracheobronchitis. The child often assumes a characteristic tripod posture with the trunk leaning forward supported by the arms and a hyperextended neck with the chin thrust forward in an effort to maximize airflow. Inspiratory stridor is a late feature and is evidence of impending complete upper airway obstruction. The course of acute epiglottitis, particularly in small children, can deteriorate rapidly and may be fatal within 6 to 12 hours of presentation. Diagnosis is based principally on the clinical picture. A lateral neck radiograph typically shows the thumb sign, representing the shadow created by a swollen epiglottis obstructing the airway. Airway obstruction is the primary concern. Other complications of epiglottitis include epiglottic abscess, secondary infections (e.g., pneumonia, cervical adenitis, meningitis, bacteremia), and necrotizing epiglottitis.

Historically, placement of an artificial airway was universally employed. Since the median age of presentation has increased, with a concomitant increase in baseline airway caliber, selected cases may be monitored without intubation. Humidified oxygen should be administered as needed. Empiric antibiotic therapy should be initiated in all cases. Use of glucocorticoids remains controversial.

Management of Anesthesia

Airway management is the principal goal, and care should involve an anesthesiologist and an otolaryngologist. The child should be kept in the tripod posture. Unnecessary physical examination and IV access should be deferred until definitive airway protection is established. Expeditious transfer of the patient to the OR by personnel with expert airway management skills is essential. Equipment for standard intubation, difficult airway, and possible emergent tracheostomy/needle cricothyrotomy must be immediately available. Styletted ETTs in one to two sizes smaller than that predicted for the child's age must be prepared because the airway caliber will invariably be reduced.

Anesthesia is induced via inhalation with the child in a sitting position. A calm induction with preservation of spontaneous respiration is critical. Application of moderate CPAP (10–15 cm H_2O) can help minimize further reduction in airway caliber from collapse of the pharyngeal soft tissues with anesthesia induction. Once the child is adequately anesthetized, IV access can be established, followed by direct laryngoscopy and orotracheal intubation. An air leak around the ETT (<25 cm H_2O) must be demonstrated to prevent additional tracheal damage.

Postoperative ICU care is mandatory. Timing of extubation depends on resolution of clinical signs and symptoms (resolution of fever and neutrophilia, and increasing air leak around the ETT) confirmed by repeat examination of the supraglottic structures with direct vision or flexible fiberoscopy. In most cases the child can be extubated in 24 to 48 hours after initiation of appropriate therapy.

Postintubation Laryngeal Edema

Postintubation laryngeal edema, also termed *postintubation croup* (not to be confused with infectious croup), is a potential complication of all tracheal intubations. It is most commonly discussed in the context of pediatric patients because infants and children have smaller absolute tracheal diameters and thus have the highest incidence of developing clinically significant postintubation laryngeal edema. Although there may be predisposing factors (Table 31.11), this is an iatrogenic disorder as a direct result of endotracheal intubation.

Signs and Symptoms

Postintubation croup typically manifests within 30 to 60 minutes of extubation and is characterized by a barking or croupy cough, hoarseness, and stridor. With increasing airflow obstruction, the patient may exhibit nasal flaring, respiratory retractions, hypoxemia, cyanosis, and depressed consciousness. Treatment is aimed at reducing airway edema. Keeping the child calm is also important; crying will further exacerbate symptoms. For mild cases, mist therapy with cool humidified air may be helpful. In general, several nebulized epinephrine treatments are needed to effect sufficient mucosal vasoconstriction to help shrink the swollen mucosa. The patient must be observed for up to 4 hours after the last nebulized epinephrine treatment in case of rebound obstructive symptoms. In severe cases, heliox treatment (helium and oxygen mixtures) can also be considered. Resolution of symptoms usually occurs within 24 hours. Dexamethasone is effective in treating and preventing postintubation laryngeal edema; it is important to recognize its slower onset of action (4–6 hours to achieve maximum effect).

TABLE 31.11 Factors Associated With Postintubation Laryngeal Edema

Age <4 years
Tight-fitting ETT, no audible leak at or below 25 cm H_2O
Traumatic or repeated intubation
Prolonged intubation
Overinflated ETT cuff
Inadequate anesthesia during intubation
Repeated head repositioning while intubated
History of infectious or postintubation croup
Neck/airway surgery
Upper respiratory infection
Trisomy 21

ETT, Endotracheal tube.

Management of Anesthesia

Prevention of postintubation laryngeal edema should be a main goal in the airway management of pediatric patients. Whether one chooses to use cuffed or uncuffed ETTs, the goal is to minimize trauma to the laryngeal and subglottic structures. Gentle laryngoscopy and ETT placement are important, as is selection of an appropriately sized ETT; confirmation of an ETT air leak at less than 25 cm H_2O should be routine.

Subglottic Stenosis

Subglottic stenosis (SGS) is a congenital or acquired narrowing of the subglottic airway. It is the most common type of laryngeal stenosis. Specifically, SGS refers to narrowing at the level of the cricoid ring. Most cases are the result of trauma.

Signs and Symptoms

Clinical presentation can range from mild respiratory symptoms to stridor and even complete airway obstruction. Mild cases of congenital SGS may not be clinically evident and are only diagnosed after the child presents with recurrent croup. SGS should always be considered in neonates and infants who have failed multiple extubation attempts.

Diagnosis of SGS is made by endoscopic examination and is graded on a severity scale from I to IV (grade I, <50% luminal obstruction; grade II, 50–70% obstruction; grade III, 71–91% obstruction; grade IV, no discernible lumen). Congenital SGS is a diagnosis of exclusion made only in the absence of trauma and other identifiable postnatal causes.

Treatment

Grades I and II SGS may be amenable to medical therapy alone using antiinflammatory and vasoconstrictive agents such as corticosteroid and nebulized epinephrine. Grades III and IV SGS require surgical intervention.

Clinical symptoms ultimately dictate the need for surgical treatment regardless of grade. Less severe SGS may be treated endoscopically with steroid injection, serial dilation, and CO_2 laser ablation with or without topical mitomycin C. More severe cases may require aggressive surgical interventions; these include anterior cricoid split, laryngotracheoplasty with cartilage graft (laryngotracheal reconstruction), and tracheotomy.

Management of Anesthesia

Since most acquired cases of SGS result from intubation-related trauma, extreme vigilance and caution must be observed in the airway management of every pediatric patient, particularly for infants and young children. There should be routine confirmation of an ETT air leak at less than 25 cm H_2O.

For patients presenting for SGS corrective procedures, standard anesthetic concerns pertaining to airway surgery should be observed. In particular, there is high risk of airway fire in the setting of laser use and electrocauterization.

In cases of open reconstruction, postoperative management is as important as the actual surgery. An ETT (often larger than that predicted for age) is left in place to act as a stent after the stenotic area has been repaired and the lumen enlarged with cartilage graft. Adequate sedation and frequently muscle relaxation are required to prevent patient movement; suture line disruption or accidental extubation can lead to disastrous airway obliteration.

Foreign Body Aspiration

Foreign body (FB) aspiration occurs when an object or substance nonnative to the laryngotracheobronchial pathway is inhaled and embedded anywhere from the level of the larynx down to the distal bronchus and beyond.

Commonly aspirated objects in the pediatric population include food particles (peanuts are most common), small toy parts, and metal objects. The size and shape of the aspirated object usually determine the level of entrapment. Entrapment at proximal locations can cause complete airway obstruction, asphyxiation, and death. Smaller and streamlined objects may travel down to the distal airways and present with a more subtle clinical picture. Secondary chemical or inflammatory reaction to the FB and postobstruction infection may also occur. Over half of all aspirated FBs are located in the right main bronchus, followed by the right lobar bronchi, left bronchi, trachea/carina, larynx, and bilateral locations.

Signs and Symptoms

Children between the ages of 1 and 3 years represent the overwhelming majority of victims of FB aspiration. Symptoms of bronchial aspiration include coughing, wheezing, dyspnea, and decreased air entry into the affected side. Laryngeal and tracheal FB aspiration present with frank or impending respiratory failure. Overall, the classic triad of cough, wheezing, and decreased breath sounds is present in fewer than 60% of all children with FB aspiration. A reported history of choking is highly suggestive of FB aspiration, but it may be missed because choking typically lasts only seconds to minutes immediately after the aspiration event. Chronically retained airway FBs have a much more insidious presentation and are often misdiagnosed as asthma, infections of the upper or lower airways, and undefined airway abnormalities.

The diagnosis of FB aspiration can be easily established with plain radiographs if the object is radiopaque. Most aspirated objects (food items, nuts) are radiolucent, however. Diagnosis can be made based on radiographic evidence suggestive of aspiration (e.g., postobstructive atelectasis, infiltrate/consolidation, air trapping) in conjunction with the history and clinical findings.

Treatment

Rigid bronchoscopy is the procedure of choice in both the diagnosis and treatment of FB aspiration. Dislodgment or fragmentation of the FB into the contralateral bronchus is a potentially lethal complication causing bilateral bronchial obstruction. It is sometimes necessary to push the FB to a more distal location to restore ventilation to as large a portion of the lungs as possible. Rarely, FB aspiration may require thoracotomy for object retrieval.

Management of Anesthesia

There is no gold standard anesthetic approach, and controversy still exists between whether to maintain spontaneous respiration

or to initiate controlled ventilation. An individualized approach should be planned based on the history, physical examination, and diagnostic images. Nitrous oxide is contraindicated if there is evidence of air trapping. Urgent/emergent need for bronchoscopic examination takes precedence over fasting status.

Inhalational induction of anesthesia with preservation of spontaneous respiration is generally preferred because positive pressure ventilation may move the FB into potentially more precarious positions. Total IV anesthesia should be established as early as possible after induction to provide uninterrupted anesthesia during rigid bronchoscopy. Topical anesthesia of the larynx and trachea with up to 3 mg/kg of lidocaine (2–4%) is extremely useful in attenuating laryngospasm and reaction to surgical manipulation. Anticholinergics such as atropine (10–20 μg/kg IV) or glycopyrrolate (3–5 μg/kg IV) should be readily available in case of a pronounced vagal response during bronchoscopy. Once the bronchoscope passes the glottis, the anesthesia circuit should be immediately connected to the side port to provide supplemental oxygen and assist spontaneous respiration, or to initiate controlled ventilation as needed. Use of a precordial stethoscope can be invaluable in assessing respiratory effort and quality in these cases.

Preservation of spontaneous respiration is ideal, but muscle relaxation is sometimes required to prevent movement during FB retrieval. Upon completion of the bronchoscopy, the patient may be intubated to establish definitive airway control and facilitate tracheal and esophageal suctioning. In general, the child can be promptly extubated once appropriate criteria are met. Although rare, pneumothorax can occur and should be considered in case of rapid deterioration.

Dexamethasone (0.4–1 mg/kg, maximum of 20 mg) is given prophylactically to reduce subglottic edema. Nebulized epinephrine treatment may be needed to treat postoperative croup.

Laryngeal Papillomatosis

Laryngeal papillomatosis is a common cause of hoarseness and airway obstruction in children. Also known as recurrent respiratory papillomatosis (warts), it is a benign neoplasm of the larynx and trachea caused by human papillomavirus (HPV). The larynx is most commonly affected, but distal involvement of the trachea and lungs can also occur.

Signs and Symptoms

Children can present between the ages of 6 months and 10 years. Dysphonia or change in voice quality (or altered cry in infants) is often the first and most prominent symptom. If left untreated, lesion growth will lead to stridor, dyspnea, and airway obstruction. Although histologically and pathologically similar in children and adults, the clinical course is quite different between the two patient populations. The main difference is the highly recurrent nature of the wart lesions in children, often necessitating numerous surgical excisions over the course of childhood. Adults usually only require a few surgical treatments for complete eradication. Lesions that begin in childhood mostly become quiescent in adolescence.

Treatment

Surgical debulking is the current standard of care in the treatment of laryngeal papillomatosis. The primary means include laser ablation (CO_2), microdébridement, and cryotherapy. Adjuvant antiviral medical therapy (cidofovir) has been used with success in moderate to severe cases. Rarely, large lesions may require tracheotomy to restore airflow. However, tracheotomy is strongly discouraged owing to the risk of inducing distal spread of disease.

Management of Anesthesia

Airway surgeries in suspension microlaryngoscopy are some of the most challenging cases in pediatric anesthesia and require close cooperation between the otolaryngologist and anesthesiologist. Patients are typically turned 90 degrees away from the anesthesia station and are suspended in a hands-free laryngoscope setup that allows for microscopic binocular operative intervention. Traditionally, intubation with a smaller ETT during surgery has been the standard approach. However, the presence of an ETT poses several problems. The most obvious is the risk of airway fire as the ETT material can serve as fuel for combustion during laser surgery; alternatives such as metal, rubber, or silicone-coated ETTs wrapped in reflective foil should be used whenever possible. The physical presence of the ETT may also compromise visualization and excision of the lesion. Tubeless techniques with or without spontaneous respiration have gained popularity.

Children generally undergo inhalational induction of anesthesia with the aim to establish IV access and a steady level of total IV anesthesia as early as possible. Topical anesthesia of the larynx and trachea should be done to further decrease reaction to surgical stimuli. Muscle relaxation for cord paralysis is sometimes required for precise surgical excision of cord lesions. Most children are intubated at the completion of the surgery, even in tubeless techniques, and then allowed to awaken for extubation.

Adenotonsillar Hypertrophy/Sleep-Disordered Breathing

Adenotonsillar hypertrophy is the most common cause of snoring in children. Snoring may or may not be associated with actual obstructive hypopnea and apnea. Sleep-disordered breathing represents a spectrum of nocturnal airflow restrictive problems ranging from physiologically inconsequential snoring to severe obstructive sleep apnea.

Signs and Symptoms

Children with OSA frequently have nonspecific behavioral difficulties such as hyperactivity and learning disability; daytime sleepiness is less common. The child will typically display audible mouth breathing, dry lips, hyponasal speech, and the so-called adenoid facies (an oblong face with the mouth open and an expression of being lost or apathetic).

Tonsillar hypertrophy is graded on the percentage of the lateral oropharyngeal space occupied by the palatine tonsillar tissues. Flexible endoscopy and lateral radiography are helpful in diagnosing adenoid hypertrophy; most cases are diagnosed clinically at the time of surgery. Adenoids are located midline in

the nasopharynx in close proximity to the opening of the eustachian tubes. As such, adenoid hypertrophy is frequently associated with chronic middle ear effusion, otitis media, and sinusitis.

History and physical examination alone are poor at differentiating simple snoring from OSA. As a symptom, snoring alone has relatively low positive and negative predictive values in the evaluation of children with sleep-disordered breathing. Polysomnography remains the gold standard for diagnosing OSA.

Treatment

Recognizing and treating sleep-disordered breathing is important as untreated OSA has neurocognitive, inflammatory, and cardiovascular sequelae. Adenotonsillectomy is the treatment of choice and can be curative for most children with OSA. It is sometimes performed even in the absence of significant adenotonsillar hypertrophy if obstructive symptoms are progressive.

Management of Anesthesia

Preoperative anxiolytic medication is not contraindicated but should be given with discretion and used sparingly given the potential for respiratory depression. Anesthesia induction is usually accomplished with inhalation of sevoflurane and oxygen, with or without nitrous oxide. Rapid airway obstruction can be expected, and oral airways of several sizes should always be readily available. Moderate CPAP is often needed to counteract the effects of relaxed upper airway muscle tone. Cuffed ETTs are necessary to minimize the chance of aspiration of blood. Opioids should be dosed conservatively to minimize the risk of prolonged emergence and postoperative upper airway obstruction. Nonsteroidal antiinflammatory drug (NSAID) use remains controversial and varies widely from center to center. IV acetaminophen is an excellent analgesic adjunct because it is devoid of coagulopathic and respiratory depressant effects. High-dose dexamethasone (up to 1 mg/kg IV, maximum of 20 mg) has been shown to reduce postoperative swelling and nausea/vomiting. Emergence delirium is common in adenotonsillectomy patients; families should be counseled accordingly, and pharmacologic prevention and treatment should be part of the anesthetic plan.

Upper Respiratory Infection

URI deserves a special mention because no other illness is encountered more frequently in the pediatric population presenting for surgery. As a group, URIs represent the most prevalent acute illness in the general population, with the highest overall incidence in children. Most cases of URI are mild and self-limited; however, URIs are associated with an increased risk of perioperative respiratory complications such as laryngospasm, bronchospasm, and hypoxemia. Specific risk factors for respiratory complications in association with active or recent URI (within 2–4 weeks of surgery) include former prematurity, age younger than 2 years, underlying reactive airway disease, asthma, copious secretions, secondhand exposure to tobacco smoke, and prior airway surgery.

Management of Anesthesia

The traditional approach—which is to postpone elective surgery for 1 to 2 weeks for mild or recent URIs and for 4 to 6 weeks for active and more severe URIs—may be too conservative and oftentimes unrealistic. The urgency and type of surgery must be considered. Emergent procedures must proceed regardless of the severity of the URI. Type of surgery is also an important consideration; some procedures such as myringotomy and adenotonsillectomy may help relieve chronic URI-like symptoms. A detailed parental interview usually provides a helpful comparison of the child's current health status to baseline condition. In general, elective surgeries should be postponed if the child has high fever, productive cough, croup symptoms, general malaise, and evidence of lower respiratory tract infection (adventitious lung sounds or dyspnea).

When feasible, airway management with mask or LMA is preferable to endotracheal intubation and has been shown to have a lower incidence of perioperative respiratory complications. If intubation is required, the trachea should only be instrumented under a deep plane of anesthesia, with or without neuromuscular blockade. A smaller-than-expected ETT should be considered because children with active or recent URI have a higher incidence of postintubation laryngeal edema; prophylactic dexamethasone treatment should be considered.

GENITOURINARY DISORDERS

Vesicoureteral Reflux

Vesicoureteral reflux (VUR) is abnormal reflux of urine from the bladder into the upper urinary tract, including the ureters and kidneys; it can be unilateral or bilateral. It is the most common urologic disorder in children and is classified into low grade (I–III) and high grade (IV–V).

Most children present with a febrile urinary tract infection (UTI). Some may present with hypertension and poor growth if chronic UTIs have gone unrecognized. Untreated VUR increases the risks of pyelonephritis and renal scarring, with subsequent reflux nephropathy and chronic kidney insufficiency. A voiding cystourethrogram (VCUG) is the most common and best diagnostic tool. Renal ultrasonography has limited sensitivity even when reflux is severe.

Treatment

Treatment is guided by severity grade and can range from watchful waiting, long-term antibiotic prophylaxis, to surgical intervention. Greater than 80% of grades I and II VUR resolve spontaneously by age 5 years. Concurrent bowel and bladder dysfunction is associated with a higher failure rate of surgical correction, higher incidence of breakthrough UTI while on antibiotic prophylaxis, and longer time to VUR resolution. The most common surgical intervention for VUR is ureteral reimplantation. The affected ureter is repositioned and retunneled into the bladder wall to create a new ureterovesical junction (UVJ) with the proper length-to-diameter ratio. Endoscopic injection of periurethral bulking agent for lower grade VUR (most commonly a copolymer of dextranomer/hyaluronic acid [or DEFLUX]) has also been used with variable long-term success rate depending on operator experience.

Cryptorchidism

Cryptorchidism is defined as congenital absence of one or both testes in the scrotum due to incomplete testicular descent of normal, atrophic, or congenitally absent testis. It is the most common congenital anomaly of the genitourinary tract. Risks of subfertility, torsion, and testicular cancer are increased.

Cryptorchidism is diagnosed by nonpalpable or palpable but malpositioned testis (e.g., inguinal canal). Forty percent of cryptorchidism have an intraabdominal location, 40% have a high inguinal location, and the rest represent atrophy or congenital absence. Most palpable undescended testes spontaneously descend by 4 months of age and rarely so thereafter.

Cryptorchidism is corrected by orchiopexy (fixation of testis to the scrotal sac) and is best performed before 2 years of age to optimize normal testicular growth and fertility potential. Cases with a high intraabdominal position and short spermatic vessels may require a two-stage procedure (Fowler-Stephens technique) to allow time for collateral vessel formation after initial vessel clipping, followed by mobilization and scrotal fixation of the testis. Orchiectomy is occasionally needed for unsalvageable testis.

Hypospadias

Hypospadias is congenital malpositioning of the urethral meatus on the ventral aspect of the penis. Meatal opening can be anywhere along the glans penis, penile shaft, scrotum, and even perineum. Chordee, an abnormal ventral curvature of the penis, often coexists.

While most distal hypospadias may only pose cosmetic concerns, proximal lesions can cause voiding difficulty and sexual dysfunction. Neonatal circumcision should be avoided due to meatal malpositioning; foreskin may also be needed for skin grafting in future repair.

Management of Anesthesia

Unless there are comorbid anomalies, most children presenting for VUR, cryptorchidism, and hypospadias surgical intervention are generally healthy and pose no specific anesthetic concerns. Patients with VUR associated with coexisting renal anomaly or chronic kidney disease should have baseline renal function evaluated to guide proper fluid and electrolyte management. Caudal or lumbar epidural analgesia is recommended for reimplantation procedures while caudal analgesia should be routine for orchiopexy and hypospadias repair. Orchiopexy is associated with a high incidence of postoperative nausea and vomiting; prophylactic antiemetic should be routinely given to children older than 1 year.

ORTHOPEDIC/MUSCULOSKELETAL DISORDERS

Clubfoot (Talipes Equinovarus)

Clubfoot is a common congenital foot deformity due to malalignment of the calcaneotalar-navicular complex, resulting in excessive plantar flexion, a medially deviated forefoot, and an inward-facing sole. Up to 60% of cases are bilateral. Clubfoot is classified as congenital, syndromic, or positional. Syndromic clubfoot is associated with chromosomal or genetic abnormalities. Positional clubfoot is generally the result of intrauterine growth constraints (e.g., oligohydramnios). The majority (80%) are idiopathic and an isolated finding at birth; prenatal detection is possible as early as 12 to 13 weeks of gestation.

All patients exhibit some degree of calf atrophy. Some also demonstrate shortening of the tibia and fibula. Nonoperative treatment (serial casting and bracing) is most effective for positional clubfoot as the deformity is flexible rather than rigid. Rigid clubfoot generally requires definitive surgical Achilles tenotomy (clipping or release of the Achilles tendon).

Management of Anesthesia

Unless there are concomitant congenital anomalies, anesthetic care of children undergoing clubfoot corrective procedures is usually straightforward. Some procedures require prone positioning necessitating proper airway management and positioning precautions. Muscle relaxants may be required for adequate stretching and casting. Neuraxial or regional analgesia can be considered for more complex cases.

Slipped Capital Femoral Epiphysis

Slipped capital femoral epiphysis (SCFE) denotes slippage of the femoral end cap (*epi*, "over"; *physis*, "growth plate") over the femoral neck secondary to growth plate fracture. SCFE typically presents between the ages of 10 and 16 years, a period of rapid bone growth with increased growth plate instability. Boys are affected more often than girls. Obesity is the major risk factor. Conditions associated with a higher risk of SCFE and an earlier age of onset include Down syndrome, endocrinopathies (hypothyroidism, precocious puberty, pituitary tumors), renal osteodystrophy, and a history of radiation therapy.

Patients can present with pain in the groin, thigh, and/or knee, as well as altered gait. Twenty to 40% have bilateral involvement even if there are only unilateral symptoms. Diagnosis is made with physical exam and plain radiography. Treatment involves single screw fixation of the growth plate to prevent further displacement. Prophylactic pinning of an unaffected contralateral hip is controversial.

Management of Anesthesia

Surgical pinning is urgent to prevent further displacement that may lead to vascular compromise. Full stomach precautions must be observed when indicated, particularly for obese patients. There are few special anesthetic considerations unless comorbid conditions are present.

Developmental Dysplasia of the Hip

Developmental dysplasia of the hip (DDH), previously termed congenital hip dysplasia, refers to abnormal growth of the hip stemming from joint laxity and acetabular dysplasia, predisposing to joint instability, subluxation, and dislocation. Time of onset can range from the antenatal period to the time of skeletal maturity.

DDH in healthy newborns is usually caused by physiologic ligamentous laxity and immature acetabulum of young age; over 50% resolve by the first week of life and up to 90% resolve by 2 months of age. Leg length discrepancy and gluteal fold

asymmetry are clues to possible DDH. Unrecognized and untreated hip joint instability can lead to chronic dislocation, contracture of adjoining muscles and tendon, as well as early hip osteoarthritis.

Uncomplicated DDH in young infants is generally treated with abduction splints (e.g., Pavlik harness) to prevent hip extension and adduction that predispose to dislocation. Serial casting (spica) may be required if DDH persists. Infants presenting after 6 months of age typically require closed or open hip joint reduction followed by spica casting for up to 6 months to stabilize a reduced hip joint. Refractory DDH may necessitate pelvic and femoral osteotomy for hip joint remodeling.

Management of Anesthesia

Spica casting requires placement of the patient on an elevated support frame for cast application. Measures must be taken to protect pressures points, to prevent inadvertent dislodgment of airway device, and to prevent accidental fall from the frame. During cast application, ventilatory changes signaling restrictive respiratory compromise must be communicated to the surgeon for cast modification. Neuraxial and regional anesthesia should be strongly considered for open hip and pelvic procedures. Antifibrinolytic therapy is useful to decrease intraoperative blood loss and reduce blood transfusion requirements.

Infantile Idiopathic Scoliosis

Infantile idiopathic scoliosis (IIS) is defined as abnormal curvature of the spine without apparent cause detected between birth and 3 years of age. As the timing of spinal deformity coincides with a period of significant spine and postnatal lung growth, two closely linked processes, IIS can severely impact thoracospinal and lung development; cardiac dysfunction may ensue in the face of high PVR. IIS is fatal if left untreated.

Termed *thoracic insufficiency syndrome* (TIS), the inability of the thorax to support postnatal lung growth and normal respiratory mechanics leads to progressive restrictive lung disease (RLD) from the effects of lung hypoplasia, perfusion defects, and impaired rib mechanics. In addition to IIS, a whole spectrum of congenital rib and spine defects can cause TIS.

Postnatal lung growth is most rapid in the first 3 years of life and continues at a slower pace until skeletal maturity is reached. Both the quantity and quality of the intrathoracic space are important for normal lung development. Thoracic spinal growth is greatest during the first 5 years of life (1.4 cm/year from 0–5 years vs 0.6 cm/year from 5–10 years vs 1.2 cm/yr from 10–18 years), thus early childhood is the most critical period for overall lung and thoracospinal development. TIS causes low lung and chest wall compliance, in contrast to the normally high respective compliance indices seen in early childhood. More baseline atelectasis is also observed.

Treatment

Spine fusion is the definitive treatment for scoliosis that occurs at any age. However, spine fusion stunts skeletal growth and is generally avoided before skeletal maturity. Several nonfusion, growth-friendly techniques have been developed for stabilizing spine deformities. The goals are to delay fusion and to preserve postnatal lung growth as best as possible. Examples of growth-guiding procedures include VEPTR (vertical expandable prosthetic titanium rib) and MAGEC (magnetic expansion control) rods. These invasive implant techniques require multiple procedures and can have serious complications such as unintended autofusion, implant fracture, and instrumentation-related infection, among others.

Serial casting is a noninvasive curvature correction technique that takes advantage of the rapid spine growth in early childhood. Such casts (EDF [elongation, derotation, flexion] or Mehta cast) are applied on a special casting table that allows for apparatus-assisted traction along with surgeon-applied manual pressure to elongate, derotate, and flex the spine. Casting is repeated every 2 to 3 months and can start as early as 12 months of age. Length of treatment is variable, but a commitment of at least 12 to 18 months of serial casting is necessary for sustained benefit. Serial EDF casting alone can provide definitive curve correction, particularly for children with moderate curves who start treatment before 2 years of age. Those with more severe curves and/or late start of treatment can often gain sufficient correction to delay invasive interventions.

Management of Anesthesia

Anesthetic considerations pertinent to any patient with RLD and potential cor pulmonale undergoing spine fusion also apply here; these are discussed extensively in Chapter 14. Similar to posterior spine fusion, MAGEC rods and initial VEPTR placement are performed in the prone position, with the latter requiring expansion thoracotomy in some cases. Blood transfusion is not usually required. The need for invasive arterial blood pressure monitoring is determined by severity of cardiorespiratory compromise.

EDF casting is performed on a special table (Fig. 31.5), where the patient is entirely suspended by straps for casting. A variable amount of weight or traction is applied via a chin strap. Careful positioning of the chin strap and padding are necessary to avoid compression of neck vessels and pressure injury to the face and ears, respectively. The eyes in particular must be covered to avoid plaster-related injury. Endotracheal intubation is

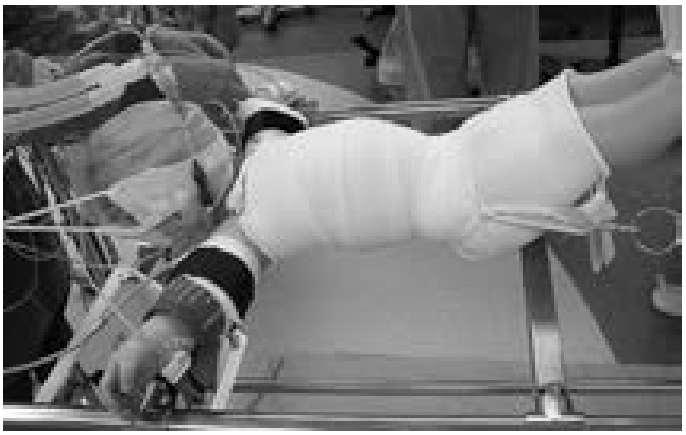

Fig. 31.5 EDF casting for infantile idiopathic scoliosis. (From D'Astous JL, Sanders JO. Casting and traction treatment methods for scoliosis. *Orthop Clin N Am.* 2007;38:477–484, fig. 1.)

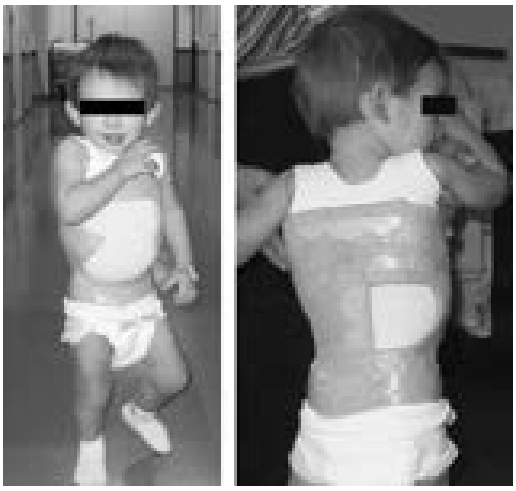

Fig. 31.6 Abdominal and back cutouts for EDF cast to reduce respiratory restriction. (From D'Astous JL, Sanders JO. Casting and traction treatment methods for scoliosis. *Orthop Clin N Am.* 2007;38:477–484, fig. 4.)

required as cast application can increase PIP by over 100%. After cast molding, abdominal and back cutouts are made to relieve the external restriction on thoracorespiratory mechanics; however, PIPs are still generally increased by over 30% above baseline (Fig. 31.6). Oxygenation and ventilation impairment must be communicated to the surgeon for appropriate cast modification. Patients are monitored closely for respiratory performance postprocedure. Except for the very first application, EDF casting is typically an outpatient procedure.

CHILDHOOD MALIGNANCIES

Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma

Acute lymphoblastic leukemia/lymphoblastic lymphoma (ALL/LBL) is the most common childhood malignancy with a peak incidence between 2 and 5 years of age. A higher incidence is seen in genetic syndromes such as trisomy 21, Fanconi anemia, neurofibromatosis type 1, and ataxia-telangiectasia. Prior total body irradiation also increases the risk of developing secondary ALL/LBL. B- and T-cell lineages are most common.

Initial symptoms are often nonspecific, such as fever, fatigue, and anorexia; a high degree of suspicion is required for expeditious diagnosis. Other clinical findings include pallor, petechiae, hepatomegaly, splenomegaly, bone pain (or a limp or refusal to walk), and persistent lymphadenopathy unresponsive to antibiotic treatment prescribed for initial misdiagnosis of an infectious process. Respiratory distress and superior vena cava syndrome may occur in the setting of a large mediastinal mass, which is most commonly associated with T-cell ALL/LBL.

Treatment is largely based on the Children's Oncology Group (COG) protocol, along with irradiation and bone marrow transplantation when indicated. Prognosis worsens with higher risk score based on cytogenetic features and response to chemotherapy (four main groups: standard risk, low risk, high risk, and very high risk). Overall cure rate for childhood ALL/LBL is greater than 80%. Five-year survival ranges from 30% (very high risk) to 95% (low risk). Infant onset ALL/LBL has particularly poor outcomes.

Management of Anesthesia

Recent cell counts should be checked in all patients presenting for invasive procedures. Thrombocytopenia can complicate even typically straightforward procedures such as dental extraction. Insertion of any device via the nares should be avoided in the setting of thrombocytopenia to avoid excessive epistaxis. Platelet count threshold for lumbar puncture is much lower than that used in the general practice of anesthesia, with some proceeding with a count as low as 10,000 without preprocedure platelet transfusion, as supported by the hematology/oncology literature and experience. Handling of long-term venous access demands fastidious aseptic technique to minimize the risk of central line–associated bloodstream infection.

Hyperleukocytosis, defined as a total leukemic cell burden greater than 100,000/μL, carries significant perioperative risk. Known as leukostasis, symptomatic hyperleukocytosis is a medical emergency and is seen in 10% to 30% of newly diagnosed ALL/LBL. The most common findings are acute dyspnea, hypoxia, diffuse pulmonary infiltrates, visual disturbance, headache, gait imbalance, and altered mental status. Hyperviscosity impairs cerebral perfusion, and the risk of intracranial hemorrhage is increased even after hyperleukocytosis resolves (for up to 1 week). Patients are at risk for fluid imbalance, postanesthetic respiratory failure, neurologic impairment, and renal failure. Hemodilution therapy for viscosity reduction should be initiated preoperatively. Care for these patients must be coordinated with experienced oncologists.

Wilms Tumor

Wilms tumor, or nephroblastoma, is the most common renal malignancy in children less than 15 years of age and the fourth most prevalent childhood cancer. It has a peak incidence between 1 and 3 years; over 95% of cases are diagnosed before the 10th birthday. The overwhelming majority (>90%) present as unilateral disease. Several congenital syndromes confer a higher risk of developing Wilms tumor; the most common ones are WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies, and retardation/intellectual disabilities; 50% risk), Beckwith-Wiedemann syndrome (5–10% risk), and Denys-Drash syndrome (male pseudohermaphroditism, progressive renal disease, and Wilms tumor; 90% risk).

The most common finding is an abdominal mass (painful or painless) that may be associated with fever, anemia, hematuria, and hypertension. The tumor pseudocapsule can rupture spontaneously or with aggressive palpation, leading to potentially life-threatening hemorrhage. Spillage of cancerous cells can also occur, which worsens tumor staging. Metastasis to the lungs is the most common, but respiratory complaints are rare. Acquired von Willebrand disease is seen in 4% to 8% of cases. Tumor staging is based solely on anatomic extent of the tumor, with a higher stage dictating more aggressive treatment (stage I–IV unilateral disease; stage V bilateral disease, based on the National Wilms Tumor Study [NWTS]). Up to

40% demonstrate tumor extension into the renal vein and less commonly into the inferior vena cava (IVC) and right atrium. Tumor staging and histology primarily determine prognosis. Overall, 5-year survival rate is close to 90% with current treatment modalities.

Management of Anesthesia

Preoperative evaluation should include details on tumor extent, particularly concerning vascular involvement, and relevant laboratory studies such as renal indices, hematologic, and coagulation status. Echocardiographic evaluation is necessary to assess for potential anthracycline cardiomyopathy when indicated. Vascular invasion carries a significant risk of sudden massive hemorrhage during tumor dissection. At least one supradiaphragmatic large-bore intravenous access should be available in case the IVC is clamped to control bleeding. Epidural analgesia is strongly recommended for open nephrectomy.

Neuroblastoma

Neuroblastoma (NB) is a group of malignant neoplasms of the sympathetic nervous system (SNS). It is the most common cancer of infancy and the third most common pediatric cancer overall. NB has a wide range of clinical behavior and can occur anywhere throughout the SNS; the adrenal gland is the most common site. Some NB can undergo spontaneous regression while others are aggressively malignant. Fifty percent have metastatic disease at presentation. Extent of disease and age of onset primarily determine prognosis. More localized disease and younger age are associated with better outcome (exception is neonatal onset of NB). Stage 4S disease is a special category of metastatic NB with significantly better outcomes (overall survival 85%); it designates age of onset before 18 months of age with metastatic disease limited to the liver, skin, and bone marrow.

The most common clinical finding is a painful or painless abdominal mass; bone pain may be present if bony metastases are present. Orbital involvement manifests as periorbital ecchymosis and proptosis and may be the first clinical findings in young infants. Tumors arising from the paraspinal ganglion may impinge on nerve roots and cause spinal cord compression. Opsoclonus myoclonus ataxia syndrome (OMAS) is a paraneoplastic syndrome consisting of rapid eye movements and rhythmic jerking of the body and/or limbs. It is seen in only 1% to 3% of NB cases, but any patient presenting with OMAS must be evaluated for potential underlying NB.

Imaging typically reveals a calcified mass. Tissue diagnosis is mandatory before initiating treatment, which consists of surgical resection, chemotherapy, monoclonal antibody, and radiotherapy. NB cells synthesize and secrete catecholamines; urinary catecholamine metabolites (homovanillic acid and vanillylmandelic acid) can be measured to monitor disease activity.

Management of Anesthesia

Patients may present for a variety of procedures ranging from bone marrow biopsy to craniotomy. Location, size, and metabolic activity of the tumor will determine relevant anesthetic considerations, such as need for invasive arterial pressure monitoring, large-bore IV access, blood product availability, and feasibility of neuraxial analgesia. Unlike pheochromocytomas, hemodynamic fluctuations with tumor manipulation are infrequent. Those with posterior mediastinal lesions can have stridor, wheezing, pleural effusion, and even positional tracheal compression, necessitating appropriate modification in anesthetic induction and airway management techniques. These cases should also prompt preoperative assessment of potential compressive effects on cardiac function.

Ewing Sarcoma

Ewing sarcoma (ES) is the second most common primary bone malignancy in children and adolescents after osteosarcoma. It is part of the ES family of tumors (EFT) that shares a common neuroectodermal origin. Primarily a disease of adolescence, ES lesions typically arise in the flat and long bones of the extremities as well as bones of the pelvis. Spine and distal extremities are affected less commonly, as are soft tissues. Localized pain, often with a tender mass or swelling, is the most common presenting symptom. Pathologic fracture is present in 15% of cases. Systemic symptoms such as fever and anorexia are uncommon (in contrast to osteosarcoma), but when present, metastatic disease is likely. Up to 25% of patients have clinically detectable metastatic disease upon diagnosis, although most are presumed to have subclinical metastases given the high rate of relapse (80%) when localized therapy is used alone.

Neoadjuvant chemotherapy has significantly increased overall survival, with additional radiotherapy improving outcome for those with unresectable disease and those with positive surgical margins. Surgical interventions now offer limb-sparing options instead of amputation when feasible. Metastasis is the most important prognostic factor. The 5-year survival rate is 70% for localized disease and 30% for ES with clinically detectable metastases.

Management of Anesthesia

The most important anesthetic consideration for patients with ES is pain control. Significant preoperative disease-related pain is common, and the risk of developing postoperative chronic pain is high. Regional and neuraxial analgesia should be strongly considered, along with parenteral multimodal analgesia. For those undergoing amputation, efforts to address phantom limb pain with a multidisciplinary approach should be the standard of care.

Tumors of the Central Nervous System

Primary CNS malignancies collectively represent the second most common cancer of childhood and adolescence. Having the highest morbidity of all childhood cancers, the overall mortality approaches 50% despite advances in treatment options. The incidence is highest among infants and young children. Genetic disorders that carry an increased risk of developing CNS malignancies include neurofibromatosis (NF1/von Recklinghausen and NF2), tuberous sclerosis, and von Hippel-Landau syndrome, among others.

There are over 100 histologic subtypes of primary brain tumors. The most common ones in children are astrocytomas, medulloblastomas, ependymomas, and craniopharyngiomas. Tumor can arise anywhere within the CNS. Supratentorial tumors occur most often in infants and adolescents, while infratentorial lesions predominate in children aged 1 to 10 years.

Symptoms depend primarily on tumor location. Tumors obstructing CSF flow can cause hydrocephalus and intracranial hypertension. Clinical manifestations may include macrocephaly (prior to suture closure), behavioral or personality changes, irritability, headache, and nausea and vomiting. Visual symptoms, such as nystagmus, diplopia, and blurry vision, are seen with midline infratentorial tumors. Supratentorial tumors generally cause widespread sensorimotor deficits as well as speech disturbance and seizures. Tumors in the suprasellar and third ventricular region often lead to neuroendocrine abnormalities due anterior and posterior pituitary dysfunction. Brainstem tumors are associated with cranial nerve palsies and occasionally upper motor neuron deficits. Finally, primary or metastatic tumors in the spinal cord can cause back pain, motor/sensory deficits, and bowel and bladder dysfunction. MRI remains the gold standard for diagnosis along with tissue biopsy for histologic confirmation.

Gliomas

Gliomas (glial cell origin) represent approximately 50% of all pediatric CNS tumors. The two most common subtypes in children are astrocytomas and ependymomas.

Astrocytomas account for approximately 40% of all CNS tumors and can occur throughout the CNS. They are generally of low histologic grade and have an indolent clinical course. Juvenile pilocytic astrocytoma is the most common subtype and typically affects the cerebellum and the third ventricular region. Overall survival is 80% to 100% if complete surgical resection can be achieved. Aggressive subtypes such as anaplastic astrocytoma and glioblastoma multiforme are rare in children and are mostly seen in adults.

Ependymomas arise from the ependymal lining of the ventricular system. They account for 10% of CNS tumors in children, with most occurring in the posterior fossa. Surgery is the primary treatment, but it is rarely curative without adjuvant radiotherapy and chemotherapy. Overall survival is approximately 40%.

Medulloblastoma

Medulloblastoma accounts for 10% to 20% of childhood brain cancer and is one of the most aggressive CNS malignancies. It is a type of CNS embryonal tumor. All medulloblastomas have a high histologic grade and are aggressively metastatic within the neuraxis. These are cerebellar tumors that affect boys more than girls, with a peak incidence between 5 and 7 years of age.

Craniopharyngiomas

Craniopharyngiomas are the most common intracranial tumors of nonglial origin. Though considered benign neoplasms, malignant transformations have been reported. Even after curative surgical resection, patients often suffer long-term visual deficits and neuroendocrine imbalance. Current treatment consists of surgical resection, radiotherapy, brachytherapy, and chemotherapy. Tumor recurrence is common.

Management of Anesthesia

Anesthetic concerns for CNS malignancies generally relate to minimizing increases in ICP, potential need for reducing brain bulk, and addressing neuroendocrine disturbances.

Diabetes insipidus (DI) is most often seen with craniopharyngiomas. It is defined as a rising serum sodium (>145 mg/dL) in the setting of copious dilute urine production (specific gravity <1.005). Preoperative DI treatment must be continued intraoperatively along with isotonic fluid at two-thirds of maintenance rate in addition to fluid replacement for blood and evaporative losses. Vasopressin dosing starts at 0.5 mU/kg/hr and increases incrementally at 0.5 mU/kg/hr until urine osmolality is twice that of serum osmolality or is titrated to keep urine output to less than 2 mL/kg/hr. DDAVP can also be used; a single dose (0.5–4 μg IV) lasts 8 to 12 hours. New-onset intraoperative DI is infrequent and more often occurs postoperatively (4–6 hours).

Retinoblastoma

Retinoblastoma (RB) is the most common pediatric intraocular malignancy with an incidence of approximately 1 in 15,000 live births and accounts for 10% to 15% of cancer presenting within the first year of life. The overwhelming majority (95%) occur before the age of 3 years.

There are two major forms of RB. Heritable RB involves germline mutations of the *RB1* gene (chromosome 13q14) whereas nonheritable RB involves somatic mutations of the same culprit tumor-suppressor gene. Heritable RB may result from de novo germline mutations and is not necessarily inherited. Those with heritable RB have an increased risk of developing secondary malignancies such as osteogenic sarcoma, soft tissue sarcomas, and melanoma.

The most common finding is leukocoria (white pupillary reflex); other symptoms include strabismus, inflamed eye, and nystagmus. Any child under the age of 3 years with leukocoria and/or strabismus requires urgent ophthalmic evaluation for RB. With current treatment, survival rate is high (>95%) even when local recurrences occur. Extraocular metastatic disease fares less well (50% survival) with CNS involvement having the worst outcome (<10% survival). Diagnosis is made by ophthalmic examination and imaging studies. Biopsy is contraindicated to prevent tumor seeding.

Treatment is dependent on extent of disease and may include cryotherapy, laser photocoagulation, brachytherapy, chemotherapy, and enucleation. Super selective ophthalmic artery chemotherapy is a technique that delivers chemotherapeutic agent(s) directly to the globe, thus minimizing systemic toxicity.

Management of Anesthesia

Serious cardiorespiratory events can occur during intraarterial chemotherapy. Also termed *ophthalmic artery chemosurgery* (OAC), a catheter is cannulated via the femoral artery, up to the internal carotid artery, and into the relevant ophthalmic artery

(OA). Performed under general anesthesia with muscle paralysis to prevent movement during vascular cannulation, cardiorespiratory perturbations, including bradycardia, systemic hypotension, and/or marked decrease in lung compliance, are seen in 20% to 30% of patients undergoing OAC. These disturbances occur at a specific time, usually within 2 minutes of cannulation of the OA or at crossing of its ostium. The hemodynamic response is likely part of the trigeminal-cardiac reflex as the OA and the dura mater lining its ostium are innervated by the fifth cranial nerve. The mechanism for the sudden and severe decrease in lung compliance is unclear. Manifesting as atypical bronchospasm, wheezing is generally not present. Usual risk factors for perioperative bronchospasm (recent URI, allergic rhinitis, asthma or reactive airway disease, and tobacco smoke exposure) are not predictive of this atypical bronchospasm. Steroid and bronchodilator offer no prophylactic benefit. Tryptase levels remain normal. A deeper plane of anesthesia has no impact on the incidence or severity of these occurrences, as reported by some to be protective against the oculocardiac reflex during strabismus surgery.

This atypical bronchospasm responds best to intravenous epinephrine bolus(es) of 0.5 to 1 µg/kg; epinephrine infusion for continued treatment is typically not needed. Pressure controlled ventilation allows for easy detection of even small changes in tidal volumes delivered, which must be communicated to the interventional radiologist. Catheter manipulation should be halted until the event resolves. With expeditious recognition and treatment, these cardiorespiratory adverse events are generally short-lived and without sequelae; patients can be safely discharged to home on the same day barring other complications.

DOWN SYNDROME (TRISOMY 21)

Down syndrome (DS), or trisomy 21, is the most common viable chromosomal abnormality, occurring in 1:700 to 1:800 live births. Advanced maternal age is the most important risk factor. Intellectual disability is nearly universal but has an extremely wide range. Life expectancy has improved greatly but is still shortened overall.

Characteristic dysmorphic features include upslanting palpebral fissures, epicanthal folds, a flattened nasal bridge, brachycephaly, and short, broad hands with a distinctive transverse palmar crease. Hypotonia is typically observed. Diagnosis is confirmed with karyotype analysis.

DS is associated with congenital and acquired pathologies of almost all organ systems (Table 31.12). Increased neuropsychiatric and behavioral disorders are also observed.

Atlantoaxial instability (AAI) denotes the instability of the joint interface between the atlas (C1) and axis (C2). The complete picture also involves instability between the occiput and the atlas; the clinical phenomenon is better described as craniovertebral instability. Hypotonia and ligamentous laxity predispose to slippage, or subluxation, of these two joint articulations. With neck flexion or extension, C1 can slip or sublux over C2, allowing the C2 odontoid process (dens) to protrude and impinge on the spinal cord and even brainstem. Of note, AAI is not exclusive to DS and can occur in other congenital, acquired, and

TABLE 31.12 Comorbid Conditions Associated With Down Syndrome

Neuropsychiatric system	• Intellectual disability • Autism • Attention deficit hyperactive disorder • Behavioral disorders • Depression • Early onset dementia • Alzheimer disease
Central nervous system	• Epilepsy • Hypotonia
Ocular system	• Strabismus • Nystagmus • Refractive errors
Cardiovascular system	• Congenital heart disease Complete atrioventricular septal defect (37%) Ventricular septal defect (31%) ASD (15%) Partial atrioventricular septal defect (6%) Tetralogy of Fallot (5%) Patent ductus arteriosus (4%) Miscellaneous/mixed (2%) • Valvular abnormalities (most common: mitral valve prolapse, aortic and mitral insufficiency) • Pulmonary hypertension
Gastrointestinal system	• Duodenal stenosis or atresia • Esophageal atresia +/− tracheal esophageal fistula • Imperforate anus • Hirschsprung disease • Celiac disease • Gastroesophageal reflux
Endocrine system/growth	• Low birth weight • Infancy: failure to thrive; childhood and beyond: obesity • Short stature • Hypothyroidism and hyperthyroidism • Diabetes mellitus
Hematologic system	• Acute lymphoblastic leukemia • Transient myeloproliferative disorder
Respiratory system	• Obstructive sleep apnea • Upper and lower airway abnormalities • Asthma • Chronic aspiration • Parenchymal lung disease
Musculoskeletal system	• Atlantoaxial instability and subluxation • Mono-, oligo-, and polyarticular arthropathy • Joint/ligamentous laxity
Renal-urologic system	• Renal anomalies • Hypospadias • Cryptorchidism • Testicular cancer
Immune system	• Intrinsic immunodeficiency
Integumentary system	• Hyperkeratosis • Seborrheic dermatitis and folliculitis • Fissured tongue

traumatic conditions. Clinical findings can range from neck pain to sensorimotor deficits of the upper and/or lower extremities, and bowel and bladder dysfunction. Especially in preverbal or verbally delayed children, findings of torticollis, easy fatiguability with activity, deterioration of motor skills, and gait abnormalities require evaluation for AAI. Asymptomatic AAI is reported to occur in 10% to 30% of patients, while symptomatic AAI occurs in 1% or less of the DS population. Urgent surgical evaluation is necessary for those with symptomatic AAI, particularly if bowel/bladder dysfunction and/or paresis are present. The American Academy of Pediatrics does *not* recommend routine radiographic screening for AAI in asymptomatic patients. However, the Special Olympics Committee requires all individuals with DS to be screened with a lateral neck radiograph prior to participation in their competitive programs.

Management of Anesthesia

A history of neck pain, head tilt, and abnormal gait suggests AAI, though the majority are asymptomatic. Older infants and toddlers can be observed for head control, passive neck range of motion, and upper motor neuron symptomatology (spasticity, hyperreflexia, clonus). Regardless, neck manipulation should be kept to a minimum for all patients with DS.

Macroglossia compounded by low tone and pharyngeal tissue redundancy predispose these children to rapid airway obstruction with sedation and upon induction of anesthesia. The high incidence of OSA necessitates careful monitoring after premedication, judicious use of opioids, and close observation for postanesthetic respiratory difficulties.

Children with DS also have a higher risk of developing postintubation croup due to their smaller subglottic tracheal caliber. A smaller ETT size than that predicted for age should be used. As in all children, an air leak at less than 25 cm H_2O must be demonstrated.

Significant bradycardia with inhaled sevoflurane induction occurs in up to 50% of children with DS even in the absence of structural heart disease. It is speculated that these children have ultrastructural myocardial defects that lead to conduction abnormalities. Increased sensitivity to atropine is occasionally seen, manifesting as mydriasis and profound tachycardia.

The nature of coexisting congenital heart disease must be defined, particularly shunt flow direction(s), shunt fractions, outflow obstruction, and ventricular function, to guide proper intraoperative management. Children with DS undergoing cardiac surgery experience increased perioperative morbidity and mortality compared to their nonsyndromic counterparts.

MALIGNANT HYPERTHERMIA

Malignant hyperthermia (MH) is a potentially lethal genetic disorder of skeletal muscle hypermetabolism triggered by exposure to halogenated anesthetics and succinylcholine. It is primarily inherited as an autosomal dominant disorder; penetrance and expression are extremely variable. Overall incidence is estimated to be 1:10,000 in children, much higher than that reported for adults (up to 1:250,000). Children account for 17% to 20% of all MH cases.

Disorders with known MH susceptibility (MHS) are King-Denborough syndrome, central core myopathy (*RYR1* mutation), multiminicore disease, Native American myopathy (*STAC3* mutation), and other myopathies linked to *RYR1*, *CACNA1S*, and *STAC3* mutations. Mitochondrial disorders and muscular dystrophies are *not* associated with increased MHS.

Pathogenesis

The *RYR1* gene (chromosome 19q13.1) is responsible for the majority of cases, with over 30 different MH-related mutations documented to date. Others include the *CACNA1S* gene (chromosome 1q32, encodes voltage-dependent, L-type calcium channel or dihydropyridine receptor) and the *STAC3* gene (Stac3 protein, essential for proper muscle contraction).

Muscle contraction depends on a rise in intracellular calcium (Ca^{++}). Upon membrane depolarization, Ca^{++} is released from the sarcoplasmic reticulum into the sarcoplasm via the dihydropyridine and ryanodine receptors, which are voltage-gated ion channels. Calcium interacts with troponin to allow cross-bridging between actin and myosin for muscle contraction to occur. MH-related *RYR1* gene mutations decrease receptor threshold for Ca^{++} release. Affected RYR1 receptors are also resistant to negative feedback (increased Ca^{++} and magnesium levels) that normally decrease Ca^{++} conductance. Triggering agents cause an exaggerated Ca^{++} release at smaller degrees of membrane depolarization. Adenosine triphosphate (ATP) is consumed in all steps of intracellular Ca^{++} handling. The result is an intensely hypermetabolic process that leads to metabolic and respiratory acidosis, hyperkalemia, rhabdomyolysis, and hyperthermia.

Signs and Symptoms

MH is a vastly heterogeneous disorder. Some individuals tolerate multiple triggering anesthetics without apparent problems, while others demonstrate fulminant MH to only traces of volatile agents. Time of onset is variable, ranging from immediate to hours after exposure to triggers. Early clinical signs and symptoms of MH are nonspecific and reflect a hypermetabolic state. Other disorders of hypermetabolism should be considered in the differential diagnosis (Table 31.13).

Early clinical signs include sinus tachycardia, tachypnea (if breathing is spontaneous), hypercarbia (typically uncorrectable with increased ventilation), and masseter muscle spasm (Table 31.14). Progressive hyperkalemia can lead to cardiac dysrhythmias. Core temperature can rise within 15 minutes of exposure to triggering agents. However, overt hyperthermia is usually a late sign; it is an early finding in less than 10% of MH cases.

Laboratory analysis reveals a mixed respiratory/metabolic acidosis (lactic acidosis), arterial hypoxemia, and hyperkalemia. Masseter muscle spasm can progress to whole body rigidity with rhabdomyolysis. At this stage, the patient will typically have cola-colored urine along with myoglobinuria and markedly increased serum creatinine kinase (CK; typically >20,000 U/L). Exhaustion of the body's capacity to meet the exaggerated oxidative demand ultimately leads to multiorgan failure and cardiovascular collapse.

TABLE 31.13 Differential Diagnosis of Malignant Hyperthermia

Diagnosis	Distinguishing Traits
Hyperthyroidism	Characteristic symptoms and physical findings often present; blood gas abnormalities increase gradually
Sepsis	Hypercarbia is unusual; severe lactic acidosis may be present
Pheochromocytoma	Similar to MH except marked blood pressure swings
Metastatic carcinoid	Same as pheochromocytoma
Cocaine intoxication	Fever, rigidity, rhabdomyolysis similar to NMS
Heat stroke	Similar to MH except patient is outside the operating room
MMR	May progress to MH, ± total body spasm
NMS	Similar to MH, usually associated with use of antidepressants

MH, Malignant hyperthermia; *MMR*, masseter muscle rigidity; *NMS*, neuroleptic malignant syndrome.
Adapted from Bissonnette B, Ryan JF. Temperature regulation: normal and abnormal [malignant hyperthermia]. In: Cote CJ, Tocres ID, Goudsouzian NG, et al., eds. *A Practice of Anesthesia for Infants and Children*. ed 3. Philadelphia, PA: Saunders; 2001:621.

TABLE 31.14 Clinical Features of Malignant Hyperthermia

Early	Late
Hypercarbia	Hyperthermia (unusual as early sign)
Tachypnea (if respiration is spontaneous)	Cola-colored urine/rhabdomyolysis
Sinus tachycardia	Elevated CPK
Masseter muscle spasm	Cardiac dysrhythmia (VT/VF)
Generalized muscular rigidity	Acute renal failure
Peaked T waves	Cardiovascular collapse
Metabolic and respiratory acidosis	Disseminated intravascular coagulation

CPK, Creatine phosphokinase; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia.

Definitive diagnosis requires muscle biopsy for the caffeine-halothane contracture test (CHCT; sensitivity 97%, sensitivity 78%). Positive CHCT results should prompt further genetic testing to better guide selection of high-risk family members for susceptibility testing. Early recognition and expeditious treatment are essential. Treatment with dantrolene and improved supportive measures have decreased overall mortality to less than 5%.

Anesthesia-Induced Rhabdomyolysis

Patients with dystrophinopathies (e.g., Duchenne and Becker muscular dystrophy) do not have increased MHS as it was long believed. These patients are susceptible to anesthesia-induced rhabdomyolysis (AIR), which is a distinct entity from MH. The incidence is unknown and not all patients with dystrophinopathies have AIR susceptibility; clinical reactivity is variable. The treatment for AIR is different, although it shares a similar clinical picture with and has the same triggering agents as MH. Acute rhabdomyolysis, which can quickly deteriorate into hyperkalemic cardiac arrest, is typically the first manifestation of AIR without preceding symptoms of hypermetabolism as seen in MH. Treatment is aimed at membrane stabilizing (for both skeletal muscle and the myocardium) with intravenous calcium along with supportive measures. Dantrolene is of no benefit. A nontriggering anesthetic technique is recommended for all patients with dystrophinopathies given the lethal potential of AIR.

Treatment

Dantrolene sodium is the only available disease-targeted treatment for MH, along with supportive measures (Table 31.15). It is thought to inhibit Ca^{++} conductance through ryanodine receptor channels and block external Ca^{++} entry into the sarcoplasm that normally occurs with membrane depolarization, thereby limiting further rise in intracellular Ca^{++} levels. Side

TABLE 31.15 Treatment of Malignant Hyperthermia

- Call for help, get MH cart
- Notify team and stop procedure, if possible
- Stop volatile anesthetic, succinylcholine immediately
- Attach charcoal filter and turn O_2 flow to 10 L/min
- Hyperventilate patient to reduce $ETCO_2$
- Give dantrolene 2.5 mg/kg IV, rapidly, through large-bore IV if possible, every 5 min until symptoms resolve. May need up to 10 mg/kg (if no response at this dose, consider alternative diagnoses)

Assign dedicated person to mix dantrolene.

  - Dantrium/Revonto: 20 mg/vial is mixed with 60 mL sterile water
  - Ryanodex: 250 mg is mixed with 5 mL sterile water

- Transition to nontriggering anesthetic
- Give sodium bicarbonate 1–2 mEq/kg IV for suspected metabolic acidosis
- Cool patient:
  - Apply ice externally to axilla, groin, and around head
  - Infuse cold saline intravenously
  - NG and open body cavity lavage with cold water
  - Stop cooling when temperature <38°C
- Hyperkalemia treatment:
  - Calcium gluconate 30 mg/kg IV or calcium chloride 10 mg/kg IV
  - Sodium bicarbonate 1–2 mEq/kg IV
  - Regular insulin 0.1 units/kg IV (MAX 10 units) and dextrose 0.5–1 g/kg IV
- VT or Vfib treatment: Do NOT use calcium channel blocker; give amiodarone 5 mg/kg
- Labs: blood gas, electrolytes, serum CK, serum/urine myoglobin, coagulation profile
- Place urinary catheter, maintain UO >2 mL/kg/hr (hydration, mannitol 0.25 g/kg IV, furosemide 0.5–1 mg/kg IV)
- If cardiac arrest occurs, begin CPR and consider ECMO
- If no response after 10 mg/kg of dantrolene, consider other Dx: sepsis, NMS, serotonin syndrome, thyrotoxicosis, myopathy, pheochromocytoma
- Call ICU for continued care. For postacute management, see http://www.mhaus.org

CK, Creatine kinase; *CPR*, cardiopulmonary resuscitation; *ECMO*, extracorporeal membrane oxygenation; *$ETCO_2$*, end-tidal carbon dioxide; *ICU*, intensive care unit; *IV*, intravenous; *MH*, malignant hyperthermia; *NMS*, neuroleptic malignant syndrome; *Vfib*, ventricular fibrillation; *UO*, urine output; *VT*, ventricular tachycardia.
From Pedi Crisis Critical Events Checklists. Society for Pediatric Anesthesia. Accessed Jan 2021. Available at: https://pedsanesthesia.org/wp-content/uploads/2020/11/SPAPediCrisisChecklistsNov2020.pdf

effects of dantrolene include muscle weakness, vein irritation, nausea, blurry vision, and diarrhea. Calcium channel blocker is contraindicated as it can worsen hyperkalemia.

Following initial management, the patient should have continued care in an ICU setting. Recrudescence occurs in 20% to 25% of patients; muscular body type, hyperthermia, and increased latency between exposure and onset are risk factors. Recrudescence usually occurs within the first few hours after the initial episode; late presentations (up to 36 hours after the initial episode) have been reported. As such, dantrolene treatment should continue (1 mg/kg every 6 hours) for 48 to 72 hours after the last observed sign of MH. Development of disseminated intravascular coagulation is an ominous sign and a common finding in fatal MH.

All patients with clinical or suspected MH should undergo CHCT. A sample size of least 2 g of deep muscle (vastus medialis or vastus lateralis) must be harvested for satisfactory testing. CHCT is generally not performed in children less than 5 years of age due to their body size. Immediate family members should be counseled and referred for muscle and genetic testing as needed. All cases of MH and significant masseter spasm should be reported to the North American Malignant Hyperthermia Registry (888-274-7899).

Management of Anesthesia

Identification of susceptible patients based on personal and family history is the most important first step. Preoperative serum creatine kinase (CK) level is not recommended as it is generally not predictive. Dantrolene prophylaxis is not indicated or recommended. However, dantrolene and other resuscitative drugs must be immediately available.

Topical local anesthetics should be applied to ease awake placement of an IV catheter. Needle-phobic children should receive adequate preoperative anxiolysis. Use of nitrous oxide (N_2O) to supplement anxiolysis can facilitate IV catheter placement.

If available, an MH-dedicated anesthesia machine sans volatile anesthetic exposure should be used. Otherwise, the anesthesia machine must be flushed with high-flow oxygen for the recommended length of time (up to 100 minutes) specific to each model. Activated charcoal filters can be placed on the inspiratory and expiratory ports of the anesthesia machine to remove volatile agents; these are effective in keeping volatile gas concentrations below 5 ppm for up to 12 hours with fresh gas flows of at least 3 L/min. Prior to their use, the anesthesia machine still requires flushing with high fresh gas flows (>10 L/min) for 90 seconds. Activated charcoal filters do not scavenge nitrous oxide. External parts such as the breathing circuit, ventilation bag, and CO_2 absorber should be changed and vaporizers removed.

Maintenance of anesthesia is achieved with nontriggering agents (Table 31.16), typically with IV anesthetics, with or without N_2O. Standard ASA monitoring (pulse oximetry, end-tidal carbon dioxide [$ETCO_2$], ECG, noninvasive blood pressure [NIBP], and core temperature) usually suffices. Even in the absence of clinical symptoms, all patients must be monitored for at least 1 hour (preferably 4 hours) postoperatively. Same-day discharge to home is acceptable if the usual discharge criteria are met. These anesthetic considerations also apply to patients who present for muscle biopsy for CHCT.

TABLE 31.16 Nontriggering Drugs for Malignant Hyperthermia

Barbiturates
Propofol
Etomidate
Benzodiazepines
Opioids
Droperidol
Nitrous oxide
Nondepolarizing muscle relaxants
Anticholinesterases
Anticholinergics
Sympathomimetics
Local anesthetics (esters and amides)
α_2 agonists (clonidine, dexmedetomidine)

KEY POINTS

- When caring for pediatric patients—from newborns to teenagers—consideration of the physical, developmental, psychological, and physiologic implications specific to each age group is essential. Neonates, in particular preterm newborns, are the most different in terms of anatomy and physiology.
- Numerous animal studies corroborate evidence of anesthetic-induced neurotoxicity, and similar human studies are lacking. A black box warning was issued for anesthetic agents in 2018; however, no change in the practice of pediatric anesthesiology is recommended, particularly for lifesaving and/or emergent and urgent procedures requiring anesthesia. Anesthesiologists and surgeons should consider delaying elective surgeries until after 3 years of age.
- The pediatric airway is characterized by a relatively larger head and tongue, a more cephalad larynx, a shorter cord-to-carina distance, and the cricoid cartilage being the narrowest part of the airway.
- Children have a higher resting O_2 consumption rate than adults. Their functional residual capacity is similar to that in adults on a per kilogram basis. Pulmonary and chest wall compliance is high. Anatomic differences predispose to early upper airway obstruction. All these predispose to rapid onset of hypoxemia upon induction of general anesthesia.
- Pulmonary vascular resistance is high at birth and decreases to adult levels over days to months, but the pulmonary vasculature remains reactive for a longer period of time. The ductus arteriosus and foramen ovale are only functionally closed at birth and may reopen with high PVR, hypercarbia, and hypoxemia, with resultant reversion to fetal circulation patterns.

- The immature myocardium of neonates and infants has limited contractile and elastic reserves, resulting in a relatively fixed stroke volume. Cardiac output and systemic blood pressure are dependent on heart rate.
- Physiologic anemia occurs between 2 and 3 months of age (nadir Hct 29–31%).
- Owing to risk of apnea of prematurity and postanesthetic apnea, preterm infants less than 50 to 60 weeks of PCA should be observed overnight for apnea monitoring.
- The MAC for sevoflurane varies with age: newborn to 6 months, 3.3%; 6 months to 12 years, 2.5%. The MAC-awake for sevoflurane in children is 0.2 to 0.3 of MAC.
- Children with Down syndrome may have atlantoaxial instability (asymptomatic in 10–30%, symptomatic in 1%); cervical manipulation should be kept to a minimum. Severe bradycardia is seen in up to 50% of these children with sevoflurane induction.
- Preservation of spontaneous respiration is often key to successful airway management of children with airway disease and craniofacial abnormalities. Well-considered use of neuromuscular blockade is helpful to prevent reactivity. Close communication between surgeon and anesthesiologist is also essential. Awake intubation is rarely necessary and can be detrimental.
- Confirming an air leak at less than 25 cm H_2O after intubation should be routine to minimize risk of tracheal mucosal injury. When an appropriately sized cuffed endotracheal tube is used, cuff pressure should be kept at less than 25 cm H_2O.
- Congenital anomalies can exist as isolated findings or as part of a syndrome. Additional congenital abnormalities such as congenital heart disease and renal defects are commonly seen. A succinct but comprehensive preoperative assessment of all organ systems is usually in order.
- Antifibrinolytics (aminocaproic acid, tranexamic acid) should be considered in children undergoing surgery with expected large blood loss, such as craniosynostosis, posterior spinal fusion, and open hip procedures.
- Anthracycline (e.g., doxorubicin) is used in chemotherapeutic protocols for numerous childhood malignancies. Preoperative cardiac evaluation should be performed to assess potential anthracycline cardiomyopathy.
- CNS diseases may be accompanied by increased ICP, sensorimotor deficits, endocrine disturbance, and brainstem dysfunction. Signs and symptoms in infants may be nonspecific. Intraoperative monitoring for diabetes insipidus is especially important for suprasellar lesions.
- MH and anesthesia-induced rhabdomyolysis (AIR) are distinct clinical entities that share similar clinical manifestations. Dantrolene is effective in the treatment of MH but not AIR. Only central core disease, King-Denborough syndrome, multiminicore disease, Native American myopathy, and other myopathies linked to *RYR1*, *CACNA1S*, and *STAC3* mutations have increased MH susceptibility. Mitochondrial disorders and muscular dystrophies are not associated with increased MH susceptibility.

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32

Pregnancy-Associated Diseases

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OUTLINE

It is not entirely clear how a chapter on pregnancy fits into a book titled *Anesthesia and Coexisting Disease*. Pregnancy is not a disease, but a normal physiologic condition, usually associated with and dependent on relatively good health. For most so-called coexisting diseases in this book, the clinical situation being analyzed and discussed is that of a patient needing surgery, usually or often unrelated to the disease under discussion, where the disease process affects anesthesia and perioperative management. In contrast, pregnant women predominantly receive care from anesthesiologists for procedures and events related to the pregnancy and undergo procedures specific to pregnancy (e.g., labor analgesia and cesarean delivery). Anesthesia for these pregnancy-related events is extensively discussed in books and chapters specifically about obstetric anesthesia and cannot possibly be treated properly in a single chapter in this book. Many coexisting medical conditions and comorbidities require only minor adjustments to obstetric anesthesia care or require the same assessments and alterations that the anesthesiologist would consider for the nonpregnant patient. In this chapter we will begin with the assumption that the reader is familiar with routine obstetric anesthesia procedures and care, then we will focus on anesthesia care of the pregnant woman in unusual clinical situations when the woman's other medical conditions add significant complexity to obstetric anesthesia care rather than on pregnancy complications or fetal issues. These areas include the care of the pregnant woman with hypertensive diseases of pregnancy (gestational hypertension and preeclampsia/eclampsia), significant cardiovascular disease, and obesity, the most common coexisting condition in pregnancy. Two areas where pregnancy (and the postpartum period) does function more as a coexisting disease are the pregnant woman who requires surgery during pregnancy but unrelated to the pregnancy itself and the breastfeeding woman who needs an anesthetic. These two areas will be included in our discussion.

PHYSIOLOGIC CHANGES ASSOCIATED WITH PREGNANCY (TABLE 32.1)

Cardiovascular System

Any anesthesiologist caring for the pregnant woman in any clinical scenario must understand the physiologic changes of pregnancy that impact anesthesia care. Most changes in the cardiovascular system are caused by the hormonal changes of early pregnancy, then later too by growth and anatomic changes of late pregnancy. Higher progesterone levels result in increased production of nitric oxide and prostacyclin, which together with a decreased response to norepinephrine and angiotensin result in relative vasodilation. Increased concentrations of relaxin lead to renal artery dilation and, through reduction in aortic stiffness, dilation of the proximal aorta. Systemic vascular resistance decreases in early pregnancy with a decrease of ~35% at 20 weeks, presumably as a result of alteration in receptor number and function as well as vascular smooth muscle changes induced by progesterone. Systemic vascular resistance slowly rises later but remains ~20% lower at term than the prepregnancy level. Despite lower vascular tone/resistance, central venous pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure remain stable throughout pregnancy due to increased vascular volume. The decrease in systemic vascular resistance during the initial weeks after conception causes a compensatory elevation of cardiac output

TABLE 32.1 Physiologic Changes Accompanying Pregnancy

Parameter	Change From Nonpregnant Value (%)
Cardiovascular/Circulatory	
Intravascular fluid volume	h 35–40
Plasma volume	h 45–50
Erythrocyte volume	h 20–25
Hemoglobin/hematocrit	g15
Cardiac output	h 40
Stroke volume	h 20
Heart rate	h 10–15
Systolic blood pressure	No change or small g
Systemic vascular resistance	g 15
Diastolic blood pressure	g 0–15
Central venous pressure	No change
Femoral venous pressure	h 15
Minute ventilation	h 50
Respiratory	
Tidal volume	h 40
Respiratory rate	h 10
Pao_2	h 10 mm Hg
$Paco_2$	g 10 mm Hg
Arterial pH	No change
Inspiratory reserve volume	h 5
Tidal volume	h 45
Expiratory reserve volume	g 25–30
Residual volume	g 0–10
Inspiratory capacity	115
Functional residual capacity	g 10–20
Vital capacity	No change
Total lung capacity	g 0–5
Minute ventilation	h 30
Oxygen consumption	h 20
Renal	
Renal blood flow and glomerular filtration rate	h 30–50
Creatinine concentration	g 20–50

Values in percentage unless otherwise indicated. The above changes are estimates and averages and may not occur or apply in women with significant alterations in cardiovascular or respiratory status or reserve, or complications of pregnancy.

(initially resulting from an increase in heart rate) and an increase in renin activity. Increased renin activity results in retention of sodium and, by osmotic gradient, water. About 1000 mEq of sodium will be retained by term, which results in retention of water. Plasma volume begins to rise in the fourth week of pregnancy and reaches a maximum (30–50% increase) at 28 to 34 weeks. The increase in plasma volume, combined with a 20% to 30% increase in total red blood cell mass, results in significantly elevated total blood volume, which reaches ~100 mL/kg at term. Cardiac output rises in parallel with plasma volume, increasing by 15% at 8 weeks of gestation and reaching a maximum increase of 50% by 28 to 32 weeks. Plasma volume and cardiac output remain stable from ~32 weeks until labor begins. In labor, cardiac output rises as a result of sympathetic stimulation (pain and stress) and autotransfusion (the displacement of blood from the contracting uterus into the circulation). Compared with prelabor output, cardiac output is increased by 20% during the first stage and 50% during the second stage of labor. Just after delivery of the placenta (the end of the third stage of labor), cardiac output is elevated 80% above prelabor levels, which corresponds to a 170% increase relative to the prepregnancy level. Cardiac output falls to the prelabor level in 24 to 48 hours and returns to the prepregnancy level in the next 12 to 24 weeks. Twin pregnancy results in a 20% greater increase in cardiac output than singleton gestation.

Pregnancy affects echocardiographic and electrocardiographic (ECG) findings so that several findings that would be interpreted as abnormal and perhaps concerning are normal findings in pregnancy. These include an increase in left ventricular mass by 6% and right ventricular mass by 15% to 20% by term. Increases in the size and dilation of the cardiac chambers result in a mild degree of insufficiency of all valves except the aortic; it is, however, *not* normal to see aortic insufficiency at any stage of pregnancy. Enlargement of the heart and cephalic displacement of the diaphragm cause a horizontal shift and rotation of the heart, which results in changes in the cardiac axis on ECG. It is *not* abnormal to see a deep S wave in lead I and a large Q wave with negative T waves in leads III and aVF. These changes resolve after pregnancy in the normal heart.

At term the uterus can and usually does completely compress the inferior vena cava while parturients are in the supine position. Twin and singleton pregnancies cause a similar degree of obstruction. Recent magnetic resonance imaging (MRI) studies suggest that this compression is often not relieved by the usual clinical recommendation of 15-degree tilt, but rather requires 30 to 45 degrees of displacement/tilt. The importance of this compression for most pregnant women is questionable, and they (and their fetuses) show no symptoms of this compression, even during anesthesia, as alternate pathways for venous blood return have developed during the pregnancy. Compression of the inferior vena cava by the gravid uterus results in supine hypotension syndrome in a subset of pregnant women, which manifests with a short period of tachycardia followed by bradycardia and profound hypotension. It is not clear why some women have significant symptoms while many/most do not. Contrary to decades of use of the term *aortocaval compression*, implying aortic obstruction in addition to caval compression, most contemporary evidence suggests that the aorta is not affected by the gravid uterus.

Respiratory System

The respiratory system is also altered by the hormonal and anatomic changes of pregnancy. Increased activity of relaxin results in relaxation of the ligaments of the rib cage, which results in displacement of the ribs to a more horizontal position. This leads to upward displacement of the diaphragm early in pregnancy even before the gravid uterus shifts the abdominal contents. The vertical dimension of the chest decreases by about 4 cm, but the diameter increases by about 5 cm, significantly increasing the volume of the lungs available for gas exchange during normal spontaneous respiration. Tidal volume increases up to 40% by term. Increased activity of progesterone, a potent respiratory stimulant, leads to an increase in tidal volume and

respiratory rate so that minute ventilation is increased by 50% at term. Chronic hyperventilation driven by hormonal changes results in respiratory alkalosis with a typical $Paco_2$ in the range of 28 to 32 mm Hg. Secondary to the decline in $Paco_2$, Pao_2 rises slightly, in the range of 104 to 108 mm Hg, during pregnancy. These changes increase the gradient between mother and fetus and improve maternal-fetal gas exchange. Clinically, the implication is that a $Paco_2$ in the normal range could indicate significant hypoventilation in a pregnant woman.

Decrease in the vertical size of the chest secondary to elevation of the diaphragm leads to a 25% decrease in expiratory reserve volume and a 15% decrease in residual volume, which results in a 20% decrease in functional residual capacity. A 20% increase in oxygen consumption caused by an elevated basal metabolic rate, combined with the decrease in functional residual capacity, produces more rapid desaturation during periods of apnea. In a fully preoxygenated healthy nonpregnant patient, desaturation from 100% to lower than 90% occurs in approximately 9 minutes. In a healthy patient at term, desaturation occurs in only 3 to 4 minutes, and in a morbidly obese pregnant patient desaturation can occur in a minute or less.

Edema and hyperemia of the oropharyngeal mucosa, glandular hyperactivity, and capillary engorgement secondary to elevated activity of estrogen, progesterone, and relaxin result in nasal stiffness, epistaxis, and upper airway narrowing. Therefore the rates of difficult and failed intubation in pregnant women are increased—historically quoted as ~3.3% and 0.4%, respectively—which are more than eight times higher than in nonpregnant patients, although recent reports suggest that these numbers may overestimate the failure rate in contemporary practice (see later discussion). When providing general anesthesia to a pregnant woman for any procedure, the anesthesiologist is thus faced with a potentially difficult airway in a patient who will undergo desaturation more rapidly than a nonpregnant patient. This is one of the factors contributing to a higher mortality rate among parturient women who undergo general anesthesia than among those who undergo regional anesthesia. The increased mortality associated with general anesthesia compared to neuraxial anesthesia for cesarean delivery from difficult intubation or aspiration of gastric contents (often during or due to difficult intubation) has lessened significantly in the past few decades presumably due to improved training, protocols and awareness, and more and improved devices for airway management. Over the last decade, better preparation and the use of video laryngoscopy has improved intubation success rates in pregnant women, and the availability of supraglottic airway devices has provided a rescue pathway for failed intubation.

Hematologic System

Normal pregnancy is a relatively hypercoagulable state. The activity of the majority of the coagulation factors (I, VII, VIII, IX, X, XII) and the levels of fibrinogen are increased, whereas the activity of physiologic anticoagulants is decreased. The latter includes a significant reduction in protein S activity and an acquired activated protein C resistance. This effect (i.e., reduction in anticoagulation activity) is doubled in in vitro fertilization (IVF) pregnancies. Deep vein thrombosis occurs in 1 per 1000 deliveries, which is 5.5 to 6 times higher than the rate in the general female population of childbearing age and reaches a maximum at 4 to 6 weeks postpartum. Platelet counts generally decrease moderately (10–20%) during gestation due to increased peripheral consumption or sequestration in a larger spleen or the placenta. Procoagulant changes during normal pregnancy are counterbalanced by significant activation of the fibrinolytic system during the postpartum period. Over the past few years protocols and national guidelines have been promulgated, increasing the indications for and use of thromboprophylaxis and anticoagulation in women during pregnancy and especially in the postpartum period. The recommendations regarding thromboprophylaxis around the time of labor and delivery or hospitalization for pregnancy-related complications should also be seriously considered in any pregnant woman undergoing nonobstetric surgery, as the surgical intervention is almost always a prothrombotic stimulus, and many of these women will be hospitalized or confined to bed for prolonged periods. Teleologically, the hypercoagulability of pregnancy has the evolutionary advantage of limiting hemorrhage at delivery, but the activated state of the coagulation system also has the somewhat counterintuitive effect of triggering disseminated intravascular coagulation due to rapid consumption of coagulation factors and platelets in response to a variety of stimuli, including bleeding/trauma itself or maternal absorption of gestational material, potentially leading to the development of a rapidly developing coagulopathic state.

Gastrointestinal System

Lower esophageal sphincter tone is decreased in pregnancy as a result of two factors: displacement of the stomach upward and muscle relaxation caused by the effects of progestins. Heartburn is a frequent occurrence among pregnant women. Contrary to the teachings of several generations of anesthesiologists, gastric emptying is not delayed in pregnancy as determined by multiple methods, including ultrasound examination of stomach volume and oral drug absorption studies, although it is slowed in labor.

Bile secretion is increased during pregnancy. Bile stasis is increased owing to the effect of progesterone, and together with changes in the composition of bile acids, this results in increased gallstone formation. Cholecystectomy is the second most frequent surgery during pregnancy (after appendectomy), with a reported incidence as high as 1 in 1600 pregnancies.

Endocrine System

Pregnancy is characterized by insulin resistance caused by increased activity of hormones such as progesterone, estrogen, cortisol (2.5-fold increase at term), and placental lactogen. This insulin resistance resolves rapidly after delivery. Fasting glucose levels are lower in pregnant than in nonpregnant patients because of the high glucose utilization by the fetus.

Estrogen increases the level of thyroxin-binding globulin, which results in an elevation of total triiodothyronine (T_3) and thyroxine (T_4) levels, but levels of free T_3 and T_4 remain stable.

Other Changes

Increased levels of progesterone and endorphins may elevate the pain threshold. Cerebrospinal fluid volume is decreased during pregnancy, but intracranial pressure remains stable. Anesthetic requirements for both local anesthetics and general anesthetics are somewhat decreased.

Renal blood flow is increased in pregnancy, due mostly to increased cardiac output. Glomerular filtration rate increases by 50% at 12 weeks of gestation, which results in a decrease in blood urea nitrogen (BUN) and creatinine concentrations. The most important clinical implication of this is that normal BUN and creatinine levels may indicate renal dysfunction (e.g., in preeclampsia).

NONOBSTETRIC SURGERY DURING PREGNANCY

This section of the chapter fits most closely within the title of this book, in that pregnancy is truly the "coexisting disease" in a woman who needs surgery and anesthesia while she is pregnant. Of all pregnant women in the United States, 1% to 2% will undergo surgery unrelated to their pregnancy (~75,000 procedures requiring anesthesia per year). The most frequent nonobstetric procedures are appendectomy, cholecystectomy, breast biopsy, and surgery required because of trauma.

Generally, elective surgery should be delayed until the patient is no longer pregnant and has returned to the nonpregnant physiologic state. Depending on how elective the procedure is, surgery is sometimes delayed until after the woman has stopped breastfeeding, but this is usually not necessary (see Anesthesia in the Breastfeeding Woman, later). Procedures that can be scheduled with some flexibility but that cannot be delayed until after delivery are best performed in the second trimester. In theory, this lessens any risk of teratogenicity with first-trimester medication administration and preterm labor, which is thought to be a greater risk in the third trimester, although both of these assumptions and recommendations have come under some scrutiny and criticism recently, and many argue that delaying indicated surgery might be the larger risk in many clinical circumstances (Fig 32.1).

The pregnancy-specific issues involved in nonobstetric surgery during pregnancy involve taking into account pregnancy-induced anatomic, physiologic, pharmacodynamic, and pharmacokinetic alterations, minimizing fetal drug exposure when possible and monitoring for and prevention of preterm labor, a particular risk with intrabdominal surgery.

Little outcome data exist to guide anesthetic choice, but when possible most anesthesiologists (and often patients) prefer a regional anesthetic (neuraxial or peripheral nerve block) with minimal sedation, as this would appear to be the best way to minimize fetal drug exposure. While logic and reasonable caution would suggest minimizing exposure to drugs having significant effects on the human brain, no commonly used anesthetic agents have been shown to cause teratogenicity or other significant effect on the fetus. Most anesthetic decisions should be based on the usual anesthetic and surgical considerations as well as maternal status and safety, not on the presence of the fetus. For the most commonly performed operative procedures during pregnancy (appendectomy and cholecystectomy), general anesthesia is required, particularly since these operations are now almost always performed laparoscopically. A decade ago there was significant controversy about whether laparoscopic surgery was safe during pregnancy. There were concerns with issues of the effect of intraperitoneal pressure and potentially increased Pa_{CO_2}, but clinical experience and some animal studies have mostly put these concerns to rest, and laparoscopic

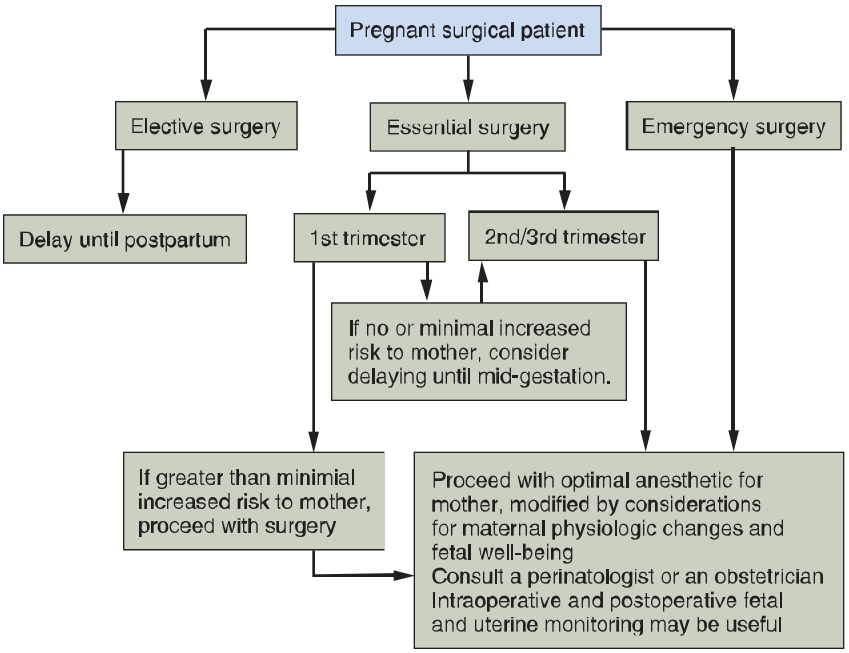

Fig. 32.1 Recommendations for management of pregnant women undergoing surgery. (Adapted from Rosen MA. Management of anesthesia for the pregnant surgical patient. *Anesthesiology*. 1999;91:1159–1163.)

appendectomies and cholecystectomies have become the standard approach, even for pregnant women.

Airway management during surgery depends on gestational age. By late second trimester, most anesthesiologists would opt for rapid-sequence induction and intubation to reduce the risk of aspiration, as is standard for cesarean delivery under general anesthesia. Earlier in gestation, before ~20 weeks, controversy exists as to the level and nature of this risk, and the need for rapid-sequence induction or intubation will depend on the specific nature of the patient and operative procedure.

Teratogenicity may occur at any stage of gestation. However, most organogenesis occurs in the first trimester. Although many commonly used anesthetics are teratogenic at high dosages in animals, no studies or data support teratogenic effects of anesthetic or sedative medications in humans at the dosages and time periods used for anesthesia care. There was literature in the 1960s suggesting a link between chronic benzodiazepine and other sedative use and fetal/neonatal cleft lip and palate, but even this issue of chronic exposure has been mostly refuted. There is some evidence of a link between maternal high-dose diazepam treatment and intrauterine growth restriction, but single or limited doses of benzodiazepines are almost certainly safe when used in the usual manner for perioperative anxiety. That being said, it is common to attempt to avoid these medications in pregnancy due to concerns about effects on the fetal brain and the history of controversy about their use.

Nitrous oxide has been suggested to be teratogenic in animals when administered for prolonged periods (1–2 days); the concern is biologically plausible given its effect on DNA synthesis through inhibition of methionine synthetase. As with other purported effects of anesthetics, however, it has been difficult to document clinical effects in humans. Teratogenesis has been seen in animals only under conditions (long, repeated exposure) that are not likely to be reproduced in clinical care or relevant to single exposure perioperatively. Nitrous oxide is of course widely used for labor analgesia, so fetal exposure near and at term is common without generating too much concern from either clinicians or patients, although actual data on fetal/neonatal safety are surprisingly limited. Recent studies suggest that volatile anesthetics stimulate neuronal apoptosis in rats, but it is not obvious whether these data can be extrapolated to humans. Widespread neuronal apoptosis is associated with memory and learning deficits in laboratory animals, but again this has not been shown in humans.

Propofol and ketamine are all safe intravenous (IV) induction agents. Induction doses for these medications are unchanged in pregnancy. The choice of induction agent is usually based on provider preference and the clinical status of the patient (e.g., presence of dehydration, valvular heart disease, dysrhythmia, hypertension, or preeclampsia). None of these agents has been clearly shown to be teratogenic or have adverse effects on human brain development. Thiopental is no longer available in the United States but is also an accepted induction agent during pregnancy.

In the past decade or so there has been increasing concern in the pediatric anesthesia arena about the possible negative effects of anesthetics on behavior and learning in children, especially upon repeat or long exposure. These concerns could also be relevant to in utero exposure. While studies in young animals show a variety of behavioral and cellular neurotoxic effects of a variety of drugs and of anesthetic exposure in general, the results from human clinical studies and reviews of large databases of pediatric anesthetics have not generally shown much effect. A detailed discussion of this complex issue that is under intense investigation around the world is beyond the scope of this chapter, but the available evidence would not support any recommendation to withhold anesthesia from a pregnant woman who needs it on the basis of concern about drug effects on the fetus.

Pregnant patients are more sensitive to the action of nondepolarizing muscle relaxants but may have increased clearance of both these medications, so dosing of these medications may need to be more frequent and based on neuromuscular monitoring. Succinylcholine dose is unchanged in pregnancy; its volume of distribution is increased, but systemic pseudocholinesterase activity is decreased, resulting in increased variability in duration of action, but this is unlikely to be of any clinical significance. Muscle relaxant reversal in pregnancy involves a few unique issues. The use of neostigmine is unproblematic, but the vagolytic medication given to prevent bradycardia and other effects requires some thought. Glycopyrrolate does not cross the placenta, but neostigmine, although also a quaternary amine, does appear to cause bradycardia in some fetuses; thus atropine, which does cross the placenta, is the recommended vagolytic adjuvant in pregnancy. Suggamadex has not been approved for use in pregnancy, as very few drugs have been, but with suggamadex there is reason to consider avoiding it due to its known effect of binding steroid hormones, including progestins, which could have unknown effects on pregnancy. However, no deleterious effects or decreases in progesterone levels were reported after high doses in early pregnancy in rats.

After almost any surgical procedure during pregnancy, fetal heart rate should be monitored in the recovery room, intermittently for previable fetuses and continuously for the viable fetus. Uterine activity should also be monitored because contractions are most likely to occur proximate to the procedure and as the tocolytic effect of volatile anesthetics wears off. The use of tocolytic drugs (e.g., magnesium, indomethacin) has not been studied perioperatively, but they are commonly used. Opioids can be used as needed to control postoperative pain, as a short course of opioids is unlikely to have any detrimental effect on the fetus, but consideration should be given to peripheral nerve blocks or epidural analgesia when possible. Nonsteroidal antiinflammatory drugs (NSAIDs) are often avoided due to concerns about an increased miscarriage rate and premature closure of the ductus arteriosus seen in some studies of chronic use, although short-term perioperative use is probably safe particularly before the third trimester.

The statement of the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice titled "Nonobstetric Surgery During Pregnancy" recommends that an obstetric consult be obtained before surgery and that use of fetal monitoring be individualized. The only absolute recommendation in our institution's policy on surgery during pregnancy is that

every pregnant woman undergoing surgery must have an obstetrician on staff who is aware of her condition and able to consult as to the decisions regarding issues of fetal and labor monitoring, timing of surgery, and other issues that may arise perioperatively, including availability for possible emergent cesarean delivery. In consultation with the surgeon and anesthesiologist, the obstetrician can also make decisions about administration of corticosteroids to increase fetal lung maturity if preterm labor seems likely and the fetus is viable, and assess venous thromboembolism risk and recommend thromboprophylaxis, which is often indicated in pregnant women who are hospitalized.

Cardiac surgery requiring cardiopulmonary bypass (CPB) is rarely needed in pregnant women and when possible should be delayed until after pregnancy as maternal and fetal mortality after CPB are 3% to 13% and 16% to 38%, respectively. If surgery and CPB are unavoidable (aortic dissection, mechanical valve thrombus, severe valvular lesion with maternal decompensation, etc.), then the parameters shown to improve fetal outcomes are shorter CPB and aortic cross-clamp times, normothermia, higher pump flows (≥ 2.5 L/min/m^2), perfusion pressure greater than 70 mm Hg, and maintaining the hematocrit above 28%. If cardiac surgery is necessary, concomitant cesarean delivery (if fetus is viable) or staged CPB may be the preferable strategy. Fetal heart monitoring may be useful intraoperatively as fetal arrhythmias or bradycardia can be treated by improving maternal hemodynamics. If cardiac surgery is performed in pregnancy, the second trimester has the best maternal and fetal outcomes. Continuous fetal monitoring and uterine contraction monitoring for 12 to 24 hours postoperatively is recommended as uterine contractions are the most important predictor for fetal demise, and contractions can occur on rewarming.

ANESTHESIA IN THE BREASTFEEDING WOMAN

The issue concerning anesthesia for a breastfeeding woman, and what to tell her to do after the anesthetic, has been controversial for years. The concern is mostly that anesthetic drugs, when passed into breast milk and consumed by the breastfeeding infant, could be toxic or at least cause sedation or behavioral problems. Recommendations that breastfeeding women who receive anesthesia care express milk and discard it ("pump and dump"), for some period of time, often 24 hours, have been common over the past decades. With increasing understanding of the magnitude of drug transfer (very low in most cases) and with improved pharmacokinetic profiles of many anesthetics, combined with the further establishment of the benefits of breastfeeding, recommendations have changed significantly in the past few years. A strong consensus appears to have been reached that there is less of an issue than there used to appear to be, and almost all women are now advised the resume breastfeeding after surgery and anesthesia as soon as they are awake and able to breastfeed. A recent formal statement from the American Society of Anesthesiologists (ASA) and a detailed set of guidelines and recommendations from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) both state that pump and dump is unnecessary.

TABLE 32.2 Anesthesia Issues in the Breastfeeding Woman

Proven benefits of breastfeeding to women and infants
Most drugs transferred in very low quantities to breast milk
Most modern anesthetic drugs leave the woman's system or decrease in concentration very quickly (e.g., propofol, volatile anesthetic agents)
Infant consumes drugs orally; oral availability low
Limit doses of long-acting opioids and sedatives (benzodiazepines) when possible
Drugs with possible issues: tramadol, codeine, analgesic dose aspirin, sugammadex

The AAGBI document contains some of the most detailed and evidenced-based guidelines. It makes the following points: (1) Breastfeeding is of proven benefit to women and infants, (2) most drugs are transferred in very low quantities into breastmilk, (3) most anesthetic drugs leave the woman's system or decrease in concentration very quickly (e.g., propofol, volatile anesthetic agents), (4) many recommendations have erred on the side of caution with little evidence that the advice to discard breast milk for 12 or 24 hours is based on science or clinical experience, and (5) as the infant will be ingesting any of the drugs of concern orally, and oral availability of most anesthetic/analgesic/sedative medications is low, there is a built-in element of safety (Table 32.2).

There are a few drugs that are controversial and might and usually can be avoided in breastfeeding women. Tramadol and codeine are both metabolized by cytochrome CYP2D6, and this metabolism is greatly affected by the specific genetic variant present; the US Food and Drug Administration (FDA) advises against their use in breastfeeding women, although similar agencies in other countries have not taken this position. As there are many other analgesics to choose from, it would seem that avoidance of these two should not be difficult. Benzodiazepines and other long-acting sedatives should be used in limited doses, but the usual perioperative use of these medications should be not be problematic. When necessary for postoperative analgesia, opioids can and should be used, but at the lowest effective doses, and the infant should be monitored for any signs of any sedation. Sugammadex is a large molecule probably not found in any significant concentration in breast milk, but it does interfere with pharmacologic contraception so could be avoided in women relying on that form of birth control.

OBSTETRIC ANESTHESIA CARE

Because this is a chapter about pregnancy as a "coexisting disease" when anesthesia care is required, we will not go into detail on general strategies of standard obstetric anesthesia management of labor pain or operative delivery in healthy pregnant women, a subject more properly accessed in books and review articles devoted exclusively to obstetric anesthesia and analgesia. We will focus on obstetric anesthesia in women with some of the more common coexisting diseases that occur or exist during pregnancy and that make anesthesia or analgesia care more complex for the anesthesiologist.

General Principles

Ideally all patients, and especially patients with significant comorbidities, should be assessed by the anesthesiology team on admission to labor and delivery. The anesthesiology team should be aware of complex pregnant patients as early as possible (i.e., preferably before admission), but at a minimum a communications pathway and system should be established between the obstetric team and the covering anesthesia team to guarantee that the anesthesiology staff is informed when a patient is admitted and a complicated delivery is anticipated or when patient characteristics indicate increased anesthetic difficulties or risk (Table 32.3). Medical comorbidities, including cardiac disease and obesity, now account for a large percentage of maternal morbidity and mortality. Pulmonary aspiration and failed intubation previously accounted for three-fourths of all maternal deaths related to anesthesia care, but significant advances in anesthetic care over the past 20 to 30 years, including the development of videolaryngoscopy, supraglottic airways, and the adoption of airway algorithms and (probably) better training of anesthesiologists, have led to a decline in the rate of aspiration and associated morbidity. In fact, there was only one case of aspiration associated with labor and delivery in the ASA's Closed Claims Project database between 2005 and 2013. Researchers also noted that no cases of death due to aspiration were reported in the United Kingdom between 2000 and 2005, compared to 1.5 cases per 1000 during the 1940s. For patients with significant medical complications (e.g., pulmonary hypertension, severe left-sided obstructive lesions, severe cardiomyopathy, respiratory failure), consideration of transfer to a tertiary or quaternary medical center with relevant experience and facilities (e.g., maternal intensive care, cardiac surgery, extracorporeal membrane oxygenation [ECMO]) should be strongly considered.

TABLE 32.3 Factors Associated With Increased Anesthesia Risk

Morbid obesity (BMI 40)
Facial and neck edema
Extremely short stature
Airway issues
History of anesthesia complications/problems (e.g., malignant hyperthermia susceptibility, history of difficult intubation)
Significant scoliosis or history of major spine surgery
Significant cardiac, respiratory, or neurologic disease
Coagulopathy/thrombocytopenia (pathophysiologic or pharmacologic)
Severe allergy/anaphylaxis history

Neuraxial Anesthesia/Analgesia

The vast majority of pregnant women with complications of pregnancy or significant medical comorbidities who require anesthesia care will receive a neuraxial anesthetic or analgesic. The advantages of neuraxial analgesia in labor are well established and include limiting sympathetic activation, tachycardia, and hypertension, all of which can be problematic for women with limited cardiovascular, respiratory, or metabolic reserve. For labor, unless there are specific contraindications related to the comorbidities (e.g., coagulopathy, anatomic abnormalities), almost all women with significant medical issues should receive early labor analgesia, with occasional adjustments in dosage, and supportive care targeted to the specific pathophysiology. An outline of analgesic choices and strategies for labor is given in Table 32.4.

TABLE 32.4 Common Neuraxial Dosing for Labor Analgesia

Labor Spinal Dosing (Single Shot or CSE)

Local Anesthetic	Opioid (Higher Range if Opioid Alone)
Bupivacaine 2–3 mg	Fentanyl 10–25 g
Ropivacaine 2.5–3.5 mg	Sufentanil 1.5–5 g

Epidural "Test" Dose[a]

3 mL lidocaine 1.5% with epinephrine 1:200K
3 mL bupivacaine 0.25%

Epidural Loading Dose

Local Anesthetic	Opioid
10–15 mL bupivacaine 0.125%	Fentanyl 50–100 g (50 g probably enough)
10–15 mL ropivacaine 0.2%	Sufentanil 10 g

Epidural Infusion (10–15 mL/hr)

Bupivacaine 0.0625–0.125% with fentanyl 2 g/mL or sufentanil 0.2–0.5 g/mL
Ropivacaine 0.10–0.20% with fentanyl 2 g/mL or sufentanil 0.2–0.5 g/mL

PCEA Recipes

4–8 mL of infusion mixture, lockout 5–15 min, maximum 30–35 mL/hr total infusion plus boluses

PIEB Strategy (usually replace 12 mL/hr infusion with timed bolus, similar dose, plus PCEA option)

6–8 mL q30min
9–10 mL q45min
12 mL q60min

CSE, Combined spinal-epidural; PCEA, patient-controlled epidural analgesia; PIEB, programmed intermittent epidural bolus.
Note: Levobupivacaine (not available in the United States) may be substituted for bupivacaine at comparable doses.
[a]The need for an actual "test" dose to detect intravascular or intrathecal placement of a catheter has been questioned. If the individual "loading" doses given are not large enough to be dangerous and would allow detection of an improperly located catheter, a specific "test dose" can often be eliminated.

For cesarean delivery, spinal or epidural anesthesia is accepted as the preferred method for similar reasons and for the ability to avoid manipulation of the maternal airway. Spinal anesthesia is usually the default choice for elective cesarean deliveries or when no epidural catheter is already present, but epidural or combined spinal-epidural (CSE) anesthesia is indicated when the procedure may outlast a single-shot spinal (obesity, complex surgery) or when the epidural catheter is desired for postoperative analgesia. In the past it was often advised that women with severe respiratory disease receive general anesthesia for cesarean delivery to control ventilation and oxygenation and that women with significant cardiac disease also be managed with general anesthesia due to concern about blood pressure and vascular tone with neuraxial techniques. Over the past two decades it has become clear that almost all of these women can and probably should be managed with a carefully performed neuraxial anesthetic. Even patients with very severe restrictive pulmonary disease can almost always be managed with a carefully performed neuraxial anesthetic with supplemental oxygen or bilevel positive airway pressure (BIPAP) support. Women with significant cardiac compromise can also almost always be managed with an epidural or CSE with a low-dose spinal component, with aggressive monitoring and use of vasopressors (phenylephrine and/or norepinephrine) to counteract the predictable effects on vascular tone and venous return, as outlined later in Heart Disease.

HYPERTENSIVE DISORDERS OF PREGNANCY

Hypertensive disorders of pregnancy encompass a range of disorders that include chronic hypertension, chronic hypertension with superimposed preeclampsia, gestational hypertension, preeclampsia, and eclampsia. These disorders complicate 8% to 12% of all pregnancies. Hypertensive disorders result in ~70 maternal deaths a year in the United States and probably 50,000 maternal deaths a year worldwide, mostly in developing countries. The only curative treatment for hypertensive disorders that develop during pregnancy is delivery. The risk of developing essential hypertension later in life is thought to be increased in women who experience gestational hypertension, although whether this association is causal or simply reflects similar mechanisms and tendencies toward increased blood pressure is not clear.

Gestational Hypertension

Gestational hypertension, or pregnancy-induced hypertension, is defined as an elevation of blood pressure above 139/89 mm Hg in a previously healthy woman after the first 19 weeks of pregnancy if the elevated blood pressures were recorded at least twice, with the readings taken a minimum of 4 hours apart, and no proteinuria is present. Gestational hypertension develops into preeclampsia in approximately one-fourth of these patients. It is distinguished from the onset of chronic hypertension by a postpartum return to a normotensive state.

Preeclampsia

Preeclampsia is a complex multisystem disorder unique to human pregnancy that is characterized by combined development of new-onset hypertension and new-onset proteinuria after the first 20 weeks of pregnancy. Risk factors for preeclampsia include obesity, nulliparity, early and advanced maternal age, chronic hypertension, renal disease, antiphospholipid syndrome, and risk factors for vascular disease in general. Of interest, smoking during pregnancy is protective against preeclampsia (although of course not recommended).

Pathophysiology

Preeclampsia is specific to human pregnancy. It is a disease of the placenta and can occur with molar pregnancies (pregnancy without the presence of fetal tissue). The hallmark of preeclampsia is an abnormal placentation-implantation. Normally cytotrophoblasts invade the uterine wall, reaching decidual arteries and interacting with the endothelium. As a result of that interaction, cytotrophoblasts acquire an endothelial phenotype, and decidual arteries become low-resistance vessels, losing their vascular smooth muscle. In preeclampsia, shallow endovascular invasion precludes this cytotrophoblast-endothelium interaction, and the spiral arteries remain constricted high-resistance blood vessels that fail to provide adequate oxygen and nutrients for the growing placenta and fetus. The abnormal placenta releases vasoactive substances that cause severe endothelial dysfunction of the maternal vasculature. This injured or hyperactivated endothelium further compromises placental blood flow. The plasma concentrations of vasodilators such as nitric oxide and prostacyclin are decreased. The current understanding suggests an important role, perhaps causal, for soluble fms-like tyrosine kinase-1 (sFlt-1), a soluble form of the vascular endothelial growth factor (VEGF) receptor, in the pathophysiology of preeclampsia. sFlt-1 levels are increased in preeclampsia and are elevated in pregnancies destined to develop preeclampsia weeks before preeclampsia develops. The soluble VEGF receptor in effect binds VEGF, decreasing its effect and ability to promote blood vessel formation. Antiangiogenic proteins and other toxins released by the impaired placenta cause endothelial damage, especially in blood vessels with fenestrated endothelium, as is found in kidney, liver, and brain. Whether sFlt-1 is a cause of placental insufficiency by impairing vascular development or a consequence of placental insufficiency and hypoxia is not completely clear and is the subject of intense investigation. There is some hope for specific therapy based on this angiogenic pathway.

The sensitivity of vascular receptors to angiotensin II and pharmacologic vasopressors such as $_1$-adrenergic agonist (phenylephrine, norepinephrine) is significantly decreased during normal pregnancy. In preeclampsia the sensitivity increases, which contributes to vasoconstriction and placental insufficiency; the dose response to exogenously administered drugs of this type in preeclampsia appears to be close to the usual nonpregnant response.

Clinical Presentation

Preeclampsia may occur with or without severe features (see later discussion), and based on symptoms and signs is classified as "preeclampsia" or "preeclampsia with severe features." Eclampsia, essentially preeclampsia with a seizure, may be viewed as one form of preeclampsia with severe features. There have

been significant advances in our understanding of the biochemical/physiologic mechanisms of preeclampsia in the past two decades but very limited advances in treatment modalities, with delivery remaining the only true treatment.

In 2013, the ACOG Task Force on Hypertension in Pregnancy updated the diagnostic and therapeutic guidelines for hypertensive disorders. The long-standing criteria of hypertension and proteinuria, defined as 300 mg urinary protein in a 24-hour collection, were retained. However, the proteinuria criterion can also be met with a single urine sample with a protein/creatinine ratio of 0.3 mg/dL or higher. A 1 reading on a urine dipstick can be accepted and tends to correlate with this level, but it is not recommended if a quantitative measure can be obtained. The criterion of 5 mg protein in 24 hours to define "preeclampsia with severe features" was removed, and only the 300 mg/24 or 0.3 protein/creatinine ratio is now accepted, with no modification of risk assessment, prognosis, or treatment based on proteinuria level. The 2013 document also presented clearer definitions of clinical signs, symptoms, and test results that may be used in the absence of proteinuria as diagnostic criteria for preeclampsia or to define when the preeclampsia includes severe features. Preeclampsia with severe features is now defined either by blood pressure criteria (systolic blood pressure ⌜ 159 mm Hg or diastolic ⌝ 110 mm Hg) or the presence of the nonproteinuria criteria, including thrombocytopenia (platelet count ⌝ 100,000/⌜L), renal insufficiency (serum creatinine ⌝ 1.1 mg/dL), pulmonary edema, or cerebral or visual symptoms or seizure (eclampsia) (Table 32.5). In the presence of hypertension but absence of proteinuria these severe signs/symptoms also allow the diagnosis of preeclampsia.

Another update of significant import for anesthesiologists included definite recommendations about when to deliver women with preeclampsia. The ACOG Task Force recommended that all women with gestational hypertension, whether preeclampsia/eclampsia or nonproteinuric gestational hypertension, be delivered (vaginal or operative) at 37 weeks of gestation, and women diagnosed with preeclampsia with severe features be delivered at 34 weeks. Women who are unstable (severe hypertension unresponsive to antihypertensive medications; severe thrombocytopenia; development of hemolysis, elevated liver enzymes, and low platelet syndrome [HELLP]; renal failure) should be stabilized and delivery plans individualized, often with delivery within a day or two. Magnesium sulfate treatment to prevent seizures is recommended if systolic blood pressure is above 160 mm Hg or diastolic is above 110 mm Hg, and the use of magnesium is left up to the obstetricians' judgment if the blood pressure is lower than this. The ACOG Task Force also made a somewhat controversial recommendation that impacts on usual postcesarean analgesia strategies when they stated that NSAIDs should not be used in "women with hypertension that persists for more than 1 day postpartum" due to an association with increased blood pressure. This recommendation was not accompanied by any supporting evidence in the released document, and several studies since these recommendations were released have not supported elimination or restriction of NSAIDs. We routinely prescribe NSAIDs for postcesarean analgesia in our patients with preeclampsia, except in some with clear evidence of renal insufficiency. ACOG Task Force recommendations of relevance to anesthesiologists are summarized in Table 32.6.

TABLE 32.5 Preeclampsia Severe Features

Systolic blood pressure (BP) ⊔ 159 mm Hg
Diastolic BP ⊔ 109 mm Hg
Thrombocytopenia (100⁄ L)[a]
h Liver function tests (transaminase concentrations above 2x upper limit of normal for the local lab) or severe right upper quadrant (RUQ) pain unresponsive to medication
gRenal function (creatinine [CR] level _ 1.1 mg/dL or doubling of prior CR)
Pulmonary edema (in absence of obvious fluid overload)
New-onset cerebral (e.g., severe headache) or visual disturbance

[a]With normal platelet count prior to 20 weeks of pregnancy (i.e., not simple gestational thrombocytopenia).
These signs and symptoms and lab values allow the diagnosis of preeclampsia in the presence of hypertension even without proteinuria, *and* if present, define the syndrome as "preeclampsia with severe features."

Treatment

The definitive treatment for preeclampsia is delivery, with the timing as suggested earlier. The mode of delivery depends on fetal gestational age, the findings on cervical examination, assessment of fetal well-being, and the fetal presenting part. Only 14% to 20% of women with preeclampsia with severe features are delivered vaginally.

At this time there are no recommendations to treat hypertension in women with preeclampsia without severe features. Indications for antihypertensive treatment during pregnancy are chronic hypertension, severe hypertension during labor and delivery, and expectant management of preeclampsia with severe features. The known benefits of antihypertensive treatment are prevention of placental abruption and prevention of cerebrovascular accident (which accounts for 15–20% of maternal

TABLE 32.6 American College of Obstetricians and Gynecologists (ACOG) 2013 Hypertension in Pregnancy Recommendations Impacting Anesthesia Care

- Preeclampsia without severe features or gestational hypertension: deliver at 37 weeks of gestation
- Preeclampsia with severe features: deliver at 34 weeks of gestation
- "Unstable": stabilize and deliver
- Treat systolic blood pressure (SBP) 160 mm Hg
- Do not treat SBP ⊔ 160 mm Hg
- Treat diastolic BP (DBP) 110 mm Hg
- Do not treat DBP ⊔ 110 mm Hg
- $MgSO_4$ for seizure prophylaxis indicated if:
  - SBP or DBP in severe range
  - Cerebral symptoms present
  - Seizure has occurred (eclampsia)
- If $MgSO_4$ is used, continue during cesarean delivery

Consider not utilizing nonsteroidal antiinflammatory drugs (NSAIDs) if hypertension persists ⌜24 hours postdelivery (no evidence given, and several studies since 2013 suggest NSAIDs are not problematic).

TABLE 32.7 Treatment of Systemic Hypertension Associated With Preeclampsia

Maintain SBP 160 mm Hg, DBP 110 mm Hg
Labetalol 5–10–20 mg IV or 20–40–80 mg PO (caution when used in women with asthma)
Hydralazine 5–10 mg IV every 20–30 min
Nifedipine 10–20 mg orally, repeat in 20 min if needed; 10–20 mg every 2–6 hr
If above unsuccessful:
Nicardipine infusion 0.5 μg/kg/min, titrated to response
or
Nitroglycerin 0.5 μg/kg/min IV, titrated to response

DBP, Diastolic blood pressure; *IV,* intravenous; *PO,* by mouth; *SBP,* systolic blood pressure.

deaths). The goal of therapy is to maintain blood pressure below 160/110 mm Hg. Hydralazine, labetalol, and nifedipine are all effective and recommended antihypertensives (Table 32.7). In practice, most anesthesiologists, and probably most obstetricians, prefer to start with labetalol due to familiarity and because most (but not all) women with preeclampsia are in a hemodynamic state characterized by hyperdynamic cardiac function and moderately elevated systemic vascular resistance. The combined β- and α-adrenergic antagonism of labetalol is often a good pharmacologic match for these hemodynamics, resulting in a mild decrease in myocardial contractility and moderate vasodilation. Dosages start at 20 mg oral labetalol and rapidly progress to 40-mg and 80-mg doses. If blood pressure is not under control, then a second drug (hydralazine or nifedipine) is added. The presence of relative bradycardia might suggest that hydralazine should be the first-line medication. Severe, refractory hypertension may necessitate continuous infusion of an antihypertensive such as nicardipine or nitroglycerin, and some current guidelines specifically state that anesthesiology or critical care consultation should be sought at this point.

In general, vascular volume is decreased moderately in preeclampsia due to low oncotic pressure due to transudation of fluid secondary to hypoalbuminemia from protein loss in the urine. Fluid management in the patient with preeclampsia is complicated by the conflict between the need to give fluids to an intravascularly depleted patient (the degree of depletion may be reflected by a rising hematocrit) and the obligation to avoid administration of fluids to a patient with leaky vasculature. This, combined with endothelial injury, leads to third spacing of fluid and intravascular volume depletion; thus fluid therapy is complicated by the need to balance intravascular volume replacement with peripheral and potentially pulmonary edema. There is no demonstrated role for albumin in this volume replacement.

Labor Analgesia

In addition to providing the common benefits of epidural labor analgesia, use of neuraxial techniques in preeclamptic patients can facilitate blood pressure control during labor. As long as perfusion pressure is maintained, epidural analgesia will also increase intervillous blood flow in preeclampsia, which will improve uteroplacental performance and can improve fetal status. Because these women are at high risk of requiring cesarean delivery, early placement of an epidural catheter is encouraged to facilitate the use of epidural anesthesia for cesarean delivery and avoid the need for and risks of general anesthesia. No significant alterations in the usual doses and strategies for labor analgesia are generally needed unless the hemodynamic condition is grossly abnormal.

Spinal anesthesia. Spinal anesthesia is the anesthetic of choice for patients with preeclampsia who undergo cesarean delivery without an epidural catheter in situ, unless neuraxial anesthesia is contraindicated because of coagulopathy or other reason. Neuraxial blockade results in sympathectomy and may lead to hypotension in healthy patients. Contrary to the beliefs and teaching two decades ago, and the known decreased intravascular volume in preeclampsia, substantial evidence over the past two decades has demonstrated that preeclamptic women develop less hypotension than normotensive pregnant women when spinal anesthesia is administered and have a good response to moderate doses of vasopressors.

General anesthesia. General anesthesia is sometimes required for cesarean delivery, either due to emergent delivery with no time for a regional procedure or thrombocytopenia (HELLP syndrome) resulting from preeclampsia. Not only are patients with preeclampsia subject to the common risks of general anesthesia during pregnancy, but these patients also have a higher risk of difficult intubation resulting from increased upper airway edema and probably a higher risk of aspiration because of the increased likelihood of difficulty in airway management. Patients with preeclampsia also have an increased hypertensive response to sympathomimetics compared to nonhypertensive pregnant women, roughly equivalent to nonpregnant patients. Patients on magnesium therapy have a much greater sensitivity to the action of nondepolarizing muscle relaxants, and very small doses should be used with careful monitoring of effect. There is concern that these patients have a higher risk of uterine atony and peripartum hemorrhage resulting from the smooth muscle–relaxant effects of magnesium therapy, although studies have not consistently shown this to be the case.

Eclampsia

Eclampsia is defined by seizure or coma in the setting of preeclampsia in the absence of any other pathologic brain condition. It is by definition considered "preeclampsia with severe features" and has an incidence of 1 in 2000 pregnancies. The majority of patients are diagnosed with preeclampsia before development of seizures; however, eclampsia is the first manifestation of preeclampsia in 20% to 38% of cases. The magnitude of hypertension does not correlate with the risk of eclampsia. Approximately half of patients with preeclampsia who develop seizures report prodromal symptoms such as headache or visual changes. Between 38% and 50% of eclamptic seizures occur before term; 16% of seizures occurring at term take place during labor or within 48 hours of delivery.

Typical eclamptic seizures last less than 10 minutes and are neither recurrent nor associated with focal neurologic signs.

Eclampsia: Not an Indication for Cesarean Delivery or Any Immediate Delivery

Management of the patient with eclampsia is directed at prevention of aspiration, maintenance of airway patency, control of seizures and prevention of their recurrence, control of hypertension, and evaluation for delivery.

Magnesium sulfate is the anticonvulsant of choice because it is more effective and has a better safety profile than benzodiazepines or phenytoin. The standard IV regimen is a loading of magnesium sulfate of 2 g every 15 minutes to a maximum of 6 g. If a patient develops seizures while receiving a magnesium infusion for seizure prophylaxis, administration of a 1- to 2-g bolus is recommended, after which a plasma magnesium level should be measured.

If the patient and fetus are in stable condition following an eclamptic seizure, management of the patient will proceed as it would for a patient with preeclampsia, and immediate delivery is not indicated unless that had been the plan before the seizure.

Heart Disease

Risk Assessment and Classification

Cardiac disease has become the leading cause of pregnancy-related mortality, as other causes (hemorrhage, hypertension) have become better controlled, and the number of women with significant cardiovascular disease who grow to childbearing age and become pregnant has increased. These women are the most high-risk patients anesthesiologists will care for around the time of delivery. The cardiovascular changes of pregnancy (higher plasma volume, increased heart rate, and need for higher cardiac output) place women with congenital or acquired heart disease at increased risk of peripartum cardiac complications. The most common complications are arrythmias and heart failure. Arrythmias occur secondary to increased volume and atrial stretch. Heart failure occurs if contractility cannot be augmented appropriately to deal with the increased vascular volume of pregnancy.

The World Health Organization (WHO) classification of cardiac lesions I through IV is a useful framework for risk stratification to predict adverse events in pregnancy and to plan for an appropriate Maternal Level of Care center for delivery (Table 32.8). The 2018 CARPREG II (Cardiac Disease in Pregnancy Study) risk index includes 10 predictors of maternal cardiac complications: 5 general predictors (prior cardiac events or arrhythmias, poor functional class or cyanosis, high-risk

TABLE 32.8 Modified World Health Organization Classification of Cardiovascular Disease in Pregnancy

Risk Classification	Cardiac Lesions
Class I *No detectable increased risk of maternal mortality and no or minimal increase in maternal morbidity*	• Uncomplicated mild pulmonary stenosis • Ventricular septal defect • Patent ductus arteriosus • Mitral valve prolapse with no more than trivial mitral regurgitation • Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage) • Isolated ventricular extrasystoles and atrial ectopic beats
Class II *Small increased risk of maternal mortality or moderate increase in morbidity*	• Unoperated atrial or ventricular septal defect • Repaired tetralogy of Fallot • Most arrhythmias
Class II–III *Depends on patient*	• Hypertrophic cardiomyopathy • Native or tissue valvular heart disease not considered mWHO I or IV • Repaired coarctation • Marfan syndrome without aortic dilatation • Bicuspid valve with aorta ≤ 45 mm • Mild ventricular impairment • Heart transplantation
Class III *Significantly increased risk of maternal mortality or severe morbidity, and expert cardiac and obstetric prepregnancy, antenatal, and postnatal care are required*	• Mechanical valve • Systemic right ventricle • Fontan circulation • Unrepaired cyanotic heart disease • Other complex congenital heart disease • Marfan syndrome with aorta 40–45 mm • Bicuspid aortic valve with aorta 45–50 mm
Class IV *Pregnancy is contraindicated*	• Pulmonary hypertension • Eisenmenger syndrome • Systemic ventricular ejection fraction <30% • Systemic ventricular dysfunction with New York Heart Association class III–IV • Severe mitral stenosis or symptomatic aortic stenosis • Marfan syndrome with aorta >45 mm • Bicuspid aortic valve with aorta ≥ 50 mm • Native severe coarctation • Prior peripartum cardiomyopathy with any residual impairment of ventricular function

Adapted from Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. *Heart*. 2006;92:1520-5; Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2018;39:3165-241.

valve disease/left ventricular outflow tract obstruction, systemic ventricular dysfunction, no prior cardiac interventions), 4 lesion-specific predictors (mechanical valves, high-risk aortopathies, pulmonary hypertension, coronary artery disease), and 1 delivery of care predictor (late pregnancy assessment). In 2019 the Registry of Pregnancy and Cardiac Disease published their risk predictors for heart failure and/or maternal mortality: clinical signs of heart failure, New York Heart Association (NYHA) class greater than II, systemic ventricular ejection fraction below 40%, WHO class IV lesion, or anticoagulation use. These are useful guides in planning appropriate centers and providers to care for these women. Often a team, including both an obstetric and cardiothoracic anesthesiologist, is helpful in managing delivery care of women with the highest risk lesions. A good partnership between a cardiothoracic and an obstetric anesthesiologist is a tremendous benefit to women with the highest risk lesions in pregnancy. The obstetric anesthesiologist is intimately familiar with neuraxial anesthesia, the stages of labor, vaginal delivery, cesarean delivery, maternal symptoms throughout the process, and communication with the obstetric team, and this familiarity can provide team and maternal anxiolysis. The cardiothoracic anesthesiologist is intimately familiar with evaluating cardiac lesions, titrating inotropes and vasoactive medications, and performing echocardiography. As a team these two providers give high-risk women the best chance of low morbidity and mortality.

The highest risk lesions in pregnancy are pulmonary hypertension, left-sided obstructive lesions (aortic stenosis, mitral stenosis, hypertrophic obstructive cardiomyopathy), aortopathies, the presence of a mechanical valve, severe cardiomyopathy with left ventricular ejection fraction (LVEF) below 30% or right heart dysfunction, complex congenital lesions and Fontan physiology, or unrepaired shunt lesions that can lead to Eisenmenger syndrome and pulmonary hypertension. Pulmonary hypertension is the most significant risk factor for poor maternal and neonatal outcome as a pulmonary circulation with a fixed resistance may be unable to vasodilate to accommodate the increase in volume/flow leading to further increased pulmonary artery pressure and right heart failure. Patients with pulmonary hypertension are usually advised against pregnancy, as mortality is very high (10–50%). Other preload-dependent lesions such as left-sided obstructive lesions also place women at higher risk due to the challenges in volume shifts during delivery and postpartum.

Management of Anesthesia

Most women with cardiac lesions benefit from a vaginal delivery with good neuraxial anesthesia. There are only a few maternal cardiac indications for cesarean delivery: cardiopulmonary decompensation requiring intubation, mechanical valve with current anticoagulation (vaginal delivery contraindicated secondary to fetal anticoagulation and cerebral hemorrhage risk with vaginal delivery, and inability to provide neuraxial labor analgesia in the face of therapeutic anticoagulation), severe aortopathy, or perhaps critical aortic or mitral stenosis. The anesthesiologist must remember that a large autotransfusion still occurs immediately after delivery of the fetus and placenta and involution of the uterus during cesarean delivery, so the avoidance of vaginal delivery alone does not avoid volume shifts, although these appear more mild or gradual with vaginal compared to cesarean delivery, and the postpartum course is characterized by a lesser inflammatory process. A general approach to anesthesia care for women with cardiovascular disease in pregnancy is outlined in Table 32.9.

Mechanical valves place women at higher risk in pregnancy due to the difficulties of anticoagulation in pregnancy and the risks of anticoagulation and thrombosis. Vitamin K antagonists (VKA) provide the best anticoagulation; however, VKAs cross the placenta and are teratogenic in the first trimester. Unfractionated heparin and low-molecular-weight heparin (LMWH) do not cross the placenta but are less effective anticoagulants; valve thrombosis can occur during pregnancy and can be catastrophic. When LMWH is used, anti-Xa peak and trough levels must be measured frequently to ensure appropriate levels in the setting of changes in maternal plasma volume and renal clearance. Anti-Xa therapeutic range goals depend on the valve position, but

TABLE 32.9 Anesthetic Management of Cardiac Disease in Pregnancy

Mild (WHO class I–II)
- Predelivery anesthesia consultation
- Vaginal delivery preferred
- Early neuraxial analgesia
- Routine monitoring with low threshold for arterial line, ECG when indicated
- Consider increasing dose via epidural catheter as patient enters second stage (limit pain and Valsalva)
- For CD, indwelling epidural catheter or spinal anesthesia

Moderate (WHO II–III)
- Predelivery anesthesia consultation
- Consider institution with proper level of care
- Vaginal delivery preferred
- Early neuraxial analgesia
- Arterial line usually, ECG when indicated
- Dose epidural catheter as patient entering second stage
- For CD, indwelling epidural or low-dose spinal CSE
- May need diuresis after vaginal delivery, probably after cesarean
- Possible ICU or similar monitoring for 24–48 hr

Severe (WHO III–IV)
- Predelivery anesthesia consultation
- Transfer to institution with proper level of care, experience, and available modalities
- Availability of cardiology, cardiothoracic surgery (ECMO)
- Vaginal delivery preferred
- Early neuraxial analgesia
- Arterial line
- Possible central line for inotropes/vasodilators
- ECG usually
- Dose epidural catheter as patient entering second stage, no Valsalva
- For CD, indwelling epidural or low-dose spinal CSE
- May need diuresis after delivery
- ICU or similar monitoring for 24–72 hr

CD, Cesarean delivery; *CSE*, combined spinal-epidural; *ECG*, electrocardiography; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit; *WHO*, World Health Organization.

usual target peak anti-Xa level is 0.8 to 1.2 U/mL 4 to 6 hours after LMWH. The choice of anticoagulation is made weighing the fetal and maternal risks. Fetal teratogenicity from VKA is dose dependent, so when the therapeutic level can be achieved with warfarin (⊥5 mg) then VKA may be considered in the first trimester.

Women with severe cardiomyopathy (LVEF ⊐30% or right heart dysfunction) may require inotropic support through delivery and in the first few days postpartum to achieve the necessary cardiac output augmentation to support the large autotransfusion of delivery and postpartum. When preeclampsia coexists with cardiomyopathy, women are at particularly high risk of pulmonary edema and heart failure peripartum. Transthoracic echocardiography is an invaluable tool in recognizing the need for and for titrating inotrope support at delivery. Women with severely depressed myocardial function may benefit from venoarterial (VA) ECMO at the time of delivery. The liters of fluid accumulated during pregnancy can overwhelm the compromised myocardium so aggressive diuresis and sodium restriction is imperative.

Women with complex congenital lesions such as those repaired via Fontan procedure are at high risk of miscarriage and maternal cardiac events should they become pregnant. Frequent complications include impairment of passive pulmonary filling, arrythmias, atrial ventricular valvular regurgitation, and systemic ventricular failure (specifically if the systemic ventricle is a morphologic right ventricle). Women with low flow circulation, such as women with Fontan physiology or reduced ejection fraction, are also at higher risk of thrombosis and should receive thromboprophylaxis or anticoagulation therapy.

Shunt lesions such as patent ductus arteriosus and ventricular or atrial septal defects that remain unrepaired for decades can lead to pulmonary overflow, pulmonary vascular remodeling, pulmonary hypertension, and subsequent Eisenmenger syndrome when pulmonary pressures exceed systemic pressures and a right-to-left shunt may appear. These patients are at highest risk or mortality in pregnancy, with mortality rates as high as 43%. The anesthesiologist must maintain systemic blood pressure higher than pulmonary pressure, use pulmonary vasodilators judiciously, and promptly employ ECMO when needed in these cases. These are cases best performed at tertiary/quaternary care centers with advanced cardiothoracic programs, with consultation among obstetricians, cardiologists, obstetric and cardiac anesthesiologists, and frequently cardiothoracic surgeons.

The women with lesions most compatible with pregnancy physiology are those with small septal defects or regurgitant valvular lesions, as the faster heart rate and lower systemic vascular resistance of pregnancy improve the hemodynamics in these patients. These women do well in pregnancy and delivery with minimal alterations in routine obstetric and obstetric anesthesia care.

Early neuraxial analgesia for labor may minimize heart rate increase and fluctuation with pain and contractions, thus preventing arrythmias. If a woman with cardiac disease requires a cesarean delivery, then neuraxial anesthesia is preferred over general anesthesia. A single-shot spinal technique can be used in women with low-risk cardiac lesions who are not overly dependent on preload. If the rapid hemodynamic changes from a single-shot technique may not be well tolerated, then a CSE anesthetic with a low-dose spinal component or an epidural technique may be used so as to slowly titrate the anesthetic level with concomitant vasopressor use to maintain maternal systemic vascular resistance at baseline. Norepinephrine rather than phenylephrine may be the vasopressor of choice in women with impaired myocardial function because it possesses some ⊓-adrenergic activity to promote myocardial contractility, but the differences are probably small.

An arterial line should be strongly considered in women with high-risk lesions. Peripherally or centrally inserted central venous lines can be useful for inotrope or vasopressor delivery. Pulmonary artery catheters are rarely used in contemporary obstetric anesthesia practice, usually in women with pulmonary hypertension to measure pulmonary pressure and response to pulmonary vasodilator therapy, as cardiac output is easily measured in other women, noninvasively with transthoracic echocardiography. Pulmonary vasodilators such as inhaled nitric oxide, oxygen, and intravenous epoprostenol are very useful in women with pulmonary hypertension. VA ECMO should be available for women with the highest-risk lesions.

The aorta dilates in normal pregnancy, but if there is muscular weakness or a preexisting aneurysm or dilation then there is a risk of catastrophic rupture. The degree and time course of aortic dilation will determine the severity of the maternal condition and the management. Generally, women with mild aortic dilation can have vaginal deliveries, but with progressive dilation of the aorta, assisted vaginal delivery or cesarean delivery is indicated. The concern with vaginal delivery is the change in aortic pressure from stage 3 of the Valsalva maneuver to stage 4 (low pressure to high pressure as a result of left-sided filling and ejection after prior depressed cardiac output and during stage 1 and 2 to 3), which results in a large shear stress to the walls of the aorta. Other women with preload-dependent lesions should be attended to closely by the anesthesiologist during maternal expulsive efforts as they may not tolerate the Valsalva maneuver. A common strategy in many women with cardiovascular disease where strenuous Valsalva maneuver may not be well tolerated is to increase the dose/density of epidural blockade in the second stage of labor to decrease the woman's need to push and allow more passive descent of the fetus and limit maternal expulsive efforts, the so-called *shortened second stage*. With this approach, it is not the second stage itself that is shortened but the time spent with maternal effort during the second stage.

Women with WHO class III or IV lesions may be advised to terminate pregnancy. Good neuraxial anesthesia combined with the aforementioned monitoring may also be the prudent strategy to prevent further maternal decompensation for termination of pregnancy, a procedure not without risk in this population (e.g., deaths have been reported from pregnancy termination in women with severe pulmonary hypertension).

Obesity

Obesity in the United States has become a national epidemic and is a major contributor to maternal morbidity. Nearly half

of US women of childbearing age are overweight or obese. Obesity is generally defined as a BMI above 30 kg/m^2, with morbid obesity defined as BMI of 40 kg/m^2 and above. It should be noted that there is no correction of this definition of obesity for the normal physiologic weight gain of pregnancy (a weight gain of 25–30 lb would correspond to 2–4 BMI units). The pathophysiologic features associated with obesity result in a greater incidence of pregnancy-related complications for both mother and infant than for nonobese patients and may have lifelong health implications for offspring. Obesity is probably the most common significant medical issue facing anesthesiologists in obstetrics.

Epidemiology/Outcomes

Hypertensive disorders, including chronic hypertension and preeclampsia, are increased in obese patients. Obese patients are more likely to develop gestational diabetes and are at increased risk of thromboembolic disease. Obese patients are more likely to have an abnormal labor, and failed induction is more likely to occur. These patients are also at greater risk of postpartum hemorrhage, regardless of the route of delivery. The overall cesarean delivery rate and emergency cesarean delivery rate are increased in obese patients. Factors that lead to these increased rates include preeclampsia and diabetes, as well as an increased incidence of fetal macrosomia. Soft tissue dystocia may also be a contributing factor. Duration of surgery can be expected to be prolonged in these patients.

Obesity has been found to increase the risk of maternal death related to the increased incidence of preeclampsia, diabetes, pulmonary embolism, and infection. Anesthesia-related maternal mortality is also increased in the obese parturient, with airway difficulties being a major cause. In one published series of anesthesia-related deaths, six of the eight deaths were in obese women, mostly due to airway issues.

Perinatal outcome is adversely affected by obesity. The increased incidence of fetal macrosomia leads to a greater risk of birth trauma and shoulder dystocia. Meconium aspiration occurs more frequently in infants of obese women, and these infants are at greater risk of neural tube defects and other congenital abnormalities. In addition, fetal exposure to hyperglycemia in utero may result in an increased risk of developing diabetes, hypertension, and premature coronary artery disease.

Management of Anesthesia

Preanesthetic. The high incidence of medical disease associated with obesity, as well as the difficulties encountered because of the patient's body habitus, present a significant challenge in the management of obese parturient patients (Table 32.10). Preanesthetic evaluation and preparation should include a thorough airway examination and assessment of the patient's pulmonary and cardiac status. The possibility of obstructive sleep apnea should be evaluated, even perhaps assumed to be present in morbid obesity. Arterial blood gas analysis to assess for carbon dioxide retention, ECG, and echocardiography may be indicated. An appropriately sized blood pressure cuff designed to fit the patient's arm must be available, and invasive arterial monitoring considered if oscillometric methods do not appear reliable.

TABLE 32.10 Anesthesia Issues With Obese Parturients

General
Vascular access
Transport/movement of patient
Accuracy of noninvasive blood pressure monitoring
High rate of cesarean delivery
Risk of OSA
Longer time required from diagnosis of fetal nonreassuring status until delivery (multifactorial)
Labor Analgesia
Difficult neuraxial procedures
Increased failure/replacement rate
Securing epidural catheter
Cesarean Delivery
More cephalad spread of neuraxial?
Need for high dermatomal level with neuraxial
Increased respiratory compromise with high level
Long surgical times
Consider CSE
Respiratory effects of opioids postop (neuraxial or systemic)
Difficult intubation
Rapid desaturation

CSE, Combined spinal-epidural; *OSA,* obstructive sleep apnea.

Neuraxial analgesia. Epidural analgesia is a reasonable choice for labor analgesia. It provides excellent pain relief, reduces oxygen consumption, and may attenuate the cardiac responses to labor and delivery. Because obese women have a higher likelihood of requiring cesarean delivery, and the risk of general anesthesia is substantial in this patient population, early epidural analgesia offers another advantage—the ability to extend the block for surgical anesthesia.

The technical challenge of performing epidural analgesia in the obese parturient may be alleviated by the use of ultrasound, although ultrasound visualization of bony landmarks and the epidural space in obesity are less than ideal and sometimes useless. Ultrasound can often at least help determine the midline. Longer needles may be required to reach the epidural space and should be readily available in the labor and delivery unit. There is a higher failure or catheter replacement rate with epidural analgesia in obese women. Placement via a CSE or dural puncture epidural (DPE—essentially CSE without a spinal dose) may provide anatomic confirmation of correct initial placement.

The high rate of need for catheter replacement among obese patients may be reduced by proper taping technique. After placing the catheter (but before taping), repositioning to the straightened-back lateral position allows the skin to move over the catheter without pulling it out of the epidural space. After this inward movement of the catheter occurs, the catheter can be taped to the skin. In some cases of morbid obesity, especially if catheter placement was difficult, placing a suture around the

catheter at the skin or tunneling the catheter under the skin may provide added security.

Continuous spinal analgesia has been suggested as an option for labor analgesia, supposedly providing advantages over epidural analgesia in morbidly obese patients (more certain placement, more reliable spread of drug). Correct placement of the catheter is confirmed by aspiration of cerebrospinal fluid, and thus initial failure rates will be lower than with epidural analgesia. A dislodged catheter will also be more readily identified than with epidural analgesia. We have not been impressed by the reliability of spinal catheters over epidural catheters, and the incidence of postdural puncture headache (PDPH) is quite high, although somewhat lower than in normal-weight parturients. Placement of an epidural catheter suing a CSE or DPE technique provides many of the advantages of confirmed placement, without the high risk of PDPH and the need to manage an unusual catheter in labor.

There is evidence that obesity decreases the dose of local anesthetic needed for initiation (and presumably maintenance) of labor analgesia. This may be due to decreases in the size of the epidural space, resulting in wider spread of any given dose.

Cesarean delivery. The incidence of cesarean delivery is higher in obese women than in nonobese women. In larger women a continuous neuraxial technique rather than a single-shot spinal anesthetic may be preferred owing to the ability to maintain anesthesia for what may be an extended period of surgery. In women with BMI greater than 35, it may be prudent to use a CSE technique with a moderately lower intrathecal local anesthetic dose (9–10.5 mg bupivacaine vs the usual 12 mg) so as to prevent a high spinal block. Studies have not consistently shown a higher level of block with spinal anesthesia in obese pregnant women, but there may be more subjective and objective respiratory compromise for any given dermatomal level of block due to the weight of the abdomen compressing the chest in the supine position. In addition, it has been shown that obese women require a higher level of anesthesia to be comfortable during cesarean delivery, presumably because more peritoneal and abdominal traction is needed by the surgical team for exposure and exploration.

If general anesthesia is unavoidable, emergency airway equipment, including videolaryngoscopy and appropriately sized laryngeal mask airways (LMAs), must be immediately available. If difficult intubation is anticipated, awake intubation should be elected.

There is controversy about the use of neuraxial opioids (morphine) in obese women, with some anesthesiologists believing that the risk of respiratory depression is high in these women, who may also have sleep apnea. The risk of low-dose (≤ 150 μg) spinal morphine or 2 to 3 mg epidural morphine is probably extremely low, compared to systemic (oral or IV) opioids, and we routinely utilize spinal and epidural morphine in our practice in preference to systemic opioid use. If there is serious concern about significant respiratory compromise from opioids, continuous epidural infusion can be utilized for postoperative analgesia.

KEY POINTS

- Physiologic changes of pregnancy affect all organ systems. They influence maternal compensation for comorbid conditions and maternal response to anesthesia.
- There is less fetal drug exposure with regional anesthesia.
- Nonobstetric surgery during pregnancy requires few alterations in normal anesthesia care, other than decisions about fetal monitoring and postoperative uterine contraction monitoring
- Breastfeeding women can resume breastfeeding as soon as awake and able after almost all anesthetics.
- Clear recommendations exist to guide delivery and blood pressure treatment decision in women with gestational hypertension.
- Delivery is the definitive treatment for gestational hypertension and preeclampsia/eclampsia.
- Cardiovascular disease is now the leading cause of pregnancy-related mortality.
- The parturient with significant cardiovascular disease should be delivered at an institution with the appropriate level of resources and expertise.
- Maternal obesity has become the most common peripartum comorbid condition and presents a variety of technical and medical/anesthetic issues.

RESOURCES

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