

**Fig. 32.5** Proposed algorithm for antiplatelet management in patients with percutaneous coronary intervention and noncardiac surgery. ASA, Aspirin; BMS, bare metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent. (From Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guidelines on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol*. 2014;64:e77–e137.)

dysfunction were both associated with increased 30-day cardiovascular event rates (OR, 2.3; 95% CI, 1.4-3.6; and OR, 1.8; 95% CI 1.1 to 2.9, respectively) and long-term cardiovascular mortality (hazard ratio, 4.6; 95% CI 2.4-8.5; and hazard ratio, 3.0; 95% CI 1.5 to 6.0, respectively).<sup>141</sup> In patients undergoing endovascular surgery ( $n = 356$ ), only symptomatic heart failure was associated with an increase in 30-day cardiovascular events and long-term cardiovascular mortality. These results suggest that stabilization of ventricular function and treatment of pulmonary congestion is prudent before elective surgery.

A recent MI has traditionally been an important predictor of perioperative risk. The more recent the MI, particularly within 3 to 6 months, the greater is the perioperative risk. However, like the Goldman Cardiac Risk Index, medicine has changed and outcomes are improved. The 2014 AHA/ACC Foundation (AHA/ACCF) guidelines advocate the use of 60 days as being high risk.<sup>119</sup> After that time, further risk stratification depends on clinical symptoms.

For those patients without overt symptoms or a history of CAD, the probability of CAD varies with the type and number of atherosclerotic risk factors present. Diabetes accelerates the progression of atherosclerosis, which can frequently be silent, leading many clinicians to assume that diabetes is a CAD equivalent and treating patients as such. Diabetes is an independent risk factor for perioperative cardiac

morbidity, and the preoperative treatment with insulin has been included in the Revised Cardiac Risk Index (RCRI). In attempting to determine the degree of the increased risk associated with diabetes, the treatment modality, duration of the disease, and other associated end-organ dysfunction should be taken into account.

Significant intraoperative factors that correlate with perioperative risk and that may be avoided or altered are (1) unnecessary use of vasopressors,<sup>142,143</sup> (2) unintentional hypotension<sup>144-146</sup> (this point is controversial, however, because some investigators have found that unintentional hypotension does not correlate with perioperative morbidity<sup>143</sup>), (3) hypothermia,<sup>147</sup> (4) too low or too high a hematocrit,<sup>148,149</sup> and (5) lengthy operations.<sup>145</sup>

Significant intraoperative factors that correlate with perioperative morbidity and probably cannot be avoided are (1) emergency surgery and (2) thoracic or intraperitoneal surgery or above-the-knee amputations.<sup>145,150-164</sup>

Several risk indices were developed in a prospective cohort study by Lee and associates.<sup>164</sup> They studied 4315 patients 50 years old or older who were undergoing elective major noncardiac procedures in a tertiary care teaching hospital. The six independent predictors of complications included in a RCRI were high-risk type of surgery, history of ischemic heart disease, history of CHF, history of cerebrovascular disease, preoperative treatment with insulin,

and preoperative serum creatinine greater than 2.0 mg/dL; increasing cardiac complication rates were noted with an increasing number of risk factors.<sup>164</sup> The RCRI has become the standard tool in the literature for assessing perioperative cardiac risk in a given individual and has been used to direct the decision to perform cardiovascular testing and implement perioperative management protocols. It has been validated for both short-term and long-term cardiovascular outcomes.<sup>165</sup> It has also been shown to predict long-term quality of life.<sup>165</sup> Therefore, the RCRI can be used to help define both the short-term and long-term risks of cardiovascular disease in the surgical patient.

The American College of Surgeons NSQIP created a Surgical Risk Calculator from 525 participating hospitals and more than 1 million operations.<sup>166</sup> This risk calculator uses the specific current procedural terminology code of the procedure being performed to enable procedure-specific risk assessment and includes 21 patient-specific variables (e.g., age, sex, body mass index, dyspnea, previous MI). From this input, it calculates the percentage of risk of a major adverse cardiac event, death, and eight other outcomes. Use of this risk calculator may offer the best estimation for surgery-specific risk of a major adverse cardiac event and death.

The American College of Surgeons NSQIP Myocardial Infarction and Cardiac Arrest risk prediction rule is more specific for cardiac complications.<sup>167</sup> Using these definitions of outcome and chart-based data collection methods, the authors derived a risk index that was robust in the derivation and validation stages and appeared to outperform the RCRI (which was tested in the same dataset) in terms of discriminative power, particularly among patients undergoing vascular surgery.

A primary issue with all these indices is that a simple estimate of risk does not help in refining perioperative management for an individual patient. Therefore, the consultant must communicate the extent and stability of the patient's CAD, rather than make a simple statement of risk classification.

The goal in providing anesthesia to patients with ischemic heart disease is to achieve the best preoperative condition obtainable by treating conditions that correlate with perioperative risk. The next step is to intraoperatively monitor for conditions that correlate with perioperative risk and avoid circumstances that lead to perioperative risk.

### Preoperative and Preprocedure Therapy

The only way known to increase oxygen supply to the myocardium of patients with coronary artery stenosis is to maintain adequate diastolic blood pressure, hemoglobin concentration, and oxygen saturation. The main goals of anesthesia practice for these patients have been to decrease the determinants of myocardial oxygen demand, heart rate, ventricular wall tension, and contractile performance, and to improve plaque stabilization. Thus medical management designed to preserve all viable myocardial tissue may include the following:

1. Multiple studies have demonstrated improved outcome in patients given perioperative  $\beta$ -blockers, especially if heart rate is controlled, acknowledging the previously discussed concerns regarding the quality of the studies from the Erasmus group.<sup>167a,b</sup> Subsequent studies dem-

onstrated that  $\beta$ -blockers may not be effective if heart rate is not well controlled, or in lower risk patients.<sup>167c-e</sup> The POISE trial was published in which 8351 high-risk  $\beta$ -blocker-naïve patients were randomized to high-dose continuous-release metoprolol versus placebo.<sup>167f</sup>

2. There was a significant reduction in the primary outcome of cardiovascular events associated with a 30% reduction in MI rate, but with a significantly increased rate of 30-day all-cause mortality and stroke. Several recent cohort studies continue to support the fact that high-risk patients on  $\beta$ -blockers were associated with improved outcome. A Canadian administrative dataset suggested that the perioperative morbidity would be higher if  $\beta$ -blockers were started within 7 days as compared to 8 days or greater. As part of the update to the current ACC/AHA Guidelines, an Evidence Review Committee was formed to independently review the data on perioperative  $\beta$ -blockade. Perioperative  $\beta$ -blockade started within 1 day or less before noncardiac surgery prevents nonfatal MI but increases risks of stroke, death, hypotension, and bradycardia.<sup>167g</sup> Without the controversial DECREASE studies, there are insufficient data on  $\beta$ -blockade started two or more days prior to surgery. Wallace and associates reported that perioperative  $\beta$ -blockade administered according to the Perioperative Cardiac Risk Reduction protocol is associated with a reduction in 30-day and 1-year mortality.<sup>167h</sup> Perioperative withdrawal of  $\beta$ -blockers is associated with increased mortality. The current ACCF/AHA Guidelines on perioperative  $\beta$ -blockade advocate that perioperative  $\beta$ -blockade is a Class I indication and should be used in patients previously on  $\beta$ -blockers. The new recommendations changed the recommendation from a Class IIa to IIb for patients undergoing vascular surgery who are at high cardiac risk owing to CAD or the finding of cardiac ischemia on preoperative testing (Box 32.3).
2. Vasodilation (with nitroglycerin or its "long-acting" analogues nitroprusside, hydralazine, or prazosin) to decrease ventricular wall tension may be beneficial, although currently no randomized trials support the prophylactic use of these agents.<sup>109,110,168</sup> There are no data to support the routine use of pulmonary artery catheters and transesophageal echocardiography for this type of patient.<sup>158,169</sup> The intraoperative management of patients with ischemic heart disease is discussed in further detail in Chapters 31 and 54 and in published guidelines.<sup>117</sup>
3. Other medications. In POISE II,  $\alpha$ -2 agonists were not shown to improve perioperative outcome.<sup>169a</sup> POISE II also evaluated the effectiveness of aspirin therapy in a cohort of patients without a recent stent. Administration of aspirin before surgery and throughout the early postsurgical period had no significant effect on the rate of a composite of death or nonfatal MI but increased the risk of major bleeding.<sup>169b</sup> Most recently, perioperative statins have been shown to improve cardiac outcome. Durazzo and colleagues published a randomized trial of 200 vascular surgery patients in which statins were started an average of 30 days prior to vascular surgery.<sup>169c</sup> A significant reduction in cardiovascular complications was demonstrated using this protocol. Le Manach and colleagues demonstrated that statin

### BOX 32.3 2014 ACC/AHA Recommendations for Perioperative $\beta$ -Blockade

#### Class I

- $\beta$ -Blockers should be continued in patients undergoing surgery who have been on  $\beta$ -blockers chronically.<sup>111-117</sup> (Level of Evidence: B)

#### Class IIa

- It is reasonable for the management of  $\beta$ -blockers after surgery to be guided by clinical circumstances, independent of when the agent was started.<sup>110,117,118</sup> (Level of Evidence: B)

#### Class IIb

- In patients with intermediate- or high-risk myocardial ischemia noted in preoperative risk stratification tests, it may be reasonable to begin perioperative  $\beta$ -blockers.<sup>119</sup> (Level of Evidence: C)
- In patients with three or more RCRI risk factors (e.g., diabetes mellitus, heart failure, coronary artery disease, renal insufficiency, cerebrovascular accident), it may be reasonable to begin  $\beta$ -blockers before surgery.<sup>117</sup> (Level of Evidence: B)
- In patients with a compelling long-term indication for  $\beta$ -blocker therapy but no other RCRI risk factors, initiating  $\beta$ -blockers in the perioperative setting as an approach to reduce perioperative risk is of uncertain benefit.<sup>111,117,120</sup> (Level of Evidence: B)
- In patients in whom  $\beta$ -blocker therapy is initiated, it may be reasonable to begin perioperative  $\beta$ -blockers long enough in advance to assess safety and tolerability, preferably more than 1 day before surgery.<sup>110,121-123</sup> (Level of Evidence: B)

#### Class III: Harm

- $\beta$ -Blocker therapy should not be started on the day of surgery.<sup>110</sup> (Level of Evidence: B)

RCRI, Revised cardiac risk index.

From Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol.* 2014;64(22):e77–e137.

withdrawal greater than 4 days was associated with a 2.9 odds ratio of increased risk of cardiac morbidity in vascular surgery.<sup>169d</sup> The guidelines advocate continuing statin therapy in patients currently taking statins as a Class I indication. A multimodal approach to medical management should be taken in high-risk patients. There continues to be controversy regarding the optimal management of ACE inhibitors and ARBs. In the Veterans Administration, withholding ARB postoperatively is strongly associated with increased 30-day mortality, especially in younger patients, although residual confounding may be present.<sup>169e</sup> In the VISION trial, compared to patients who continued their ACE inhibitors/angiotensin II receptor blockers, the ACE/ARB users who withheld their agents in the 24 hours before surgery were less likely to suffer the primary composite outcome of all-cause death, stroke, or myocardial injury (adjusted relative risk, 0.82; 95% CI, 0.70 to 0.96;  $P = .01$ ); and intraoperative hypotension (adjusted relative risk, 0.80; 95% CI, 0.72-0.93;  $P < .001$ ).<sup>169f</sup> The current AHA/ACC Guidelines suggest that continuation of ACE inhibitors or angiotensin-receptor ARBs periopera-

tively is reasonable, but should be restarted as soon as reasonable. The new study questions this recommendation, but further randomized trials are needed.

4. Perioperative transfusion therapy is discussed in more detail in Chapter 49. The FOCUS (Functional Outcomes in Cardiovascular Patients Undergoing Surgical Repair of Hip Fracture) trial was unable to demonstrate benefit in high-risk patients with hip fracture between a high and low transfusion trigger.<sup>170</sup>

## VALVULAR HEART DISEASE

Major alterations in the preoperative management of patients with valvular heart disease have been made regarding the use of anticoagulant therapy and are now based on the causes of the disease. Preoperative and intraoperative management of patients with valvular heart disease is discussed in Chapters 31 and 54.

The prognosis and the perioperative risk for patients with valvular heart disease depend on the stage of the disease. Although stenotic lesions typically progress faster than regurgitant lesions, regurgitant lesions from infective endocarditis, rupture of the chordae tendineae, or ischemic heart disease can be rapidly fatal. Left ventricular dysfunction is common in the late stage of valvular heart disease, both stenotic and regurgitant.

Preoperative maintenance of drug therapy can be crucial; for example, a patient with severe aortic stenosis can deteriorate rapidly with the onset of atrial fibrillation or flutter because the atrial contribution to left ventricular filling can be critical in maintaining cardiac output. One of the most serious complications of valvular heart surgery and of preoperative valvular heart disease is cardiac arrhythmia. Conduction disorders and long-term therapy with antiarrhythmic and inotropic drugs are discussed elsewhere in this chapter. The reader is referred to Chapter 78 and to other sources for discussion of the management of a child with congenital heart disease who is undergoing noncardiac surgery.<sup>171</sup>

### Preoperative Antibiotic Prophylaxis for Endocarditis

Patients who have any form of valvular heart disease, as well as those with intracardiac (ventricular septal or atrial septal defects) or intravascular shunts, should be protected against endocarditis at the time of a known bacteremic event. Endocarditis has occurred in a sufficiently significant number of patients with hypertrophic cardiomyopathy (subvalvular aortic stenosis, asymmetric septal hypertrophy) and mitral valve prolapse to warrant the inclusion of these two conditions in the prophylaxis regimen.

Bacteremia occurs after the following events: dental extraction, 30% to 80%; brushing of teeth, 20% to 24%; use of oral irrigation devices, 20% to 24%; barium enema, 11%; transurethral resection of the prostate (TURP), 10% to 57%; upper GI endoscopy, 8%; nasotracheal intubation, 16% (4 of 25 patients); and orotracheal intubation, 0% (0 of 25 patients). The most recent guidelines from the AHA consisted of an update in 2008 from the AHA/ACC on endocarditis in patients with valvular heart disease, with changes from the 2006 document shown in Table 32.6.<sup>172</sup>

**TABLE 32.6** Changes Related to Endocarditis Prophylaxis: American College of Cardiology/American Heart Association Guidelines on Valvular Heart Disease

2006 VHD Guideline Recommendations	2008 VHD Focused Update Recommendations	Comments
<b>Class I</b> <p>Prophylaxis against infective endocarditis is recommended for the following patients:</p> <ul style="list-style-type: none"> <li>Patients with prosthetic heart valves and patients with a history of infective endocarditis (<i>level of evidence: C</i>)</li> <li>Patients who have complex cyanotic congenital heart disease (e.g., single-ventricle states, transposition of the great arteries, tetralogy of Fallot) (<i>level of evidence: C</i>)</li> <li>Patients with surgically constructed systemic pulmonary shunts or conduits (<i>level of evidence: C</i>)</li> <li>Patients with congenital cardiac valve malformations, particularly those with bicuspid aortic valves, and patients with acquired valvular dysfunction (e.g., rheumatic heart disease) (<i>level of evidence: C</i>)</li> <li>Patients who have undergone valve repair (<i>level of evidence: C</i>)</li> <li>Patients who have hypertrophic cardiomyopathy when there is latent or resting obstruction (<i>level of evidence: C</i>)</li> <li>Patients with MVP and auscultatory evidence of valvular regurgitation and/or thickened leaflets on echocardiography* (<i>level of evidence: C</i>)</li> </ul>	<b>Class IIa</b> <p>Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa:</p> <ul style="list-style-type: none"> <li>Patients with prosthetic cardiac valves or prosthetic material used for cardiac valve repair (<i>level of evidence: B</i>)</li> <li>Patients with previous infective endocarditis (<i>level of evidence: B</i>)</li> <li>Patients with CHD (<i>level of evidence: B</i>)</li> <li>Unrepaired cyanotic CHD, including palliative shunts and conduits (<i>level of evidence: B</i>)</li> <li>Completely repaired congenital heart defect repaired with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure (<i>level of evidence: B</i>)</li> <li>Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (both of which inhibit endothelialization) (<i>level of evidence: B</i>)</li> <li>Cardiac transplant recipients with valve regurgitation as a result of a structurally abnormal valve (<i>level of evidence: C</i>)</li> </ul>	Modified recommendation (changed class of recommendation from I to IIa, changed text); no class I recommendations exist for infective endocarditis prophylaxis

CHD, Congenital heart disease; MVP, mitral valve prolapse; VHD, valvular heart disease.

\*This footnote is obsolete. Please see 2006 VHD Guideline 3 for footnote text, in Bonow RO, Carabello BA, Kanu C et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation*. 2006;114:e84–e231.

From Nishimura RA, Carabello BA, Faxon DP, et al. ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines: endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2008;118:887–896.

### Cardiac Valve Prostheses and Anticoagulant Therapy and Prophylaxis for Deep Vein Thrombosis

In patients with prosthetic valves, the risk of increased bleeding during a procedure in a patient receiving anti-thrombotic therapy must be weighed against the increased risk of thromboembolism caused by stopping the therapy. Common practice in patients undergoing noncardiac surgery with a mechanical prosthetic valve in place is cessation of anticoagulant therapy 3 days preoperatively. This time frame allows the international normalized ratio to fall to less than 1.5 times normal. The oral anticoagulants can then be resumed on postoperative day 1. Using a similar protocol, Katholi and colleagues found no perioperative episodes of thromboembolism or hemorrhage in 25 patients.<sup>173</sup> An alternative approach in patients at high risk for thromboembolism is conversion to heparin during the perioperative period. The heparin can then be discontinued 4 to 6 hours preoperatively and resumed shortly thereafter. Current prosthetic valves may have a lower incidence of this complication, and the risk associated with heparin may outweigh its benefit in the perioperative setting. According to the AHA/ACC guidelines, heparin can usually be reserved for patients who have had a recent thrombus or embolus within 1 year, those with demonstrated thrombotic problems when previously off therapy, and those with more than three risk factors (atrial fibrillation, previous thromboembolism, hypercoagulable condition, and mechanical prosthesis).<sup>174</sup> A lower threshold for

recommending heparin should be considered in patients with mechanical valves in the mitral position, in whom a single risk factor would be sufficient evidence of high risk. Subcutaneous low-molecular-weight heparin offers an alternative outpatient approach.<sup>175</sup> It is appropriate for the surgeon and cardiologist to discuss the optimal perioperative management for such a patient, including a review of the most recent guidelines.<sup>176</sup> A new guideline publication was published in 2014.<sup>176a</sup>

Regional anesthetic techniques may be avoided, although this issue is controversial as many practitioners will use regional anesthesia in patients who are receiving prophylaxis for deep vein thrombosis.<sup>177–180</sup> However, epidural hematoma has been associated with anticoagulant therapy in many reports. Large retrospective reviews of outcome after epidural or spinal anesthesia, or both, during or shortly before initiation of anticoagulant therapy with heparin have not reported neurologic dysfunction related to hematoma formation in any patient.<sup>181,182</sup> This paucity of damaging epidemiologic evidence, although reassuring, does not reduce the need for frequent evaluation of neurologic function and a search for back pain in the perioperative period after regional anesthesia in any patient receiving any anticoagulation or antiplatelet.<sup>177,183–185</sup> The risk of regional anesthesia concurrent with prophylaxis for deep vein thrombosis with heparin is greater with the use of low-molecular-weight heparin. Heparin-induced thrombocytopenia has been treated successfully with intravenous immunoglobulin.<sup>179</sup> The American Society of Regional

Anesthesia and Pain Management has issued a consensus statement on the use of regional anesthesia in anticoagulated patients.<sup>186</sup> They suggest that the decision to perform spinal or epidural anesthesia or analgesia, and the timing of catheter removal in a patient receiving antithrombotic therapy should be made on an individual basis, with the small but definite risk of spinal hematoma weighed against the benefits of regional anesthesia for a specific patient.

It was, previously, determined that venous thromboembolism is so common in postoperative patients that almost 1% of postsurgical patients die of fatal pulmonary embolism (Table 32.7).<sup>187</sup> More recently, it has been estimated that venous thromboembolism is responsible for up to 10% of all hospital-related deaths.<sup>187a</sup> Because of this high mortality risk, prophylaxis against deep vein thrombosis has attained widespread acceptance; thus prophylaxis begins with 5000 units of heparin given subcutaneously 2 hours preoperatively.<sup>187-189</sup> Other trials have shown equal effect with external pneumatic sequential compression devices.<sup>188,190</sup> The most current recommendations are available from the American College of Chest Physicians for prophylaxis against venous thromboembolism in 2012.<sup>190a</sup>

Another problem that can arise is managing a pregnant patient with a prosthetic valve during delivery. It is recommended that warfarin be replaced by subcutaneous heparin during the peripartum period. During labor and delivery, elective induction of labor is advocated with discontinuance of all anticoagulant therapy, as indicated for the particular valve prosthesis (discussed earlier).<sup>191</sup>

Auscultation of the prosthetic valve should be performed preoperatively to verify normal functioning. Abnormalities in such sounds warrant preoperative consultation and verification of functioning.

## CARDIAC CONDUCTION DISTURBANCES: CARDIAC ARRHYTHMIAS

Bradyarrhythmias, especially if profound or associated with dizziness or syncope, are generally managed with pacemakers. However, chronic bifascicular block (right bundle branch block with a left anterior or posterior hemiblock or left bundle branch block with combined left anterior and posterior hemiblocks), even when only a first-degree heart block is present, can progress to complete heart block and sudden perioperative death on rare occasion. In six studies, less than 2% of the approximately 266 patients with bifascicular block progressed to complete heart block perioperatively.<sup>192</sup> Conversely, these patients have a high 5-year mortality rate (160 of 554 patients, or 29%). Most of the deaths were related to tachyarrhythmias or ischemic events not usually preventable by traditional pacemakers.<sup>193</sup> Thus the presence of a bifascicular block on the ECG should make the anesthesiologist worried about associated CAD or left ventricular dysfunction; an echocardiogram should be evaluated perioperatively. Nevertheless, these patients rarely have complete heart block perioperatively. Therefore, prophylactic preoperative insertion of temporary pacing wires for bifascicular block does not seem warranted; however, central access can be established in advance in the event that a temporary pacemaker needs to be inserted (most operating rooms do not rely on transthoracic pacing, although it may be attempted if available).<sup>194</sup> The actual pacemaker equipment and appropriate personnel

**TABLE 32.7** Incidence of Deep Vein Thrombosis and Fatal Pulmonary Embolism

Type of Surgery	INCIDENCE OF		
	Deep Vein Thrombosis (%)	Proximal Deep Vein Thrombosis (%)	Fatal Pulmonary Embolism (%)
<b>GENERAL</b>			
Age >40 years	10	<1	0.1
Age >60 years	10-40	3-15	0.8
Malignancy	50-60		
Thoracic	30		
<b>VASCULAR</b>			
Aortic repair	26		
Peripheral	12		
<b>UROLOGIC</b>			
Open prostatectomy	40		
TURP	10		
Other urologic	30-40		
<b>MAJOR GYNECOLOGIC</b>			
With malignancy	40		
Without malignancy	10-20		
<b>NEUROSURGERY</b>			
Craniotomy	20-80		
Laminectomy	4-25		1.5-3.0
<b>ORTHOPEDIC</b>			
Total hip replacement	40-80	10-20	1.0-5.0
Hip fracture	48-75		1.0-5.0
Tibial fracture	45		
Total knee replacement	60-70	20	1.0-5.0
Head, neck, chest wall	11		
<b>MEDICAL</b>			
Acute myocardial infarction	30	6	
Stroke	60-75		
Acute spine injury	60-100		
Other bed bound	26		

TURP, Transurethral resection of the prostate.

should be immediately available, and the equipment should be tested regularly, because symptomatic heart block does occur perioperatively in more than 1% of patients. One study appears to have confirmed this rate of at least 1% for patients undergoing cardiac surgery.<sup>195</sup> One percent of patients in whom a pacing pulmonary artery catheter was not inserted preoperatively subsequently required pacing before cardiopulmonary bypass. By contrast, 19% of patients who had such a catheter in place underwent cardiac pacing before cardiopulmonary bypass. Predictors of the need for pacing included previous symptomatic bradyarrhythmia, a history of transient complete AV block, and aortic valve disease.

Older studies demonstrated that a rate of more than five PVCs per minute on preoperative examination correlates

with perioperative cardiac morbidity.<sup>144,151-153</sup> To the classic criteria for treating PVCs (the presence of R-on-T couplets, the occurrence of more than three PVCs per minute, and multifocality of PVCs) must be added frequent ( $>10/\text{h}$  over a 24-hour period) and repetitive ventricular beats. Electrophysiologic and programmed ventricular stimulation studies are being used to indicate and guide treatment of patients with ischemic heart disease or recurrent arrhythmias and survivors of out-of-hospital cardiac arrest. Although such patients are often treated with antiarrhythmic therapy, attention to their underlying condition should be a focus of our preoperative management. Long-term antiarrhythmic therapy is discussed in the last section of this chapter, on drug therapy. Torsades de pointes is an arrhythmia characterized by episodes of alternating electrical polarity such that the major vector of the QRS complex seems to alternate around an isoelectric line. The hallmark enabling differential diagnosis from ventricular tachycardia is the unusual response of this arrhythmia to commonly used antiarrhythmic drugs. In other words, the use of drugs that prolong the QT interval (e.g., quinidine, procainamide, disopyramide, some of the antihistamines, and the antipsychotic phenothiazines) may well make the arrhythmia more frequent or of longer duration. Reports of the sudden occurrence of torsades de pointes during surgical procedures have been rare in the anesthesia literature. Immediate therapy consists of the administration of magnesium or electrical cardioversion, followed by overdrive cardiac pacing or the administration of  $\beta$ -adrenergic agonists and discontinuation of drugs that prolong the QT interval.

Premature atrial contractions and cardiac rhythms other than sinus also correlate with perioperative cardiac morbidity.<sup>144,152</sup> These arrhythmias may be more a marker of poor cardiovascular reserve than a specific cause of perioperative cardiac complications.

Preexcitation syndrome is the name for supraventricular tachycardias associated with AV bypass tracts.<sup>196</sup> Successful treatment, which is predicated on an understanding of the clinical and electrophysiologic manifestations of the syndrome, consists of either catheter ablation techniques or surgery using preoperative and intraoperative techniques that avoid release of sympathetic and other vasoactive substances and therefore tachyarrhythmias.<sup>193,197,198</sup> Anesthesia for electrophysiologic procedures is discussed in Chapter 55.

## Disorders of the Respiratory and Immune Systems

### GENERAL PREOPERATIVE AND PREPROCEDURE CONSIDERATIONS

Pulmonary complications after procedures requiring anesthesia are as common as cardiovascular complications—even more common if venous thromboembolism is included. It has, relatively recently, been estimated that postoperative respiratory complications can occur in up to 80% of surgical patients, noting obesity, preexisting pulmonary disease, and advanced age are among the chief risk factors.<sup>198a</sup> Thus pulmonary complications are equally as important or more important to the patient and the health system in terms of

morbidity, mortality, length-of-stay extension, and cost. Today there is an even greater appreciation of the effects of smoking and sleep apnea on perioperative and long-term care has increased.<sup>199-216</sup> (Preoperative and preprocedure identification and perioperative care of patients with sleep apnea are discussed in the earlier section on obesity and in Chapter 58.)

The main purpose of preoperative testing is to identify patients at risk for perioperative complications so that appropriate perioperative therapy can be instituted to foster return to functional status. Preoperative assessment can also establish baseline function and the feasibility of surgical intervention. Whereas numerous investigators have used pulmonary function tests to define inoperability or high-risk versus low-risk groups for pulmonary complications, few have been able to demonstrate that the performance of any specific preoperative or intraoperative measure, except perhaps smoking cessation and physical activity such as a walking program, reliably decreases perioperative pulmonary morbidity or mortality and improves patient outcomes. Because routine preoperative pulmonary testing and care are discussed extensively in Chapter 41, the current discussion is limited to an assessment of the effectiveness of this type of care.

In fact, few randomized prospective studies indicate an outcome benefit of preoperative preparation. Stein and Cassara randomly allocated 48 patients to undergo preoperative therapy (cessation of smoking, administration of antibiotics for purulent sputum, and use of bronchodilating drugs, postural drainage, chest physiotherapy, and ultrasonic nebulizer) or no preoperative therapy.<sup>212</sup> The no-treatment group had a mortality of 16% and morbidity of 60%, as opposed to 0% and 20%, respectively, for the treatment group. In addition, the treatment group spent an average of 12 postoperative days in the hospital as compared with 24 days for the 21 survivors in the no-treatment group.<sup>212</sup>

Collins and colleagues prospectively examined the benefits of preoperative antibiotics, perioperative chest physiotherapy and therapy with bronchodilating drugs, and routine postoperative analgesia (morphine) on postoperative respiratory complications in patients with COPD.<sup>217</sup> Of these therapies, only preoperative treatment with antibiotics had a beneficial effect.

Hulzebos and colleagues performed a single-center randomized trial of intensive inspiratory muscle training.<sup>218</sup> Preoperative inspiratory muscle training reduced the incidence of postoperative pulmonary complications and the duration of postoperative hospitalization in patients at high risk of developing a pulmonary complication who were undergoing CABG surgery.

Warner and coworkers collected data retrospectively about smoking history and prospectively (concurrently) about pulmonary complications for 200 patients undergoing CABG.<sup>219</sup> These investigators documented that 8 weeks or more of smoking cessation was associated with a 66% reduction in postoperative pulmonary complications. Smokers who stopped for less than 8 weeks actually had an increase (from 33% for current smokers to 57.1% for recent quitters) in the rate of one or more of the six complications surveyed: purulent sputum with pyrexia; need for respiratory therapy care; bronchospasm requiring therapy; pleural effusion or pneumothorax (or both)

necessitating drainage; segmental pulmonary collapse, as confirmed by radiography; or pneumonia necessitating antibiotic therapy. Other investigators have found that both shorter and longer periods of cessation of smoking were needed before achieving cardiovascular<sup>220</sup> and hematologic benefit.<sup>221</sup> Bluman and associates performed a retrospective chart review of 410 patients undergoing noncardiac surgery at a VA hospital.<sup>222</sup> Current smoking was associated with a nearly 6-fold increase in the risk of a postoperative pulmonary complication. Reduction in smoking within 1 month of surgery was not associated with a decreased risk for postoperative pulmonary complications. Nakagawa and coauthors also reported higher pulmonary complication rates in patients undergoing pulmonary surgery who quit within 4 weeks of surgery than in current smokers or those who had stopped smoking for more than 4 weeks.<sup>223</sup> Wong and colleagues performed a systematic review of 25 studies of smoking cessation.<sup>224</sup> At least 4 weeks of abstinence from smoking reduced respiratory complications, and abstinence of at least 3 to 4 weeks reduced wound healing complications. Short-term (<4 weeks) smoking cessation did not appear to affect the risk of postoperative respiratory complications.

Two randomized trials focused on smoking cessation. Wong and colleagues performed a prospective, multicenter, double-blind, placebo-controlled trial, in which 286 patients were randomized to receive varenicline or placebo.<sup>225</sup> A perioperative smoking cessation intervention with varenicline increased abstinence from smoking 3, 6, and 12 months after elective noncardiac surgery with no increase in serious adverse events. Lee and colleagues randomized patients to a group receiving no specific smoking cessation intervention or to an intervention group that received (1) brief counseling by the preadmission nurse, (2) brochures on smoking cessation, (3) referral to the Canadian Cancer Society's Smokers' Helpline, and (4) a free 6-week supply of transdermal nicotine replacement therapy.<sup>226</sup> All outcome assessors and caregivers on the operative day were blinded to group assignment. Smoking cessation occurred in 12 patients (14.3%) in the intervention group as compared with 3 patients (3.6%) in the control group (relative risk, 4.0; 95% CI, 1.2-13.7;  $P = .03$ ). The overall rate of combined intraoperative and immediate postoperative complications was not significantly different between intervention and control groups. At follow-up 30 days postoperatively, smoking cessation was reported in 22 patients (28.6%) in the intervention group compared with 8 patients (11%) in controls (relative risk, 2.6; 95% CI, 1.2-5.5;  $P = .008$ ).

When Skolnick and coworkers studied 602 children prospectively, exposure to passive smoking (as measured by urinary cotinine, the major metabolite of nicotine) correlated directly with airway complications. Children with the least exposure to passive smoke had the fewest complications.<sup>210</sup> Secondhand smoke may be a model for particulate air pollution, which can have immediate and long-term effects in increasing lung dysfunction and inflammatory stimuli throughout the body.<sup>227,228</sup>

Celli and associates performed a randomized prospective controlled trial of intermittent positive-pressure breathing (IPPB) versus incentive spirometry and deep-breathing exercises in 81 patients undergoing abdominal surgery.<sup>229</sup> The groups exposed to a respiratory therapist (regardless of the treatment given) had more than a 50% lower incidence

of clinical complications (30%-33% vs. 88%) and shorter hospital stays than did the control group. Thus this demonstrates that the outcome improves when any concern about lung function is shown by someone knowledgeable in maneuvers designed to clear lung secretions.

Bartlett and coworkers randomly assigned 150 patients undergoing extensive laparotomy to 1 of 2 groups.<sup>230</sup> One group received preoperative instruction in and postoperative use of incentive spirometry (10 times/h). The other group received similar medical care but no incentive spirometry. Only 7 of 75 patients using incentive spirometry had postoperative pulmonary complications, as opposed to 19 of 75 in the control group. However, Lyager and colleagues randomly assigned 103 patients undergoing biliary or gastric surgery to receive either incentive spirometry with preoperative and postoperative chest physiotherapy or only preoperative and postoperative chest physiotherapy.<sup>231</sup> No difference in the postoperative course or pulmonary complications was found between the groups. Other studies have shown a specific benefit (i.e., greater than that provided by routine care) for chest physiotherapy and IPPB. These studies are usually poorly controlled, not randomized, or retrospective in design (or any combination); these deficiencies probably substantially bias the results toward finding a benefit in reducing postoperative pulmonary complications. Although randomized prospective studies showed no benefit or actual harm from chest physiotherapy and IPPB on the resolution of pneumonia or postoperative pulmonary complications, the studies cited earlier<sup>212,217,229,230</sup> and numerous retrospective studies strongly suggest that preoperative evaluation and treatment of patients with pulmonary disease actually decrease perioperative respiratory complications.

Meta-analyses have suggested a benefit of anesthetic and pain management with respect to respiratory outcomes. Rodgers and associates reviewed 141 trials involving 9559 patients who had been randomized to receive neuraxial blockade or general anesthesia. Overall mortality was significantly less frequent in the neuraxial blockade group (2.1% vs. 3.1%). The relative risk of pneumonia in the neuraxial blockade group was 0.61 (CI, 0.48-0.81), and the relative risk of respiratory depression was 0.41 (CI, 0.23-0.73).<sup>211</sup> Further, Neuman and colleagues examined a retrospective cohort of 18,158 patients undergoing surgery for hip fracture in 126 hospitals in New York in 2007 and 2008.<sup>232</sup> Patients receiving regional anesthesia experienced fewer pulmonary complications (359 [6.8%] vs. 1040 [8.1%];  $P < .005$ ). Regional anesthesia was associated with a lower adjusted odds of mortality (OR, 0.710; 95% CI, 0.541, 0.932;  $P = .014$ ) and pulmonary complications (OR, 0.752; 95% CI, 0.637, 0.887;  $P < .0001$ ) relative to general anesthesia. In subgroup analyses, regional anesthesia was associated with improved survival and fewer pulmonary complications among patients with intertrochanteric fractures but not among patients with femoral neck fractures.

Not all studies demonstrate beneficial effects of pharmacologic pretreatment. In afebrile outpatient American Society of Anesthesiologists (ASA) class I and II children with no lung disease or findings who underwent noncavitory, non-airway surgery lasting less than 3 hours, neither albuterol nor ipratropium premedication decreased adverse events.<sup>233</sup>

Evaluation of dyspnea is especially useful. Boushy and coworkers found that grades of preoperative dyspnea correlated with postoperative survival. (Grades of respiratory

**TABLE 32.8** Grade of Dyspnea Caused by Respiratory Problems (Assessed in Terms of Walking on a Level Surface at a Normal Pace)

Category	Description
0	No dyspnea while walking on a level surface at a normal pace
I	"I am able to walk as far as I like, provided I take my time"
II	Specific (street) block limitation ("I have to stop for a while after one or two blocks")
III	Dyspnea on mild exertion ("I have to stop and rest while going from the kitchen to the bathroom")
IV	Dyspnea at rest

Modified from Boushy SF, Billing DM, North LB, et al. Clinical course related to preoperative pulmonary function in patients with bronchogenic carcinoma. *Chest*. 1971;59:383–391.

dyspnea are provided in Table 32.8.<sup>234</sup> Mittman demonstrated an increased risk of death after thoracic surgery, from 8% in patients without dyspnea to 56% in patients with dyspnea.<sup>235</sup> Similarly, Reichel found that no patients died after pneumonectomy if they were able to complete a preoperative treadmill test for 4 minutes at the rate of 2 mph on level ground.<sup>236</sup> Other studies have found that the history and physical examination of an asthmatic subject can also predict the need for hospitalization.<sup>201</sup> Wong and colleagues found that the risk index correlated with postoperative pulmonary complications (Table 32.9).<sup>237</sup>

Arozullah and associates developed the first validated multifactorial risk index for postoperative respiratory failure, defined as mechanical ventilation for more than 48 hours after surgical procedures, or reintubation and mechanical ventilation after postoperative extubation.<sup>238</sup> In a prospective cohort study of 181,000 male veterans as part of the National Veterans Administration Surgical Quality Improvement Program, seven factors independently predicted risk (Table 32.10). With increasing numbers of risk factors present, the rate of complications increased from 0.5% (class 1) to 26.6% (class 4). Arozullah and colleagues subsequently developed a risk index for postoperative pneumonia by using data on 160,805 patients undergoing major noncardiac surgery and validated the index by using data on an additional 155,266 patients.<sup>239</sup> Patients were divided into five risk classes by using risk index scores (Table 32.11). Pneumonia rates were 0.2% in patients with 0 to 15 risk points, 1.2% in those with 16 to 25 risk points, 4.0% in those with 26 to 40 risk points, 9.4% in those with 41 to 55 risk points, and 15.3% in those with more than 55 risk points.

Gupta and colleagues used the American College of Surgeons NSQIP to develop a risk model for postoperative respiratory failure.<sup>167</sup> On multivariate logistic regression analysis, five preoperative predictors of postoperative respiratory failure were identified: type of surgery, emergency case, dependent functional status, preoperative sepsis, and higher ASA class (Table 32.12).

## SPECIFIC DISEASES

### Pulmonary Vascular Diseases

Pulmonary vascular diseases include pulmonary hypertension secondary to heart disease (postcapillary disorders),

**TABLE 32.9** Classification of Risk of Pulmonary Complications for Thoracic and Abdominal Procedures

Category	Points
<b>I. EXPIRATORY SPIROGRAM</b>	
A. Normal (% FVC + [% FEV <sub>1</sub> /FVC] > 150)	0
B. % FVC + (% FEV <sub>1</sub> /FVC) = 100-150	1
C. % FVC + (% FEV <sub>1</sub> /FVC) < 100	2
D. Preoperative FVC < 20 mL/kg	3
E. Post bronchodilator FEV <sub>1</sub> /FVC < 50%	3
<b>II. CARDIOVASCULAR SYSTEM</b>	
A. Normal	0
B. Controlled hypertension, myocardial infarction without sequelae for > 2 years	0
C. Dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, dependent edema, congestive heart failure, angina	1
<b>III. NERVOUS SYSTEM</b>	
A. Normal	0
B. Confusion, obtundation, agitation, spasticity, coordination, bulbar malfunction	1
C. Significant muscular weakness	1
<b>IV. ARTERIAL BLOOD GASES</b>	
A. Acceptable	0
B. Paco <sub>2</sub> > 50 mm Hg or PaO <sub>2</sub> < 60 mm Hg on room air	1
C. Metabolic pH abnormality > 7.50 or < 7.30	1
<b>V. POSTOPERATIVE AMBULATION</b>	
A. Expected ambulation (minimum, sitting at bedside) within 36 h	0
B. Expected complete bed confinement for ≥ 36 h	1

FEV<sub>1</sub>, Forced expiratory volume in 1 second; FVC, forced vital capacity; Paco<sub>2</sub>, arterial partial pressure of carbon dioxide; PaO<sub>2</sub>, arterial partial pressure of oxygen.

Modified from Wong DH, Weber EC, Schell MJ, et al. Factors associated with postoperative pulmonary complications in patients with severe COPD. *Anesth Analg*. 1995;80:276–284.

parenchymal lung disease (pulmonary precapillary disorders), pulmonary embolism, and cor pulmonale from COPD.<sup>240</sup> Optimal preoperative management of these conditions requires treatment of the underlying disease and avoidance of worsening the process.<sup>240-242</sup> Because pulmonary embolism can be particularly difficult to diagnose as clinical findings of pulmonary emboli are not always present or specific for the diagnosis and include a history of tachypnea, dyspnea, palpitations, syncope, chest pain, or hemoptysis. Physical examination can reveal a pleural rub, wheezing, rales, a fixed and split second heart sound, right ventricular lift, or evidence of venous thrombosis. If the ECG shows an S<sub>1</sub>Q<sub>3</sub> pattern, spiral CT or lung perfusion scans can be obtained to rule out the diagnosis of pulmonary emboli. A high degree of suspicion is necessary to warrant angiography and anticoagulation or fibrinolytic therapy. If possible, the reactivity of the pulmonary vasculature should be determined because it may be enhanced or decreased by such drugs as nifedipine, hydralazine, nitroglycerin, prazosin, tolazoline, phentolamine, sildenafil citrate, and nitric oxide.

**TABLE 32.10** Preoperative Predictors of Postoperative Respiratory Failure

Variable	Odds Ratio (95% Confidence Interval)
<b>TYPE OF SURGERY</b>	
Abdominal aortic aneurysm	14.3 (12.0-16.9)
Thoracic	8.14 (7.17-9.25)
Neurosurgery, upper abdominal, or peripheral vascular	4.21 (3.80-4.67)
Neck	3.10 (2.40-4.01)
Other surgery*	1.00 (reference)
Emergency surgery	3.12 (2.83-3.43)
<b>Albumin &lt; 30 g/L</b>	2.53 (2.28-2.80)
<b>Blood urea nitrogen &gt; 30 mg/dL</b>	2.29 (2.04-2.56)
<b>Partially or fully dependent status</b>	1.92 (1.74-2.11)
<b>History of COPD</b>	1.81 (1.66-1.98)
<b>AGE (YEARS)</b>	
≥70	1.91 (1.71-2.13)
0-69	1.51 (1.36-1.69)
<60	1.00 (reference)

COPD, Chronic obstructive pulmonary disease.

\*Other surgery includes ophthalmologic, ear, nose, mouth, lower abdominal, extremity, dermatologic, spine, and back surgery.

From Arozullah AM, Daley J, Henderson WG, et al. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery: the National Veterans Administration Surgical Quality Improvement Program. *Ann Surg.* 2000;232:242-253.

Monitoring of pulmonary artery pressure is often required. Preoperative measures should be undertaken to ensure that the patient is not exposed to conditions that elevate pulmonary vascular resistance (e.g., hypoxia, hypercapnia, acidosis, lung hyperinflation, hypothermia)<sup>243</sup> or increased systemic vascular resistance, as this can precipitate acute or worsened right heart failure.

### Infectious Diseases of the Lung

Preoperative evaluation and treatment should follow the basic guidelines outlined in the introduction to this section and in Chapter 31. Treatment of the underlying disease should be completed before all but emergency surgery is performed.

Even though elective surgery should be postponed whenever infectious diseases of the lung are present, patients undergoing emergency surgery can have nosocomial infections and immunocompromised systems. The predominant pathogens for nosocomial pneumonia are gram-negative bacilli, *Staphylococcus aureus*, *Haemophilus influenzae*, anaerobes, and pneumococci. Previously, the incidence of tuberculosis increased in the late 1980s and in the 1990s, probably because of reactivation in patients infected with HIV, through increased funding and directly observed anti-tuberculosis treatment the incidence has steadily declined. Tuberculosis can lead to chronic pulmonary and systemic symptoms. Affected patients may have malaise, headache, fever, hemoptysis, and extrapulmonary diseases affecting the skin, cervical lymph nodes, kidneys, pericardium, and meninges. Active disease is treated with four-drug therapy:

**TABLE 32.11** Postoperative Pneumonia Risk Index

Preoperative Risk Factor	Point Value
<b>TYPE OF SURGERY</b>	
Abdominal aortic aneurysm repair	15
Thoracic	14
Upper abdominal	10
Neck	8
Neurosurgery	8
Vascular	3
<b>AGE</b>	
80 years	17
70-79 years	13
60-69 years	9
50-59 years	4
<b>FUNCTIONAL STATUS</b>	
Totally dependent	10
Partially dependent	6
Weight loss >10% in past 6 months	7
History of COPD	5
General anesthesia	4
Impaired sensorium	4
History of cerebrovascular accident	4
<b>BLOOD UREA NITROGEN LEVEL</b>	
<2.86 mmol/L (0.8 mg/dL)	4
7.85-10.7 mmol/L (22-30 mg/dL)	2
≥10.7 mmol/L (≥30 mg/dL)	3
Transfusion >4 units	3
Emergency surgery	3
Steroid use for chronic condition	3
Current smoker within 1 year	3
Alcohol intake >2 drinks/day in past 2 weeks	2

COPD, Chronic obstructive pulmonary disease.

From Arozullah AM, Khuri SF, Henderson WG, et al. Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. *Ann Intern Med.* 2001;135:847-857.

isoniazid, pyrazinamide, ethambutol or streptomycin, and rifampin for 9 months. Therapy should probably be started preoperatively.

Management of these emergency patients (many of whom have adult respiratory distress syndrome [ARDS]) before they are brought to the operating room may include initiation of antiinfective therapy, optimization of fluid status, facilitation of gas exchange, and therapy for the underlying pathophysiologic process.

### Chronic Diseases of the Lung

Treatment of COPD may include the use of short and long acting  $\beta$ -adrenergic drugs, parasympatholytic agents (especially for exercise-induced asthma), systemic or inhaled corticosteroids, and leukotriene antagonists. An estimated

**TABLE 32.12** Preoperative Variables Significantly Associated With an Increased Risk for Postoperative Respiratory Failure in 2007 Model from the American College of Surgeons National Surgical Quality Improvement Project\*

Parameter	Adjusted OR	95% Wald CI
Totally dependent functional status <sup>†</sup>	4.07	3.68-4.51
Partially dependent functional status <sup>†</sup>	2.16	1.98-2.34
ASA class 1 <sup>‡</sup>	0.03	0.02-0.05
ASA class 2 <sup>‡</sup>	0.14	0.11-0.17
ASA class 3 <sup>‡</sup>	0.54	0.44-0.67
ASA class 4 <sup>‡</sup>	1.28	1.04-1.57
Preoperative sepsis (none) <sup>§</sup>	0.46	0.42-0.50
Preoperative sepsis <sup>§</sup>	1.32	1.16-1.49
Preoperative septic shock <sup>§</sup>	2.47	2.16-2.82
Emergency case (absence versus presence)	0.56	0.52-0.61
Anorectal <sup>¶</sup>	0.26	0.15-0.44
Aortic <sup>¶</sup>	2.94	2.35-3.68
Bariatric <sup>¶</sup>	0.36	0.27-0.49
Brain <sup>¶</sup>	2.08	1.15-3.78
Breast <sup>¶</sup>	0.07	0.04-0.12
Cardiac <sup>¶</sup>	1.32	0.92-1.88
Ear, nose, and throat <sup>¶</sup>	1.11	0.26-4.71
Foregut/hepatopancreatobiliary <sup>¶</sup>	2.64	2.13-3.27
Gallbladder, appendix, adrenals, and spleen <sup>¶</sup>	0.57	0.45-0.71
Intestinal <sup>¶</sup>	1.78	1.44-2.18
Neck <sup>¶</sup>	0.59	0.33-1.07
Obstetrics and gynecology <sup>¶</sup>	0.29	0.09-0.94
Orthopedic <sup>¶</sup>	0.42	0.33-0.55
Other abdominal <sup>¶</sup>	1.27	1.001-1.62
Peripheral vascular <sup>¶</sup>	0.79	0.63-0.98
Skin <sup>¶</sup>	0.73	0.55-0.95
Spine <sup>¶</sup>	0.593	0.25-1.39
Thoracic <sup>¶</sup>	1.96	1.43-2.68
Venous <sup>¶</sup>	0.134	0.05-0.37
Urologic <sup>¶</sup>	1.36	0.82-2.28

ASA, American Society of Anesthesiologists; *Cl*, confidence interval; *OR*, odds ratio.

\*The estimate and the standard error (SE) refer to the estimate of the logistic regression coefficient for the specific variable and its associated SE. C-statistic, 0.894.

<sup>†</sup>Reference group, independent functional status.<sup>‡</sup>Reference group, ASA class 5.<sup>§</sup>Reference group, preoperative systemic inflammatory response syndrome.<sup>¶</sup>Reference group, hernia surgery.From Gupta H, Gupta PK, Fang X, et al. Development and validation of a risk calculator predicting postoperative respiratory failure. *Chest*. 2011;140:1207-1215.

5% of this population has bronchospasm. Some investigators recommend using inhaled bronchodilators as first-line drugs and reducing the dose of inhaled steroids, such as beclomethasone dipropionate, budesonide, mometasone, and fluticasone, which are inactivated after absorption. However, in large doses, these “inhaled” steroids can suppress adrenal function, and supplemental systemic corticosteroids may be needed at times of stress (see the earlier discussion in the section on adrenocortical malfunction). Preoperative assessment must include gaining knowledge of

drug regimens and their effects and education of the patient regarding proper use of an inhaler (Box 32.4), given that these drugs can interact dangerously with anesthetics (see the last section of this chapter) or can be used inappropriately and therefore produce side effects without maximum benefit.<sup>199-209</sup> No known interaction between the inhaled anticholinergic ipratropium bromide and muscle relaxants has been reported. An estimated 10% of asthmatic patients exhibit sensitivity to aspirin and may react not only to compounds containing aspirin but also to tartrazine, yellow dye

#### BOX 32.4 Procedures for Correct Use of a Metered-Dose Inhaler

Remove the cap and hold the inhaler upright.  
Shake the inhaler.  
Tilt the head back slightly and exhale steadily to functional residual capacity.  
Position the inhaler by using a spacer between the actuator and the mouth.  
Press down on the inhaler while taking a slow, deep breath (3-5 s). Hold the full inspiration for at least 5 and up to 10 s, if possible, to allow the medication to reach deeply into the lungs.  
Repeat inhalations as directed. Waiting 1 min after inhalation of the bronchodilator may permit subsequent inhalations to penetrate more deeply into the lungs and is necessary to ensure proper delivery of the dose. Rinse your mouth and expectorate after using the inhaler.

number five, indomethacin, other nonsteroidal antiinflammatory drugs, and aminopyrine.<sup>244</sup>

Cystic fibrosis is characterized by dilatation and hypertrophy of the bronchial glands, mucous plugging of the peripheral airways, and frequently, bronchitis, bronchiectasis, and bronchiolectasis. For all these conditions, the measures recommended earlier in this section, as well as appropriate hydration to allow mobilization of secretions, constitute optimal preprocedure therapy.

Surgical resection is the primary therapy for non–small cell carcinomas (e.g., adenocarcinoma, squamous cell carcinoma, and large cell carcinoma). These carcinomas account for 75% of all lung carcinomas, 12% of all malignant tumors, and 20% of all cancer deaths in the United States.<sup>245</sup> Success of surgery can be predicted by the stage of the tumor.

The combination of chemotherapy and radiation therapy is the current treatment of choice for small cell carcinomas of the lung.<sup>246</sup> Oat cell (small cell) carcinoma of the lung and bronchial adenomas are known for their secretion of endocrinologically active substances, such as ACTH-like hormones. Squamous cell cancers in the superior pulmonary sulcus produce Horner syndrome, as well as characteristic pain in areas served by the eighth cervical nerves and first and second thoracic nerves. These tumors are now treated with preoperative radiation; surgical resection leads to an almost 30% “cure” rate. For all these patients, their preoperative assessment should be viewed as a “three-legged stool,” including lung mechanics, parenchymal function, and cardiopulmonary reserve.

#### Anaphylaxis, Anaphylactoid Responses, and Allergic Disorders Other than Those Related to Lung Diseases and Asthma

**Anaphylactic and Anaphylactoid Reactions.** Anaphylaxis is a severe life-threatening allergic reaction. Allergic applies to immunologically mediated reactions, as opposed to those caused by pharmacologic idiosyncrasy, direct toxicity or drug overdosage, or drug-drug interaction.<sup>247-249</sup> Anaphylaxis is the typical immediate hypersensitivity reaction (type I) produced by immunoglobulin E (IgE) mediated release of pharmacologically active substances. These

mediators in turn produce specific end-organ responses in the skin (urticaria), the respiratory system (bronchospasm and upper airway edema), and the cardiovascular system (vasodilation, changes in inotropy, and increased capillary permeability). Vasodilation occurs at the level of the capillary and postcapillary venule and leads to erythema, edema, and smooth muscle contraction. This clinical syndrome is called *anaphylaxis*. By contrast, an *anaphylactoid reaction* denotes an identical or very similar clinical response that is not mediated by IgE or (usually) an antigen-antibody process.<sup>248,249</sup> A large perioperative database review found that hemodynamically significant anaphylaxis occurred in 1 of every 8400 cases.<sup>249a</sup> Further, a personal history of anaphylaxis was the best predictor of occurrence.

In anaphylactic reactions, an injected or inhaled (or ingested) substance—usually drugs, food, or insect venom—can serve as the allergen itself. Low-molecular-weight agents are believed to act as haptens that form immunologic conjugates with host proteins. The offending substance, regardless of whether it is a hapten, may be the parent compound, a nonenzymatically generated product, or a metabolic product formed in the patient’s body. When an allergen binds immunospecific IgE antibodies on the surface of mast cells and basophils, histamine and eosinophilic chemotactic factors of anaphylaxis are released from storage granules in a calcium- and energy-dependent process.<sup>248,249</sup> Other chemical mediators are rapidly synthesized and are subsequently released in response to cellular activation. These mediators include the following: slow-reacting substance of anaphylaxis, which is a combination of three leukotrienes; other leukotrienes;<sup>248,249</sup> kinins; platelet-activating factors; adenosine; chemotactic factors; heparin; tryptase; chymase; and prostaglandins, including the potent bronchoconstrictor prostaglandin D<sub>2</sub>; eosinophil growth and activating factors; mast cell growth factors; and proinflammatory and other factors that contribute to the IgE isotype switch.

The end-organ effects of the mediators produce the clinical syndrome of anaphylaxis. Usually, a first wave of symptoms, including those caused by vasodilation and a feeling of impending doom, is quickly followed by a second wave as the cascade of mediators amplifies the reactions. In a sensitized patient, onset of the signs and symptoms caused by these mediators is usually immediate but may be delayed 2 to 15 minutes or, in rare instances, as long as 2.5 hours after the parenteral injection of antigen.<sup>250,251</sup> After oral administration, manifestations may occur at unpredictable times.

Mast cell proliferation, together with severe progressive inflammation, contributes to the worsening of symptoms that occurs even after an allergen load is no longer present. The antigen present in cells and lymphocytes, as well as activated mast cells, starts to induce the production of cytokines. These proinflammatory cytokines recruit more inflammatory cells, a process that leads to tissue edema and mediates a second wave of mast cell degranulation. This second wave can promote the recurrence of severe symptoms 6 to 8 hours later and necessitates, some believe, at least 8 hours of continued ICU-like observation.

In addition, biologically active mediators can be generated by multiple effector processes to produce an anaphylactoid reaction. Activation of the blood coagulation and fibrinolytic systems, the kinin-generating sequence, or the

complement cascade can produce the same inflammatory substances that result in an anaphylactic reaction. The two mechanisms known to activate the complement system are called classical and alternative. The classical pathway can be initiated through IgG or IgM (transfusion reactions) or plasmin. The alternative pathway can be activated by lipopolysaccharides (endotoxin), drugs (Althesin), radiographic contrast media,<sup>252</sup> membranes (nylon tricot membranes for bubble oxygenators), cellophane membranes of dialyzers, vascular graft material,<sup>253</sup> latex or latex-containing products,<sup>254,255</sup> and perfluorocarbon artificial blood.

Muscle relaxants were previously believed to be the most common drug associated with anaphylaxis, though recent evidence supports protamine and antibiotics with increased risk.<sup>249a</sup> However, this may change with the recent approval of sugammadex as one of the primary concerns regarding the delaying its approval in the United States was "hypersensitivity reactions," which includes anaphylaxis. Latex continues to account for a significant number of these reactions, and the incidence of intraoperative anaphylaxis caused by latex is increasing. In addition, histamine can be liberated independent of immunologic reactions.<sup>256</sup> Mast cells and basophils release histamine in response to chemicals or drugs. Most narcotics can release histamine,<sup>256</sup> and they can produce an anaphylactoid reaction, as can radiographic contrast media.<sup>252</sup> What makes some patients more susceptible to the release of histamine in response to drugs is unknown, but hereditary and environmental factors may play a role.

Intravenous contrast material is probably the most frequently used agent that causes anaphylactoid reactions. Because diagnostic (skin and other) tests are helpful only in IgE-mediated reactions, pretesting is not useful for contrast reactions. Pretreatment with diphenhydramine, cimetidine (or ranitidine), and corticosteroids has been reported to be useful in preventing or ameliorating anaphylactoid reactions to intravenous contrast material.<sup>252,257</sup> Unfortunately, very large doses of steroids (1 g of methylprednisolone intravenously) may be necessary to obtain a beneficial effect, though the efficacy of large-dose steroid therapy has not been confirmed.<sup>258</sup> Other common substances associated with anaphylactic or anaphylactoid reactions that may merit preoperative therapy include antibiotics, intravascular volume expanders, and blood products.<sup>258</sup> The anesthesiologist should always be prepared perioperatively to treat an anaphylactic or anaphylactoid response.

**Minimizing Risks Preoperatively.** Although virtually all evidence on this subject is merely anecdotal, enough consistent thought recurs through the literature to justify proposing an optimal approach to these problems. First, predisposing factors should be sought; patients with a history of atopy or allergic rhinitis should be suspected of being at risk. Other risk factors of note include multiple previous procedures, history of spina bifida, history of asthma, food allergies associated with latex allergy (including avocado, kiwi, banana, pineapple, papaya, chestnut, and buckwheat), systemic mastocytosis, and hereditary angioedema.<sup>258a</sup> Because anaphylactic and anaphylactoid reactions to contrast media occur 5 to 10 times more frequently in patients with a previously suspected reaction, consideration should be given to the administration of low-osmotic agents and both H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists for 16 to 24 hours before exposing these patients to a

suspected allergen. H<sub>1</sub>-receptor antagonists appear to require this much time to act on the receptor. Volume status can be optimized,<sup>248</sup> and perhaps large doses of steroids (1 g of hydrocortisone) should also be administered before exposing patients to agents associated with a high incidence of anaphylactic or anaphylactoid reactions.<sup>258</sup> Older patients and patients taking β-adrenergic blocking drugs present special problems; they are at higher risk of having complications from both pretreatment (especially vigorous hydration) and therapy for anaphylactic reactions (glucagon is useful here to overcome epinephrine resistance) and are less responsive to treatment regimens.<sup>259</sup> One approach is to avoid drugs likely to trigger anaphylactic or anaphylactoid reactions or alter the treatment protocol for this group. Drawing blood for later analysis, especially of tryptase, can be useful in clarifying the diagnosis.<sup>260</sup>

With the increasing incidence of latex hypersensitivity, attempts have been made to make much of the operating room environment latex free; however, costs and preferences have resulted in the continued use of latex-containing gloves in many hospitals. Nonetheless, more hospitals are totally latex free. In allergic patients, care should be taken to ensure that no latex-containing products are present in the operating room.

### Primary Immunodeficiency Diseases

Primary immunodeficiency diseases usually manifest early in life as recurrent infections. Along with survival achieved with antibiotic and antibody treatment have come new prominent features: cancer and allergic and autoimmune disorders.

Heredity angioedema is an autosomal dominant genetic disease characterized by episodes of angioedema involving the subcutaneous tissues and submucosa of the GI tract and airway and often manifested as abdominal pain. These patients have a functionally impotent inhibitor or deficiency of an inhibitor to complement component C1 leading to an overproduction of bradykinin resulting in vascular permeability. The most feared complication for the anesthesiologist is airway edema resulting in an unexpected difficult airway.<sup>260a</sup> The mainstay of treatment of an acute attack is supportive because epinephrine, antihistamines, and corticosteroids often fail to work. The severity of attacks can be prevented or decreased by drugs that are either antifibrinolitics (e.g., ε-aminocaproic acid [EACA] and tranexamic acid) or attenuated androgens (e.g., danazol and stanozolol). Because trauma can precipitate acute attacks, prophylactic therapy with plasma derived C1-INH, attenuated androgens, antifibrinolitics, or all three is recommended before elective surgery; a repeat dose of C1-INH can be given if edema develops.<sup>260a</sup> Fresh frozen plasma has been used during acute attacks with success because it contains C1-INH, though FFP could theoretically worsen an attack, as it contains other complement components and should only be used if no other treatment is available.<sup>260a</sup>

Most of the 1 in 700 persons who have selective IgA deficiency (i.e., <5 mg/dL) have repeated serious infections or connective tissue disorders. These infections commonly involve the respiratory tract (e.g., sinusitis, otitis) or GI tract (manifested as diarrhea, malabsorption, or both). If the patient has rheumatoid arthritis, Sjögren syndrome, or systemic lupus erythematosus, the anesthesiologist should consider the possibility of an isolated IgA deficiency;

however, patients with this disorder can be otherwise healthy. Because antibodies to IgA may develop in these patients if they were previously exposed to IgA (as could occur from a previous blood transfusion), subsequent blood transfusions can cause anaphylaxis, even when they contain washed erythrocytes. Transfusions should therefore consist of blood donated by another IgA-deficient patient.

Many immunomodulators are now being given to augment cancer treatments<sup>261</sup>; no interactions among these modulators, no effects on the incidence of immune reactions during anesthesia, and no interactions with anesthetic effects have been reported except those regarding immunosuppressant drugs (see the last section of this chapter).

Immunonutrition is increasingly being used preoperatively by patients and prescribed by providers to decrease inflammatory responses.<sup>254</sup> Whereas excellent data on the benefits of probiotics in changing the intestinal milieu to decrease inflammation can be found, data on probiotics' role in prevention of intestinal complications, improvement in wound healing, incidence of perioperative infections is under investigation, though benefits may outweigh the risks.<sup>261a-c</sup>

## Diseases of the Central Nervous System, Neuromuscular Diseases, and Psychiatric Disorders

Evaluation of a patient with neurologic or psychiatric disease can be found in [Chapter 31](#). Information gathered from the history that warrants further investigation includes a previous need for postoperative ventilation in a patient without inordinate lung disease, which indicates the possibility of metabolic neurologic disorders such as porphyria, myopathies, neuropathies, and neuromuscular disorders such as myasthenia gravis. Other historical information warranting further investigation includes the use of drugs such as the following: steroids; guanidine; anticonvulsant, anticoagulant, and antiplatelet drugs; lithium; tricyclic antidepressants; phenothiazines; and butyrophenones.

Although preoperative treatment of most neurologic disorders may not lessen perioperative morbidity, knowledge of the pathophysiologic characteristics of these disorders is important in planning intraoperative and postoperative management. Thus preoperative knowledge about these disorders and their associated conditions (e.g., cardiac arrhythmias with Duchenne muscular dystrophy, or respiratory and cardiac muscle weakness with dermatomyositis) may reduce perioperative morbidity. A primary goal of neurologic evaluation is to determine the site of the lesion in the nervous system. Such localization to one of four levels (supratentorial compartment, posterior fossa, spinal cord, peripheral nervous system) is essential for accurate diagnosis and appropriate management. (Disorders accompanied by increased intracranial pressure and cerebrovascular disorders are discussed in [Chapters 11 and 57](#).)

### COMA

Little is known about specific anesthetic, perioperative, or periprocedural choices that alter outcome for a comatose patient, but as for all other conditions, the cause of the

coma should be known so that drugs can be avoided that may worsen the condition or that may not be metabolized because of organ dysfunction. First, the patient should be observed. Yawning, swallowing, or licking of the lips implies a "light" coma with major brainstem function intact. If consciousness is depressed but respiration, pupillary reactivity to light, and eye movements are normal and no focal motor signs are present, metabolic depression is likely. Abnormal pupillary responses may indicate hypoxia, hypothermia, local eye disease, or drug intoxication with belladonna alkaloids, narcotics, benzodiazepines, or glutethimide; pupillary responses may also be abnormal, however, after the use of eye drops. Other metabolic causes of coma include uremia, hypoglycemia, hepatic coma, alcohol ingestion, hypophosphatemia, myxedema, and hyperosmolar nonketotic coma. Except in extreme emergencies, such as uncontrolled bleeding or a perforated viscus, care should be taken to render the patient as metabolically normal as possible before the surgical procedure. This practice and documenting the findings on the chart preoperatively lessen any confusion regarding the cause of intraoperative and postoperative problems. However, too rapid correction of uremia or hyperosmolar nonketotic coma can lead to cerebral edema, a shift of water into the brain as a result of a reverse osmotic effect caused by dysequilibrium of the urea concentration.

The physical examination is extremely helpful preoperatively in assessing the prognosis. Arms flexed at the elbow (i.e., decorticate posture) imply bilateral hemisphere dysfunction but an intact brainstem, whereas extension of the legs and arms (bilateral decerebrate posture) implies bilateral damage to structures at the upper brainstem or deep hemisphere level. Seizures are often seen in patients with uremia and other metabolic encephalopathies. Hyperreflexia and upward-pointing toes suggest a structural CNS lesion or uremia, hypoglycemia, or hepatic coma; hyporeflexia and downward-pointing toes with no hemiplegia generally indicate the absence of a structural CNS lesion. It is important to compare preoperative physical examination with previous different providers' examinations, trending Glasgow Coma Scores can provide utility and standardization.

### EPILEPTIC SEIZURES

A seizure is the term for the clinical event defined as a paroxysmal alteration in neurologic function caused by a synchronous, rhythmic depolarization of brain cortical neurons. Epilepsy is the condition manifested by recurrent, unprovoked seizures. Epileptic seizures result from paroxysmal neuronal discharges of abnormally excitable neurons. Six percent to 10% of individuals younger than 70 years old will experience a seizure at some time during their lifetime. Fifty percent to 70% of patients with one seizure will never have another. However, 70% of people with two seizures will have an epileptic focus, be candidates for antiseizure medications, and be subject to withdrawal seizures after anesthesia if such medications are not continued.<sup>262</sup> Overall, epilepsy has a prevalence of 0.5% to 1% of the population, with the highest incidence in extremes of age and in those with anatomic neurologic abnormalities.<sup>262a</sup>

Sometimes syncopal episodes can be mistaken for seizures, especially when interviews are compressed in the short time

frame of a preoperative visit. Twenty-five percent of patients with a seizure have a normal electroencephalogram (EEG) when they are interictal; thus a negative EEG result does not indicate that someone with a seizure will not have a withdrawal seizure when emerging from anesthesia. Seizures can be generalized (arising from deep midline structures in the brainstem or thalamus, usually without an aura or focal features during the seizure), partial focal motor, or sensory (the initial discharge comes from a focal unilateral area of the brain, often preceded by an aura). As with cerebrovascular accidents and coma, knowing the origin may be crucial to understanding the pathophysiologic processes of the disease and to managing the patient's intraoperative and postoperative course.

Epileptic seizures can arise from discontinuation of sedative-hypnotic drugs or alcohol, use of narcotics, uremia, traumatic injury, neoplasms, infection, congenital malformation, birth injury, drug use (e.g., amphetamines, cocaine), hypercalcemia or hypocalcemia, blood in the ventricle or hypoxia, and vascular disease and vascular accidents. Up to 30% of patients with severe traumatic brain injury develop early seizures (within 7 days of injury).<sup>262b</sup> Thirty percent of epileptic seizures have no known cause. Most partial seizures are caused by structural brain abnormalities (secondary to tumor, trauma, stroke, infection, and other causes).

Most authorities believe that anticonvulsant medications should be given in the therapeutic range,<sup>262-264</sup> and they should be continued through the morning of the surgical procedure, even in pregnant women. They should also be given postoperatively, even in mothers who plan to breastfeed, according to guidelines published by the American Academy of Neurology. Many of the epileptic drugs, including phenytoin, carbamazepine, and phenobarbital, alter the hepatic metabolism of many drugs and induce cytochrome P450 enzyme activity. Drug-drug interactions are much less problematic with the newer epileptic drugs such as gabapentin and topiramate.<sup>262</sup> Appropriate treatment of status epilepticus refractory to anti-epileptic drugs includes general anesthesia and carries high morbidity.<sup>264</sup> In one controlled trial, phenobarbital was more rapidly effective in controlling status epilepticus than was diazepam followed by phenytoin.<sup>264</sup> The frequency of side effects and of required tracheal intubation was similar for both regimens. Thus other than the use of current drug therapy and heeding precautions taken for the underlying disease, no known changes in perioperative management seem to be indicated, though many agents may possess both proconvulsant and anticonvulsant properties pending dose utilized; therefore knowledge of anesthetics agents is crucial.

## INFECTIOUS DISEASES OF THE CENTRAL NERVOUS SYSTEM, DEGENERATIVE DISORDERS OF THE CENTRAL NERVOUS SYSTEM, AND HEADACHE

Many degenerative CNS disorders have been traced to slowly developing viral diseases or even the presence of certain proteins or viral particles ("prions"). No special perioperative anesthetic considerations appear to apply for infectious disorders of the CNS other than those for increased intracranial pressure and avoidance of occupational exposure and transmission of disease to healthcare workers. The appropriate prophylactic measures to take if one comes in contact with

meningococcal disease or other infectious CNS diseases are still not well established. The use of *H. influenzae* type B vaccine has made meningitis an adult disease.<sup>265</sup>

Parkinson disease is a degenerative disorder of the CNS that may or may not be caused by a virus. Clinically, Parkinson disease, chronic manganese intoxication, phenothiazine or butyrophenone toxicity, Wilson disease, Huntington chorea, the effects of street drug toxins such as methylphenyltetrahydropyridine, and carbon monoxide encephalopathy all have similar initial features: bradykinesia, muscular rigidity, and tremor.

In Parkinson disease, therapy is directed at (1) increasing presence of dopamine, (2) increasing the neuronal release of dopamine or the receptor's response to dopamine, (3) stimulating the receptor directly with dopamine agonists (i.e., bromocriptine), (4) direct stimulation of dopaminergic tissue (i.e., deep brain stimulator), or (5) decreasing cholinergic activity. Anticholinergic agents have been the initial drugs of choice because they decrease tremor more than muscle rigidity. Dopamine does not pass the blood-brain barrier, so its precursor L-dopa (levodopa) is used. Unfortunately, L-dopa is decarboxylated to dopamine in the periphery and can cause nausea, vomiting, and arrhythmia. These side effects are diminished by the administration of  $\alpha$ -methylhydrazine (carbidopa), a decarboxylase inhibitor that does not pass the blood-brain barrier. Refractoriness to L-dopa develops, and it is now debated whether the drug should be used only when symptoms cannot be controlled with other anticholinergic medications. "Drug holidays" have been suggested as one means of restoring the effectiveness of these compounds, but cessation of such therapy may result in marked deterioration of function and need for hospitalization. Therapy for Parkinson disease should be initiated preoperatively and be continued through the morning of the surgical procedure; such treatment seems to decrease drooling, the potential for aspiration, and ventilatory weakness.<sup>266,267</sup> Reinstating therapy promptly after surgery is crucial,<sup>263,266-270</sup> as is avoiding drugs such as the phenothiazines and butyrophenones, which inhibit the release of dopamine or compete with dopamine at the receptor.<sup>266</sup> Carbidopa or levodopa in low doses (20-200 mg nightly vs. the usual 60-600 mg/day for Parkinson disease) is commonly used in the nonparkinsonian restless leg syndrome of older adults (present in 2%-5% of individuals >60 years old). This drug also should be given the night before and the night immediately after the surgical procedure. Clozapine does not appear to worsen the movement disorders of Parkinson disease and has been used postoperatively to stop levodopa-induced hallucinations. Patients with Parkinson disease may also undergo deep brain stimulation under monitored anesthesia care. Postoperatively patients with Parkinson disease benefit from early physical therapy, appropriate analgesia, pulmonary hygiene, and autonomic assessment with necessary intervention.<sup>270a</sup>

Dementia, a progressive decline in intellectual function, can be caused by treatable infections (e.g., syphilis, cryptococcosis, coccidioidomycosis, Lyme disease, tuberculosis), depression (a trial of antidepressants is indicated in most patients), side effects of medications (digitalis has slowed brain function more than the heart rate), myxedema, vitamin B<sub>12</sub> deficiency, chronic drug or alcohol intoxication, metabolic causes (liver and renal failure), neoplasms, partially treatable infections (HIV), untreatable infections (Creutzfeldt-Jakob syndrome), or decreased acetylcholine in

the cerebral cortex (Alzheimer disease). This last condition occurs in more than 0.5% of Americans.<sup>271-274</sup> As of 2013, some degree of Alzheimer disease affects approximately 11% of Americans aged 65 and older, and affects approximately 32% of Americans aged 85 and older.<sup>274a</sup> Although these patients are often given cholinergic agonists, controlled trials of these drugs have not as yet shown major significant benefit.<sup>272,273,275</sup> Gingko has improved subjective symptoms in 37% of patients versus 23% of those given placebo. Although further controlled trials failed to confirm its benefit in early Alzheimer disease or in healthy older individuals, gingko is still popular. Cholinergic medications improve functioning in patients with Alzheimer disease.<sup>276</sup> These families often desire surgery, but the interactions of these drugs and therapies with perioperative analgesic and anesthetic drug therapies are not well established. One case report noted intraoperative bradycardia in such patients with two cholinergic drugs.<sup>277</sup> A link may exist among Alzheimer disease, postoperative cognitive dysfunction, and inhaled anesthetics.<sup>278,278a</sup> Deposition of  $\beta$ -amyloid can occur in animals exposed to inhaled anesthetics.<sup>279-281</sup> Whether this link is clinically relevant in humans remains to be determined. Most reversible dementias represent either delirium (commonly infection, metabolic, or drug induced) or depression.<sup>272,273,282</sup> Creutzfeldt-Jakob disease (prion driven) has been transmitted inadvertently by surgical instruments and corneal transplants; the causative virus or protein particle is not inactivated by heat, disinfectants, or formaldehyde.

More than 90% of patients with chronic recurring headaches are categorized as having migraine, tension, or cluster headaches. The mechanism of tension or cluster headaches may not differ qualitatively from that of migraine headaches; all may be manifestations of labile vasomotor regulation.<sup>283</sup> A headache is said to be migraine if it is characterized by four of the following five “POUNDING” conditions: if it is Pulsating, if it lasts One day or more, if it is Unilateral, if Nausea occurs, and if it Disturbs daily activities.<sup>284</sup>

Treatment of cluster and migraine headaches centers on the use of serotonin drugs such as sumatriptan or ergotamine and its derivatives.<sup>283-285</sup> Other drugs that may be effective are propranolol, calcium channel inhibitors, cyproheptadine, prednisone, antihistamines, tricyclic antidepressants, phenytoin, and diuretic drugs, as well as biofeedback techniques. Giant cell arteritis, glaucoma, and all the meningitides, including Lyme disease, are other causes of headache that may benefit from preoperative treatment.<sup>286</sup> No other special treatment is indicated preoperatively for a patient who has a well-delineated cause for the headaches. Acute migraine attacks can sometimes be terminated by ergotamine tartrate aerosol or by injection of sumatriptan or dihydroergotamine mesylate intravenously; general anesthesia has also been used. We normally continue all prophylactic headache medicine, although the decision to continue aspirin through the morning of the surgical procedure is usually left to the surgeon.

## BACK PAIN, NECK PAIN, AND SPINAL CANAL SYNDROMES

Acute spinal cord injury is discussed earlier in the section on autonomic dysfunction. Although it is a common problem,

little is written about the anesthetic management of syndromes related to herniated disks, spondylosis (usually of advancing age), and the congenital narrowing of the cervical and lumbar spinal canal that gives rise to symptoms of nerve root compression. One report stresses the importance of the vascular component in the mechanism of damage to the spinal cord and hence the theoretic desirability of slight hypertension perioperatively.<sup>287</sup> Another report suggests the use of awake intubation, a fiberoptic bronchoscope, and monitoring of evoked potentials.<sup>288</sup> Patients with back pain may be receiving large doses of narcotics that may influence the anesthetic plan and necessitate the need for a perioperative multimodal analgesic approach, including the continuation of home analgesic regimens. A thoughtful preanesthetic discussion with the patient regarding analgesia following surgery is essential for a successful postsurgical regimen.

## DEMYELINATING DISEASES

Demyelinating diseases constitute a diffuse group of diseases ranging from those with uncertain cause (e.g., multiple sclerosis, in which genetic, epidemiologic, and immunologic factors are probably all involved and interferon- $\beta$  appears to be a promising treatment<sup>289</sup>) to those that follow infection, vaccination (e.g., Guillain-Barré syndrome), or antimetabolite treatment of cancer. Therefore, demyelinating diseases can have very diverse symptoms, with a risk of relapse of disease existing immediately after surgery. Because relapse may occur as a result of rapid electrolyte changes and hyperthermia in the perioperative period, such changes should be avoided and temperature tightly regulated.<sup>289a</sup> In addition, perioperative administration of steroids may be a protective measure.<sup>100</sup> Both spinal anesthesia and epidural anesthesia have been administered without problems.<sup>290,291</sup> Multiple sclerosis and demyelinating diseases in general are the most common causes of nontraumatic disability in young adults with a prevalence reported between 2 and 150/100,000 people.<sup>289a</sup> The age-adjusted survival rate is 80% of that of unaffected individuals (i.e., the average patient with multiple sclerosis ages 1.2 years for every year with the disease). No treatment alters most of these disease processes, although ACTH, steroids, interferon- $\beta$ , glatiramer acetate (Copaxone), and plasmapheresis may ameliorate or abbreviate a relapse, or even alter disease progression, especially progression of multiple sclerosis and (if started within 2 weeks of onset) Guillain-Barré syndrome.<sup>292</sup> Such an effect is consonant with the hypothesis of an immunologic disorder as the cause of these diseases. Care should be taken to avoid succinylcholine in these patients because of the risk of hyperkalemia secondary to extrajunctional acetylcholine receptors.

## METABOLIC DISEASES

Included in the category of metabolic diseases is nervous system dysfunction secondary to porphyrias, alcoholism, uremia, hepatic failure, and vitamin B<sub>12</sub> deficiency. The periodic paralysis that can accompany thyroid disease is discussed in the later section on neuromuscular disorders.

Alcoholism or heavy alcohol intake is associated with the following: acute alcoholic hepatitis, the activity of

which declines as alcohol is withdrawn; myopathy and cardiomyopathy, which can be severe; and withdrawal syndromes. Within 6 to 8 hours of withdrawal, the patient may become tremulous, a state that usually subsides within days or weeks. Alcoholic hallucinosis and withdrawal seizures generally occur within 24 to 36 hours. These seizures are generalized grand mal attacks; when focal seizures occur, other causes should be sought. Delirium tremens usually appears within 72 hours of withdrawal and is often preceded by tremulousness, hallucinations, or seizures. These three symptoms, combined with perceptual distortions, insomnia, psychomotor disturbances, autonomic hyperactivity, and, in a large percentage of cases, another potentially fatal illness (e.g., bowel infarction or subdural hematoma), are components of delirium tremens. This syndrome is now treated with benzodiazepines. Nutritional disorders of alcoholism include alcoholic hypoglycemia and hypothermia, alcoholic polyneuropathy, Wernicke-Korsakoff syndrome, and cerebellar degeneration. In patients with alcoholism (i.e., those who drink at least two six packs of beer or one pint of hard alcohol/day or the equivalent), emergency surgery and anesthesia (despite alcoholic hepatitis), are not associated with worsening abnormalities in liver enzymes. In addition, approximately 20% of patients with alcoholism also have respiratory disease. Further, postoperatively these patients can have poor wound healing, altering levels of consciousness/delirium, and difficulty with analgesia.<sup>292a</sup> A patient who has a history of alcohol abuse therefore warrants careful examination of many systems for quantification of preoperative physical status.

Although hepatic failure can lead to coma with high-output cardiac failure, unlike uremia, it does not lead to chronic polyneuropathy. Uremic polyneuropathy is a distal symmetric sensorimotor polyneuropathy that may be improved by dialysis. The use of depolarizing muscle relaxants in patients with polyneuropathies has been questioned. We believe that patients who have neuropathy associated with uremia should not be given succinylcholine because of a possible exaggerated hyperkalemic response.

Pernicious anemia caused by vitamin B<sub>12</sub> deficiency may result in subacute combined degeneration of the spinal cord; the signs are similar to those of chronic nitrous oxide toxicity. Both pernicious anemia and nitrous oxide toxicity are associated with peripheral neuropathy and disorders of the pyramidal tract and posterior column (which governs fine motor skills and the sense of body position). Combined-system disease can also occur without anemia, as can nitrous oxide toxicity in dentists and nitrous oxide abusers. Patients with vitamin B<sub>12</sub> deficiency and anemia, if treated with folate, improve hematologically but progress to dementia and severe neuropathy. It may thus be prudent to give an intramuscular injection of 100 µg of vitamin B<sub>12</sub> or 800 µg orally before giving folate to a patient who has signs of combined-system degeneration.<sup>293</sup>

The porphyrias are a constellation of metabolic diseases that result from an autosomally inherited lack of functional enzymes active in the synthesis of hemoglobin. Fig. 32.6 schematically depicts the abnormalities that result from these enzyme deficits. Type 1, 3, and 4 porphyrias can cause life-threatening neurologic abnormalities. These conditions are characterized by the presence of aminolevulinic

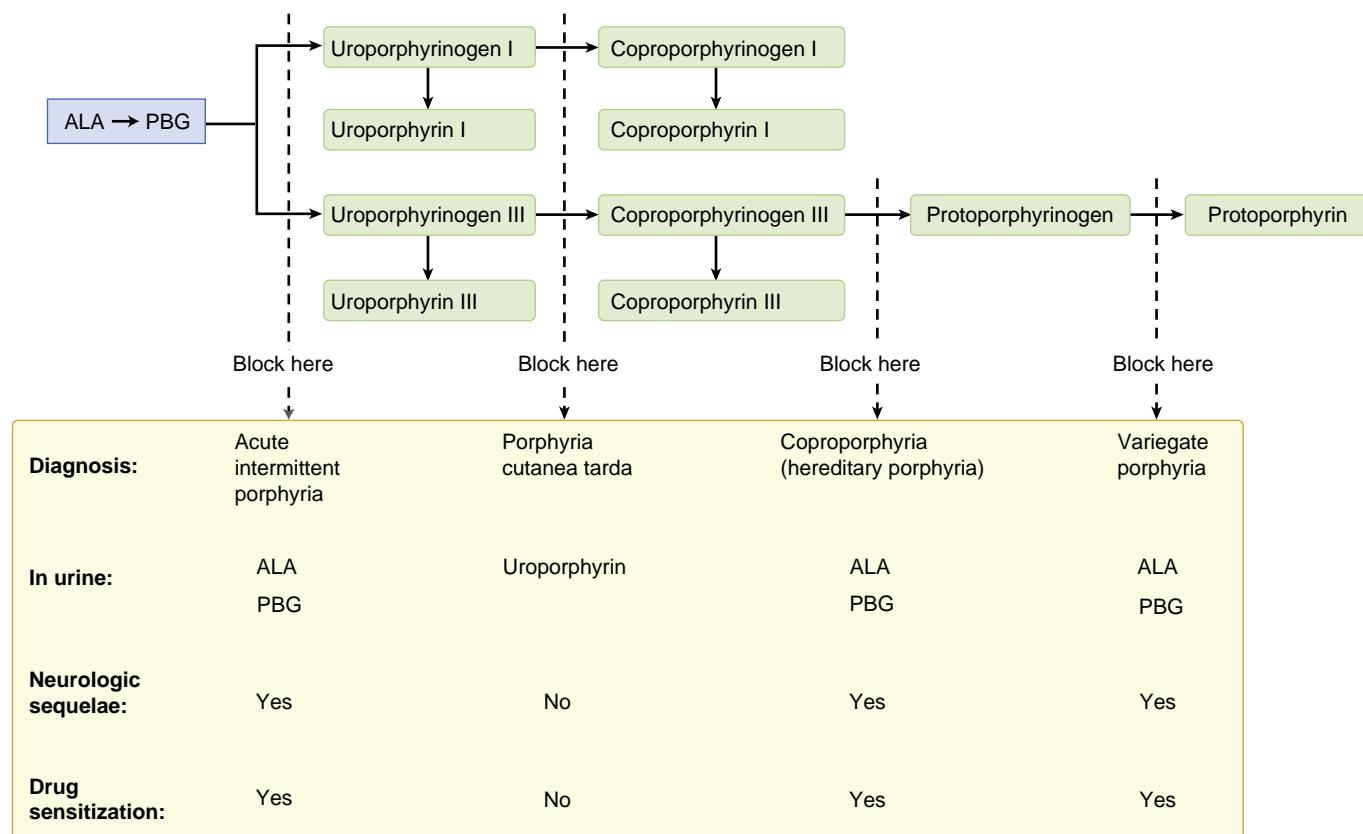


Fig. 32.6 Schematic depiction of the functional enzyme deficits that occur in some of the porphyrias. ALA, Aminolevulinic acid; PBG, porphobilinogen.

acid (ALA) or porphobilinogen, or both, in urine; these substances do not occur in porphyria cutanea tarda, a disease that does not incur neurologic sequelae.<sup>294</sup> In acute intermittent porphyria, the typical pattern consists of acute attacks of colicky pain, nausea, vomiting, severe constipation, psychiatric disorders, and lesions of the lower motoneuron that can progress to bulbar paralysis. Often, these patients will have had multiple previous surgeries. Certain drugs can induce the enzyme ALA synthetase and thereby exacerbate the disease process.<sup>295-297</sup> Drugs considered unsafe include barbiturates (all types), phenytoin, valproic acid, carbamazepine, primidone, oral contraceptives, progestins, carisoprodol, and sprinolactone.<sup>297a</sup> Clonazepam, ketamine, imipramine, sulfa antibiotics, erythromycin, flucconazole, nitrofurantoin, and rifampicin are considered possibly unsafe and should be used with caution.<sup>297a</sup> Patients can have attacks during infection, fasting, or menstruation. Administration of glucose suppresses ALA synthetase activity and prevents or ablates acute attacks. Drugs used in anesthetic management that are reported to be safe for patients with porphyria include neostigmine, atropine, succinylcholine, nitrous oxide, procaine, propofol, etomidate, meperidine, fentanyl, morphine, droperidol, promazine, promethazine, and chlorpromazine.<sup>295-297</sup> Although ketamine has previously been used, postoperative psychoses attributable to the disease may be difficult to distinguish from those possibly caused by ketamine. Propofol has been used without provoking porphyria in at least two susceptible patients.<sup>295,296</sup>

## NEUROMUSCULAR DISORDERS

Neuromuscular disorders consist of conditions affecting any major component of the motor unit: motoneuron, peripheral nerve, neuromuscular junction, and muscle. Neuropathies may involve all components of the nerve, thereby producing sensory, motor, and autonomic dysfunction, or only one component. Myopathies may involve the proximal muscles, the distal muscles, or both.

Myasthenia gravis is a disorder of the muscular system caused by partial blockade or destruction of nicotinic acetylcholine receptors by IgG antibodies. The severity of the disease correlates with the ability of antibodies to decrease the number of available acetylcholine receptors.<sup>298</sup> Treatment of myasthenia is usually begun with anticholinesterase drugs, but in moderate and severe disease, treatment progresses to steroids and thymectomy.<sup>298,299</sup> Immunosuppressive drugs and plasmapheresis are initiated if the more conservative measures fail, and intravenous immunoglobulin, a rapid-onset therapy, is reserved for acute exacerbations and myasthenic crises.<sup>298,299</sup>

One major problem for the anesthesiologist involves the use of muscle relaxants and their reversal.<sup>300</sup> Because much of the care of patients with myasthenia gravis involves tailoring the amount of anticholinesterase medication to the maximal muscle strength of the patient, derangement of the course of the patient during the surgical procedure could necessitate reassessment of the drug dosage. For that reason, all anticholinergic drugs may be withheld for 6 hours preoperatively, and medication should be reinstated postoperatively with extreme caution because the sensitivity of these patients to such drugs may have changed. Small

doses of succinylcholine can be used to facilitate endotracheal intubation; extremely small doses of nondepolarizing drugs can be used for intraoperative relaxation not achieved by regional anesthesia or volatile anesthetics. Of prime importance is monitoring neuromuscular blockade as the guide for muscle relaxant administration and their reversal. Previously, controlled mechanical ventilation was frequently required for 24 to 48 hours postoperatively; however, immediate extubation has become more common.<sup>299-301</sup> Postoperative ventilation is especially important in patients with myasthenia gravis of more than 6 years' duration, COPD, a daily pyridostigmine requirement of 750 mg in association with significant bulbar weakness, and vital capacity of less than 40 mL/kg (PFTs are an important part of the preoperative workup).<sup>301</sup> One study in myasthenic patients found rapid recovery of neuromuscular function in patients receiving rocuronium when sugammadex was used for reversal.<sup>302</sup> This combination could be a rational alternative for myasthenic patients for whom neuromuscular blockade is mandatory during surgical procedures. Another study found that epidural analgesia intra- and postoperatively reduced the requirement of mechanical ventilation following thymectomy, though this was retrospective in nature.<sup>302a</sup> This technique may provide benefit and allow for minimal use of muscle relaxation.

Lambert-Eaton syndrome (myasthenic syndrome) is characterized by proximal limb muscle weakness and is associated with antibodies directed against the voltage-gated calcium channels in presynaptic nerve terminals. Strength or reflexes typically increase with repetitive effort, as affected patients exhibit decreased release of acetylcholine at the neuromuscular junction and repetitive use increases the available junctional acetylcholine. Guanidine therapy enhances the release of acetylcholine from nerve terminals and improves strength. Men with this syndrome generally have small cell carcinoma of the lung or other malignant disease, whereas women often have malignant disease, sarcoidosis, thyroiditis, or a collagen-related vascular disease. In addition, these patients have increased sensitivity to both depolarizing and nondepolarizing muscle relaxants.<sup>303</sup> These patients have an increased risk of prolonged muscle weakness or postoperative respiratory failure after exposure to neuromuscular blocking drugs, particularly when untreated preoperatively.<sup>303a</sup> Lambert-Eaton syndrome is also associated with an autonomic nervous system defect manifested by gastroparesis, orthostatic hypotension, and urinary retention.

Dermatomyositis and polymyositis are characterized by proximal limb muscle weakness with dysphagia. These conditions are associated with malignant disease or collagen-related vascular disease and often involve respiratory and cardiac muscle.

Periodic paralysis is another disease in which sensitivity to muscle relaxants increases. Periodic weakness starts in childhood or adolescence and is precipitated by rest after exercise, sleep, cold, surgery, or pregnancy. Hypokalemic and hyperkalemic forms exist and are associated with cardiac arrhythmias. Like thyrotoxic periodic paralysis, these hypokalemic and hyperkalemic forms usually spare the respiratory muscles. Anesthetic management consists of minimizing stress, maintaining normal fluid and electrolyte status, and controlling body temperature.<sup>303-306</sup>

Patients with muscular dystrophy now survive into their late 20s or early 30s. Because the disease involves the muscles themselves and not their innervation, conduction anesthesia cannot produce adequate relaxation of tonic muscles. Gastric dilation is also a problem. As with the other forms of muscular dystrophy, most problems in myotonic dystrophy arise from cardiac arrhythmias and inadequacy of the respiratory muscles.<sup>307</sup> The preoperative workup for all muscular dystrophies should include echocardiography and PFTs.<sup>307a</sup> For all the forms of muscular dystrophy, problems have been related to exaggerated release of serum potassium after the administration of depolarizing muscle relaxants. Volatile anesthetics are associated with anesthesia-induced rhabdomyolysis, hyperkalemia, and cardiac arrest; therefore, total intravenous anesthesia is the preferred method of general anesthesia. Of note, sugammadex has been used with success for muscle relaxation reversal.<sup>307a</sup>

Malignant hyperthermia in the patient or in a relative of the patient merits careful history taking and at least consideration of performing a test for susceptibility to the condition. Prophylaxis with intravenous dantrolene sodium may also be warranted with high risk patients. Through genotyping malignant hyperthermia has been associated with central core disease, multimiccore myopathy, congenital myopathy with cores and rods, centronuclear myopathy, congenital fiber type disproportion, King-Denborough syndrome, periodic paralysis, nemaline rod myopathy, Native American myopathy, and idiopathic hyperCKemia.<sup>307b</sup> Further genotyping has demonstrated that Duchene muscular dystrophy and Beck muscular dystrophy are better classified as a nonmalignant hyperthermia anesthetic-induced rhabdomyolysis, despite similar clinical appearances.<sup>307b</sup> Appropriate preparation for a patient with previous masseter spasm, or trismus, remains a matter of considerable debate. Malignant hyperthermia occurs most frequently in children and adolescents; the incidence is 1 in 14,000 administrations of anesthesia. The incidence increases to 1 in 2500 patients requiring strabismus surgery.

## DOWN SYNDROME

Down syndrome (trisomy 21) occurs once in 1000 live births. It is associated with congenital cardiac lesions such as endocardial cushion defects (40%), ventricular septal defects (27%), patent ductus arteriosus (12%), and tetralogy of Fallot (8%). Prophylactic antibiotics should be used before predictable bacteremic events. Down syndrome is also associated with upper respiratory infections, with atlantooccipital instability (in approximately 15% of patients<sup>308-311</sup>) and laxity of other joints, with thyroid hypofunction (50%), with an increased incidence of subglottic stenosis, and with enlargement of the tongue (or a decreased oral cavity size for a normal-sized tongue).<sup>310,312</sup> Often, the atlantooccipital instability is asymptomatic and undiagnosed, so all patients should be treated as though they have atlantooccipital instability. No abnormal responses to anesthetic agents or anesthetic adjuvants have been substantiated. A reported sensitivity to atropine has been disproved, although administration of atropine to any patient receiving digoxin for atrial fibrillation should be done with care.<sup>312</sup> Examination

for the conditions associated with Down syndrome should precede surgery.

## PREOPERATIVE PREDICTION OF INCREASED INTRACRANIAL PRESSURE DURING NEUROSURGERY

Symptoms and signs of increased intracranial pressure include morning headache or headache made worse by coughing, nausea, vomiting, disturbances in consciousness, history of large tumors, tumors involving the brainstem, neck rigidity, and papilledema. Patients with these signs, large ventricles (as seen on radiography or images of the brain), or edema surrounding supratentorial tumors should be considered at risk for intraoperative intracranial hypertension. These patients may benefit from preoperative treatment or anesthetic management that assumes this possibility.<sup>313</sup>

## MENTAL DISORDERS

Perhaps the most important preoperative consideration for patients with mental disorders, in addition to developing rapport, is understanding their specific drug therapy and its effects and side effects. Lithium, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), other antidepressants that defy classification (e.g., bupropion), phenothiazines, butyrophenones, and MAOIs are used in these patients.<sup>314</sup> These drugs have potent effects and side effects that are discussed in the last section of this chapter, on drug therapy.

## Renal Disease and Electrolyte Disorders

The anesthesiologist has an important role to play in preventing the onset and consequences of renal failure and its initiators. The linking of renal failure to electrolyte disorders is more obvious: the kidney is the primary organ for regulating body osmolality and fluid volume and has a major role in excretion of the end products of metabolism. In performing these functions, the kidney becomes intimately involved in the excretion of electrolytes.

A patient with renal insufficiency whose own kidneys are still functioning is distinct not only from a patient with end-stage renal disease whose renal functions are provided by dialysis but also from a patient who has a transplanted kidney. These three groups of patients require very different preoperative preparation. In addition, acute changes in renal function present quite a different problem than do chronic alterations in function. Certain renal diseases require different preoperative preparation than others, but generally, renal disease of any origin presents the same preoperative problems.

## RENAL DISEASE

### Causes and Systemic Effects of Renal Disorders

Nephrotic syndrome may develop in patients with glomerular diseases without disturbing tubular function. The soundness of tubular function is an important consideration

because tubular dysfunction with attendant uremia presents problems quite different from those presented by glomerular disease with only nephrotic syndrome. This is not to minimize the adverse effects of glomerular disease; nephrotic syndrome consists of massive proteinuria and consequent hypoalbuminemia. The resulting reduction in plasma oncotic pressure diminishes plasma volume and calls forth compensatory mechanisms that result in retention of sodium and water. As a result, a common clinical finding in nephrotic syndrome is diffuse edema. Thus patients with nephrotic syndrome may have excess total-body water and decreased intravascular volume. In addition, diuretics are often given in an attempt to decrease edema. Although serum creatinine and creatinine clearance estimations have limitations as indices of the GFR (insulin clearance is the reference standard), these measurements are, for now, the most readily available to the anesthesiologist. Plasma creatinine levels reflect endogenous muscle catabolism and dietary intake, as well as urinary excretion. Urinary excretion depends on both filtration and secretion by the kidney. Drugs that are commonly used in the preoperative and perioperative periods can distort this measure of glomerular filtration. Moreover, the commonly used methods for measuring creatinine have a 95% confidence limit of greater than 20% for a GFR higher than 30 mL/min. Thus a normal creatinine level of 1.3 mg/dL may give a measured value ranging from 1.1 to 1.5 mg/dL.

Furthermore, in patients with nephrotic syndrome in whom renal tubular function has been preserved, hypovolemia appears to be a significant cause of deteriorating tubular renal function.<sup>315-317</sup> No randomized study has shown that close control of intravascular volume status in these groups of patients preserves renal tubular function (or any other measure of perioperative morbidity) to a greater degree than does less rigid control.

Uremia, the end result of renal tubular failure (i.e., failure of the concentrating, diluting, acidifying, and filtering functions) manifests in many ways. Changes occur in the cardiovascular, immunologic, hematologic, neuromuscular, pulmonary, and endocrine systems, as well as in bone. These alterations are ascribed either to the toxic end products of protein metabolism or to an imbalance in functioning of the kidney. As the number of functioning nephrons diminishes, the still-functioning nephrons attempt to increase some solute and body composition preservation functions at the expense of other functions, such as excretion of phosphate. The accumulation of phosphate increases PTH levels, which in turn produce osteodystrophy. Osteodystrophy can be managed by (1) restriction of dietary phosphate, (2) the use of binding agents (e.g., aluminum hydroxide or carbonate) that bind with intestinal phosphate, (3) calcium supplementation, or (4) parathyroidectomy.

Certain alterations in patients with uremia, such as neuropathy, are most logically attributed to an accumulation of toxic metabolites. Peripheral neuropathy is most often sensory and involves the lower extremities, but it may also be motor; peripheral neuropathies are frequently improved with hemodialysis and can be dramatically reversed with renal transplantation. Tubular function is commonly assessed by acidifying and concentrating capabilities.<sup>318</sup> Although such tests are crude, these capabilities are usually readily evaluated by measuring urine pH and specific gravity. Along with the altered volume status and cardiac complications in uremic patients, autonomic neuropathy

may contribute to hypotension during anesthesia. Atherosclerosis is often accelerated in uremic patients; hypertension, with its attendant consequences, is very common.

Cardiac failure frequently occurs in uremic patients because of the presence of many adverse conditions: anemia with increasing myocardial work, hypertension, atherosclerosis, and altered volume status. Pericarditis can manifest by pericardial rub alone or by pain (with or without hemorrhage), the ECG will show diffuse ST changes in multiple coronary distributions—when available, these should be correlated to previous coronary catherization findings. Cardiac tamponade should be ruled out on the basis of clinical features and by echocardiography if this diagnosis is seriously suspected preoperatively. In addition, cardiac tamponade should be treated or planned for preoperatively.

If anemia is present, its severity generally parallels the degree of uremia; chronically uremic patients seem to adapt well to anemia. No hard data have substantiated the need to give a preoperative blood transfusion to a chronically uremic patient, even when the preoperative hemoglobin is approaching 7 g/dL. Even in nonuremic patients in an ICU and during cardiac surgery, randomized trials were unable to demonstrate improved outcomes with a liberal transfusion strategy,<sup>319</sup> and transfusions increase the risk for immune system compromise.<sup>320,321a</sup> In uremic patients, coagulation and platelet adhesiveness may be abnormal, and factor VIII and von Willebrand factor activity may be decreased; often, these patients may require DDAVP for enhancement of coagulation intraoperatively. However, DDAVP must be used with caution as it can lead to fluid retention and hypotension with rapid infusion.<sup>321b</sup>

Uremic patients exhibit a wide variety of metabolic and endocrinologic disorders in addition to hyperparathyroidism, including impaired carbohydrate tolerance, insulin resistance, type IV hyperlipoproteinemia, autonomic insufficiency, hyperkalemia, and anion-gap acidosis (caused by an inability of the kidneys to reabsorb filtered bicarbonate and excrete sufficient ammonium into urine). Furthermore, the excretion and pharmacokinetics of drugs are different in uremic patients than in normal patients. In addition, complications of hemodialysis include nutritional deficiencies, electrolyte and fluid imbalances, and mental disorders. Because these conditions can lead to serious perioperative morbidity, they should be evaluated preoperatively.

As with uremic patients, preoperative optimization of volume status is paramount in patients with kidney stones, and both are affected by carbohydrate intolerance.<sup>321,322</sup> Seventy-five percent of all kidney stones are composed of calcium oxalate. Patients with these stones frequently take diuretic drugs, consume calcium- and citrate-rich foods, and restrict salt intake. Prevention of dehydration by institution of intravenous fluid therapy along with restricted oral intake of protein may be as important for these patients as it is for patients with struvite or uric acid stones. Struvite stones often result from urinary infection. Uric acid stones can be prevented by treatment with allopurinol, by preoperative hydration, or by alkalinization of urine. Acidosis may contribute to stone formation. Again, optimal intravascular volume status is important in preventing stones and preserving renal function. More thorough discussion of renal function and physiology is provided in [Chapter 17](#). [Chapter 59](#) deals with the complexities of managing patients for renal surgery and other urologic procedures.

Creatinine clearance in conjunction with free water clearance appears to be the most accurate way of quantifying, for pharmacokinetic purposes, the degree of decreased renal function.<sup>322</sup> For a patient with stable renal function, creatinine clearance, which is a rough estimate of GFR, can be approximated by noting the serum creatinine level: a doubling of the creatinine level represents a halving of the GFR. Thus a patient with a stable serum creatinine level of 2 mg/dL would have a GFR of approximately 60 mL/min. A stable serum creatinine level of 4 mg/dL would accompany a GFR of approximately 30 mL/min, and a stable serum creatinine level of 8 mg/dL would accompany a GFR of 15 mL/min or less.

$$\text{Creatinine clearance} = \frac{(140 - \text{Age [yr]}) \times \text{Body weight (kg)}}{72 \times \text{serum creatinine } \left( \frac{\text{mg}}{\text{dL}} \right)}$$

$$\text{Free water clearance} = \text{Urine flow (mL/hour)}$$

$$\text{Urine osmolality } \left( \frac{\text{mOsm}}{\text{L}} \right) \times \text{Urine flow } \left( \frac{\text{mL}}{\text{hour}} \right)$$

$$\text{Plasma osmolality } \left( \frac{\text{mOsm}}{\text{L}} \right)$$

Free water clearance is a measure of renal concentrating ability, and it is normally  $-25$  to  $+100$  mL/h; it becomes more positive in renal insufficiency states. It may also become more positive in patients who have a head injury or high blood alcohol levels or in those undergoing aggressive fluid infusion or administration of diuretics.<sup>323</sup>

### **Patients With Insufficient but Functioning Kidneys**

One of the greatest challenges for the anesthesiologist is presented by patients with insufficient renal function whose renal function must be preserved during surgical procedures. In addition, the presence of chronic renal failure is associated with higher rates of perioperative cardiac morbidity, which may warrant further evaluation for the presence of occult CAD.<sup>324</sup> The many uremic symptoms and great perioperative morbidity associated with uremia can probably be avoided by attention to detail in the preoperative and perioperative management of patients with insufficient but still functioning kidneys.<sup>315-317</sup>

First, studies demonstrate that acute postoperative renal failure is associated with an extremely high mortality rate.<sup>325</sup> The development of perioperative renal dysfunction has multiple risk factors, the most important of which include preexisting renal disease, heart surgery involving

cardiopulmonary bypass or aortic surgery involving cross-clamping of the thoracic or abdominal aorta, and ongoing sepsis. Perioperative renal dysfunction accounts for upward of 40% of all in-hospital cases of acute kidney injury.<sup>325a</sup>

Moreover, acute perioperative renal failure is most likely to occur in patients who have renal insufficiency before the surgical procedure, are older than 60 years, and have preoperative left ventricular dysfunction.<sup>323,325</sup> Proper preoperative hydration probably decreases mortality after acute renal failure induced by radiocontrast agents.<sup>317</sup> Clues to the presence of hypovolemia or hypervolemia should be sought from the history and physical examination (e.g., weight loss or gain, thirst, edema, orthostatic hypotension and tachycardia, flat neck veins, dry mucous membranes, decreased skin turgor). Other causes of deterioration in function in chronic renal insufficiency are low cardiac output or low renal blood flow (in prerenal azotemia, whether because of cardiac failure or fluid depletion from diuretic drugs, BUN often increases disproportionately to increases in creatinine), urinary tract infection, use of nephrotoxic drugs, hypercalcemia, and hyperuricemia. These conditions and drugs should be avoided; if any of these conditions exist, they should be treated preoperatively.

Management of patients with renal disease is discussed in [Chapter 59](#).

### **Patients Undergoing Dialysis**

Patients with chronic (and at times acute) renal failure require renal replacement therapy, including conventional intermittent hemodialysis, peritoneal dialysis, and continuous renal replacement therapy (CRRT). CRRT includes a wide variety of techniques whose perioperative management has been reviewed ([Table 32.13](#)).<sup>326</sup> Although the primary indication for CRRT is acute renal failure, it can also be used for fluid clearance, correction of electrolyte abnormalities, management of metabolic acidosis, and removal of some toxins. It can be used in surgical patients without significant hemodynamic abnormalities. These patients may return to the operating room, and their assessment and management may be complicated by the underlying disease and the use of systemic anticoagulation to prevent filter and circuit clotting. In patients undergoing intermittent treatment with hemodialysis or peritoneal dialysis, the procedure is discontinued before entering the operating room. For patients on CRRT, the anesthesiologist must determine the appropriateness of discontinuing the therapy. With short procedures,

**TABLE 32.13** Characteristics of Renal Replacement Therapy

Renal Replacement Therapy	Blood Pump	Replacement Fluid (RF)/Dialysate (D)	Intraoperative Use
Conventional intermittent hemodialysis	Yes	D	No
Peritoneal dialysis	No	D	No
Slow continuous ultrafiltration	Yes/no	None	Yes
Continuous arteriovenous hemodialysis	No	D	No
Continuous arteriovenous hemodiafiltration	No	RF/D	No
Continuous venovenous hemofiltration	Yes	RF	Yes
Continuous venovenous hemodialysis	Yes	D	Yes
Continuous venovenous hemodiafiltration	Yes	RF/D	Yes

the therapy can usually be stopped safely provided the initial indication for therapy has improved (i.e., resolution of acidosis or hyperkalemia). If continued, CRRT can also be used to manage fluids during the surgical procedure by changing the dialysate, but the effect on drug dosing must be recognized. In addition to effects on renal elimination of drugs, CRRT has effects resulting from changes in protein binding and volume of distribution, as well as drug removal effects from membrane permeability, membrane surface area, the ultrafiltration rate, and the dialysate flow rate.

Because a patient undergoing conventional dialysis has already lost natural renal functioning, the emphasis in preoperative assessment shifts toward protecting other organ systems and optimally maintaining vascular access sites for cannulation. Usually, this does not require invasive monitoring. Emphasis is placed on intravascular fluid volume and electrolyte status, which can be ascertained by knowing when the patient last underwent dialysis, how much weight was normally gained or lost with dialysis, whether the fluid loss was peritoneal or intravascular, and what electrolyte composition the blood was dialyzed against. Although preoperative dialysis may benefit patients who have hyperkalemia, hypercalcemia, acidosis, neuropathy, and fluid overload, the resulting dysequilibrium between fluid and electrolytes can cause problems. Because hypovolemia induced by dialysis can lead to intraoperative hypotension, we try to avoid weight and fluid reduction in patients undergoing preoperative dialysis focusing on clearance of solutes and management of acid-base balance.

When renal transplant recipients have subsequent surgical procedures, the status of their renal function must be determined (i.e., whether they have normal renal function, insufficient but still functioning kidneys, or end-stage renal disease requiring hemodialysis). Descriptions of side effects of immunosuppressive drugs should also be sought. The drugs used preoperatively and intraoperatively to prevent acute rejection themselves have serious side effects that encourage close monitoring of blood glucose and cardiovascular function.<sup>327</sup> Because renal transplantation greatly increases the risk of infection, it is very important to consider invasive monitoring carefully and if indicated follow strict aseptic technique.

### Drugs in Patients With Renal Failure

Patients with renal azotemia have a threefold or higher risk of having an adverse drug reaction than do patients with normal renal function.<sup>328-330</sup> The risk is increased by two conditions. First, excessive pharmacologic effects result from high levels of a drug or its metabolite (e.g., the metabolite of meperidine) in blood because of physiologic changes in target tissues induced by the uremic state. An example is excessive sedation in a uremic patient with standard blood levels of sedative-hypnotic drugs. Second, excessive administration of electrolytes with drugs also increases the risk of having an adverse drug reaction. Administration of standard doses of drugs that depend on renal excretion for their elimination can result in drug accumulation and enhanced pharmacologic effect. In one report, patients with end-stage renal disease required significantly higher propofol doses to achieve the clinical endpoint of hypnosis than did patients with normal renal function.<sup>330</sup>

### INFECTIOUS DISEASE

Sepsis is a leading cause of postoperative morbidity,<sup>317,331</sup> probably through a decrease in systemic vascular resistance

related to activation of the complement system and other mediators. Thus attention to the effects of antibiotic drugs must be supplemented by attention to intravascular volume status.<sup>315-317,331-333</sup> The degree of impairment of the infected organ and its effect on anesthesia should be assessed. Further, note that not all sepsis is the same, and often the source requires special consideration. For instance, endocarditis merits examination of the following: intravascular volume status; antibiotic and other drug therapy and side effects<sup>334</sup>; myocardial function; and renal, pulmonary, neurologic, and hepatic function—organ systems that can be affected by endocarditis.

Although all surgery except emergency or essential operations is proscribed when an acute infectious disease is present, many such diseases (e.g., influenza and pneumococcal pneumonia) and even inflammatory conditions are becoming less frequent because of successful immunization recommendations and programs.<sup>335</sup> Furthermore, even though acute infections are less common, surgery in patients with chronic viral diseases such as hepatitis and HIV infection is more frequent. Many of these patients may also harbor opportunistic infections such as tuberculosis or may have other systemic problems. Whether anesthesia or surgery, or both, exacerbates these infections or their systemic manifestations is not clear.

## ELECTROLYTE DISORDERS

Disorders of calcium, magnesium, and phosphate balance are discussed in the earlier section on diseases involving the endocrine system and disorders of nutrition.

### Hyponatremia and Hypernatremia

Electrolyte disorders are usually detected by determining the levels of electrolytes in serum. These concentrations reflect the balance between water and electrolytes. The osmolality of all body fluids is normally maintained within the narrow physiologic range of 285 to 295 mOsm/kg H<sub>2</sub>O by integration of three key processes: thirst, release of ADH, and responsiveness of the medullary collecting ducts to ADH. Because of the permeability of biologic membranes, intracellular osmolality and extracellular osmolality are almost always equal.

$$2 \left[ \text{Na}^{2+} \right] (\text{mEq/L}) + \frac{[\text{Glucose}] (\text{mg/dL})}{18} + \frac{[\text{BUN}] (\text{mg/dL})}{2.8} = \text{mOsm/kg}$$

Hyponatremia is the most common electrolyte disorder in hospitalized patients, with a prevalence in ICUs patients as high as 40%, highlighting hyponatremia as a common and important clinical condition that adds complexity to the care.<sup>335a</sup> Hyponatremia can occur in isotonic, hypertonic, or hypotonic forms. For example, isotonic hyponatremia can develop in protein or liquid accumulation states such as myeloma. Hypertonic hyponatremia can be present with hyperglycemia or with infusions of glycine (as in the TURP syndrome). Hypotonic hyponatremia is the largest classification and is subdivided according to the status of the extracellular fluid into hypovolemic, isovolumic, or hypervolemic hypotonic hyponatremia. All three types require that excretion of renal water be impaired despite continued intake of dilute fluid. Common causes of hypovolemic

### BOX 32.5 Types and Causes of Hypotonic Hyponatremia

#### Hypovolemic

- Gastrointestinal losses
  - Vomiting
  - Diarrhea
- Skin losses
- Third-space losses
- Lung losses
- Renal losses
  - Diuretics
  - Renal damage
  - Urinary tract obstruction
- Adrenal insufficiency

#### Isovolumic

- Syndrome of inappropriate secretion of antidiuretic hormone
- Renal failure
- Water intoxication
- Hypokalemia
- Dysfunctional osmostat

#### Hypervolemic

- Congestive heart failure
- Nephrosis
- Liver dysfunction

Serum osmolality less than 280 mOsm/L.

hypotonic hyponatremia are GI losses (vomiting, diarrhea), third-space losses (diuretics or salt-wasting nephropathy), and adrenal insufficiency (Box 32.5). Hypervolemic hypotonic hyponatremic states complicate severe cardiac failure, cirrhosis, nephrotic syndrome, and renal failure, and are characterized by retention of sodium with disproportionately larger amounts of water.

The most common isovolumic hypotonic hyponatremia is caused by retention of water without sodium, often edema is not usually clinically apparent. Edema is most often caused by SIADH, which in turn may be caused by CNS or pulmonary tumors or dysfunction. Secretion of ADH increases with age, thus rendering older adults more prone to hyponatremia. Drugs that potentiate the secretion of ADH (tricyclic antidepressants and vincristine) or its effects on the medullary collecting duct system in the kidney (nonsteroidal antiinflammatory drugs and thiazides) or that have similar effects (oxytocin and desmopressin) may be more likely to cause hyponatremia in older adults. To establish the diagnosis of SIADH, the physician should determine that the patient is free of renal and cardiac dysfunction, has normal adrenal and thyroid function, and is normovolemic—it is a diagnosis of exclusion. Urine osmolality would then be found to exceed 100 mOsm/kg, serum osmolality would be low, and urine sodium excretion would be higher than 20 mEq/L (20 mOsm/L).

Disturbances in serum sodium therefore may reflect alterations in glucose metabolism, renal function, or accumulation of body water. The last can be affected by disturbances in thirst, release of ADH, and renal function. Thus hyponatremia reflects a relative excess of free water and can occur when total-body sodium increases (as in edematous disorders), when total-body sodium is normal (as in excess of free water because of SIADH), or when total-body sodium decreases (as

occurs with too aggressive use of diuretic drugs). Definition of the cause defines the treatment. For instance, water restriction is the mainstay of therapy for SIADH. Administration of demeclocycline is another option that corrects severe SIADH by inducing a reversible nephrogenic diabetes insipidus. The anesthesiologist is faced with the question of which levels of electrolytes require treatment before anesthesia. Although slowly developing hyponatremia usually produces few symptoms, the patient may be lethargic, apathetic, or unbalanced. Chronic hyponatremia is better tolerated than acute hyponatremia because of mechanisms regulating intracellular fluid volume that alleviate brain edema; the loss of other solutes from cells decreases the osmotic movement of water into cells. Nonetheless, severe chronic hyponatremia (i.e., serum sodium levels <123 mEq/L) can cause the development of brain edema.

By contrast, acute hyponatremia may be manifested by severe symptoms requiring emergency treatment: profound cerebral edema with obtundation, coma, convulsions, and disordered reflexes and thermoregulatory control.<sup>100,101,336</sup> Depending on the cause and relative total sodium and water content, treatment can range from the administration of hypertonic saline (with or without diuretic drugs) to restriction of fluids or administration of other drugs.<sup>100,101,336</sup> Because neurologic damage may develop if the serum sodium concentration is increased too rapidly, the rate of increase should not exceed 1 mEq/L/h.<sup>100,101,336</sup> After the serum sodium concentration has reached 125 mEq/L, therapy may consist of water restriction; more rapid correction may result in the osmotic demyelination syndrome.<sup>335a</sup> In hyponatremic patients who have excess total-body water secondary to SIADH, serum levels can be corrected by giving furosemide and saline to replace the loss of electrolytes in urine.<sup>100,101,336</sup> The diagnosis of SIADH is discussed earlier in this chapter (see the section on pituitary abnormalities).

Neither acute nor chronic hyponatremia necessitates restoration of serum sodium to normal levels, just until resolution of neurologic symptoms; brain swelling usually resolves at a serum sodium level of 130 mEq/L.

Hypernatremia occurs much less commonly than hyponatremia. It is often iatrogenic (e.g., it can be caused by failure to provide sufficient free water to a patient who is unconscious or who has had a recent stroke-induced deficit of the thirst mechanism) and can occur in the presence of low, normal, or excess total-body sodium. The primary symptoms of hypernatremia relate to brain cell shrinkage. Because too rapid correction of hypernatremia can lead to cerebral edema and possibly osmotic demyelination syndrome with convulsions, coma, and death; correction should be made gradually. Despite lack of data, there is general belief that all patients undergoing surgical procedures should have serum sodium concentrations of less than 150 mEq/L before anesthesia unless a therapeutic for hypernatremia exists (i.e., hypertonic therapy for cerebral edema in neurologic injury).

#### Hypokalemia and Hyperkalemia

Hypokalemia and hyperkalemia are also discussed in [Chapters 31 and 47](#). The relationship between the measured potassium concentration in serum and total-body potassium stores can best be described with a scattergram. Only 2% of total-body potassium is stored in plasma (4200 mEq in cells and 60 mEq in extracellular fluid). In normal persons, 75% of the 50 to 60 mEq/L of total-body potassium is

stored in skeletal muscle, 6% in red blood cells, and 5% in the liver. Thus a 20% to 25% change in potassium levels in plasma could represent a change in total-body potassium of 1000 mEq or more if the change were chronic or as little as 10 to 20 mEq if the change were acute.

As with serum sodium levels, acute changes in serum potassium levels are less well tolerated than chronic changes. Chronic changes are relatively well tolerated because of the equilibration of serum and intracellular stores that takes place over time to return the resting membrane potential of excitable cells to nearly normal levels.

Hyperkalemia can result from the following: factitious increase of potassium administration (as in red blood cell hemolysis); excessive exogenous potassium from sources such as salt substitutes; cellular shifts in potassium (as a result of metabolic acidosis, tissue and muscle damage after burns, use of depolarizing muscle relaxants, or intense catabolism of protein); and decreased renal excretion (as occurs in renal failure, renal insufficiency with trauma, and therapy with potassium-sparing diuretic drugs, especially when combined with ACE inhibitors or mineralocorticoid deficiency).<sup>337-339</sup> Factitious hyperkalemia can occur when a tourniquet is left on too long or even by simple fist clenching.<sup>340</sup>

The major danger in anesthetizing patients who have disorders of potassium balance appears to be abnormal cardiac function (i.e., both electrical disturbances and poor cardiac contractility).<sup>337</sup> Hyperkalemia lowers the resting membrane potential of excitable cardiac cells and decreases the duration of the myocardial action potential and upstroke velocity. This decreased rate of ventricular depolarization, in addition to the beginning of repolarization in some areas of the myocardium while other areas are still undergoing depolarization, produces a progressively widening QRS complex that merges with the T wave into a sine wave on the ECG.

At a potassium level greater than 6.7 mEq/L, the degree of hyperkalemia and the duration of the QRS complex correlate well.<sup>337</sup> This correlation is even better than the correlation between the serum potassium level and T-wave changes. Nevertheless, the earliest manifestations of hyperkalemia are narrowing and peaking of the T wave. Although not diagnostic of hyperkalemia, T waves are almost invariably peaked and narrow when serum potassium levels are 7 to 9 mEq/L. When serum potassium levels exceed 7 mEq/L, atrial conduction disturbances appear, as manifested by a decrease in P-wave amplitude and an increase in the PR interval. Supraventricular tachycardia, atrial fibrillation, PVCs, ventricular tachycardia, ventricular fibrillation, or sinus arrest may all occur.

The ECG and cardiac alterations associated with hyperkalemia are potentiated by low serum levels of calcium and sodium. Intravenous administration of bicarbonate, glucose with insulin (1 unit/2 g glucose), can reverse these changes temporarily by shifting extracellular potassium into the cells. Calcium is administered to stabilize the cardiac membrane; it has no effect on plasma concentrations of potassium. Furosemide should be given to start the removal process of excess potassium from the body and decrease serum potassium levels. Sodium polystyrene sulfonate (Kayexalate) enemas can be given to bind potassium in the gut in exchange for sodium, these should be used with caution in perioperative patients as there are reports of intestinal necrosis.<sup>340a,340b</sup> Dialysis against a hypokalemic solution also decreases serum potassium levels.

$\beta$ -Adrenergic stimuli also cause redistribution of potassium into the cell. Indeed, the plasma potassium concentration measured in samples immediately before surgical procedures is usually 0.2 to 0.8 mEq/L lower than that measured during the less stressful period 1 to 3 days before surgery.<sup>341</sup>  $\beta$ -Adrenergic receptor blocking drugs can be used to prevent such an effect preoperatively. A  $\beta$ -adrenergic receptor stimulating agent (20 mg of nebulized albuterol for a 70-kg patient) can be used to treat hyperkalemia when it occurs; it decreases potassium levels 1.0 mEq/L within 30 minutes, and its effect lasts 2 hours.<sup>342</sup> Although nebulized  $\beta_2$ -agonists effectively lower plasma potassium concentrations by stimulating sodium- and potassium-dependent adenosine triphosphatase, this therapy should be used as an adjunct to rather than a substitute for more established measures.

In a hyperkalemic patient, hypoventilation can be dangerous during anesthesia because each 0.1 change in pH can produce a 0.4 to 1.5 mEq/L change in serum potassium levels in the opposite direction. For example, if pH decreases from 7.4 to 7.3, serum potassium levels could increase from 5.5 to 6.5 mEq/L.

Hypokalemia can be caused by inadequate intake of potassium, excessive GI loss (through diarrhea, vomiting, nasopharyngeal suctioning, long-term use of laxatives, or ingestion of cation exchange resins, as in certain wines), excessive renal loss (because of the use of diuretic drugs, renal tubular acidosis, chronic chloride deficiency, metabolic alkalosis, mineralocorticoid excess, excessive ingestion of licorice, use of antibiotics, uretersigmoidostomy, and diabetic ketoacidosis), and shifts of potassium from extracellular to intracellular compartments (as occurs in alkalosis, insulin administration, administration of a  $\beta$ -adrenergic agonist, stress, barium poisoning, and periodic paralysis). As with hyperkalemia, knowledge of the cause of the potassium deficiency and appropriate preoperative evaluation and treatment of that cause may be as important as treatment of the deficiency itself. Also like hyperkalemia, hypokalemia may reflect small or vast changes in total-body potassium. Acute hypokalemia may be much less well tolerated than chronic hypokalemia. The major worrisome manifestations of hypokalemia pertain to the circulatory system, both the cardiac and peripheral components. In addition, chronic hypokalemia results in muscle weakness, hypoperistalsis, and nephropathy.

Cardiovascular manifestations of hypokalemia include the following: autonomic neuropathy, orthostatic hypotension, decreased sympathetic reserve, impaired myocardial contractility, and electrical conduction abnormalities. Conduction abnormalities can present as sinus tachycardia, atrial and ventricular arrhythmias, and intraventricular conduction disturbances that can progress to ventricular fibrillation. In addition to arrhythmias, the ECG shows widening of the QRS complex, ST-segment abnormalities, progressive diminution of the T-wave amplitude, and a progressive increase in the U-wave amplitude. Surawicz found these changes to be invariably present when serum potassium levels decreased to less than 2.3 mEq/L.<sup>337</sup> Although U waves are not specific for hypokalemia, they are sensitive indicators of the condition. Replenishing the total-body potassium deficit for a depletion reflected by a serum deficit of 1 mEq/L (e.g., from 3.3 to 4.3 mEq/L) may require 1000 mEq of potassium. Even if this amount could be given instantaneously (and it should not

be replenished at a rate exceeding 250 mEq/day), it would take 24 to 48 hours to equilibrate in all tissues. Potassium-depleted myocardium is unusually sensitive to digoxin, calcium, and most important, potassium. Rapid potassium infusion in a hypokalemic patient can produce arrhythmias as severe as those produced by hypokalemia itself, again, slow correction is preferred.<sup>343</sup>

Thus the decision to proceed with surgery and anesthesia in the presence of acute or chronic depletions or excesses of potassium depends on many factors.<sup>344-349</sup> The cause and treatment of the underlying condition creating the electrolyte imbalance and the effect of that imbalance on perioperative risk and physiologic processes must be known. The urgency of the operation, the degree of electrolyte abnormality, the medications given, the acid-base balance, and the suddenness or persistence of the electrolyte disturbance are all considerations. For example, a small study of patients undergoing vascular access procedures with preoperative potassium levels of higher than 6 mmol/L demonstrated no adverse outcomes.<sup>347</sup> Similarly, in a cohort study in which 38 patients had a preoperative potassium level higher than 5.5 mEq/L, no dysrhythmias or major morbidity were associated with the use of succinylcholine.<sup>348</sup>

Retrospective epidemiologic studies attribute significant risk to the administration of potassium (even long-term oral administration).<sup>344</sup> In one study, 1910 of 16,048 consecutive hospitalized patients were given oral potassium supplements. Of these 1910 patients, hyperkalemia contributed to death in 7, and the incidence of complications of potassium therapy was 1 in 250.<sup>350</sup> Armed with such data, many internists do not prescribe oral potassium therapy for patients given diuretic drugs, yet these patients frequently become moderately hypokalemic.<sup>350</sup> Modest hypokalemia occurs in 10% to 50% of patients given diuretic drugs.

Three studies investigated whether modest hypokalemia was a problem by prospectively seeking arrhythmias on the ECGs of patients who had various preoperative levels of potassium.<sup>345,346,349</sup> No difference in the incidence of arrhythmias occurred in 25 normokalemic ( $K^+ > 3.4$  mEq/L) patients, 25 moderately hypokalemic ( $K^+ = 3-3.4$  mEq/L) patients, and 10 severely hypokalemic ( $K^+ < 2.9$  mEq/L) patients.<sup>345</sup> Wahr and coauthors studied 2402 patients undergoing elective CABG and concluded that a serum potassium level less than 3.5 mmol/L was a predictor of perioperative arrhythmia (OR, 2.2; 95% CI, 1.2-4.0), intraoperative arrhythmia (OR, 2.0; 95% CI, 1.0-3.6), and postoperative atrial fibrillation/flutter (OR, 1.7; 95% CI, 1.0-2.7).<sup>349</sup>

Modest hypokalemia can have severe consequences.<sup>350,351</sup> Holland and coworkers treated 21 patients with 50 mg of hydrochlorothiazide twice a day for 4 weeks.<sup>351</sup> These patients had a history of becoming hypokalemic during diuretic therapy; no patients had cardiac disease or were taking other medications. Before and after diuretic therapy, 24-hour ambulatory ECGs were recorded. This study is also subject to the limitations of Holter monitoring. Ventricular ectopy, including complex ventricular ectopy (multifocal PVCs, ventricular couplets, ventricular tachycardia), developed in 7 of the 21 patients (33%). Potassium repletion decreased the number of ectopic ventricular beats per patient from 71.2 to 5.4/h. Apparently, some patients are sensitive to even minor potassium depletion. In the Multiple Risk Factor Intervention Trial involving 361,662 patients, more than 2000 of whom were

treated for hypertension with diuretics, the reduction in serum potassium after diuretic therapy was greater in patients with PVCs.<sup>350</sup>

## Gastrointestinal and Liver Diseases

### GASTROINTESTINAL DISEASE

#### Preoperative Search for Diverse Associated Disorders in Gastrointestinal Disease

Although preoperative preparation of the GI tract is usually the responsibility of the surgeon, GI disease can and often does cause derangements in many or all other systems. Such disturbances can affect the safety of anesthesia for the patient. Preoperative preparation should include knowledge of disease processes and their effects to guide the patient smoothly through the perioperative period. The major advances of correcting fluid and electrolyte disorders and optimizing nutritional status preoperatively allow surgical procedures to be performed in patients with GI disease previously deemed to be at too great a risk and may have lessened the risk for others.<sup>45-47,352</sup> Nonetheless, in patients with GI disease, thorough assessment of intravascular fluid volume, electrolyte concentrations, and nutrition is essential, including an evaluation of the supervening side effects of these therapies (e.g., hypophosphatemia from parenteral nutrition, hyperkalemia or cardiac arrhythmias from too vigorous treatment of hypokalemia, and volume overload from too rapid or too vigorous treatment of hypovolemia).

In addition to the vast alterations in fluids, electrolytes, and nutrition that can occur with such diverse GI diseases as neoplasms and pancreatitis, patients with GI disorders can have gastroesophageal reflux disease,<sup>353</sup> bowel obstruction, vomiting, or hypersecretion of acid. These effects may merit rapid induction of anesthesia with the application of cricoid pressure or endotracheal intubation with the patient unanesthetized (awake), preoperative nasogastric suctioning, or preoperative use of histamine receptor blocking drugs. Clotting abnormalities may need to be corrected because fat-soluble vitamin K (often malabsorbed) is necessary for the synthesis of factors II, VII, IX, and X in the liver. Liver disease is often associated with GI disease and, if severe enough, can also result in a deficiency of clotting factors synthesized by the liver.

Other factors should be remembered in the perioperative management of any patient with GI disease. First, closed spaces containing gas expand by absorbing nitrous oxide, as such expansion can lead to ischemic injury, rupture of GI viscera, or both. Second, GI surgery predisposes the patient to blood stream contamination, which can lead to sepsis and decreased peripheral vascular resistance, massive fluid requirements, cardiac failure, and renal insufficiency. The surgical site infection rate has been declining. This decrease may be attributable to the use of better technique, more appropriate prophylactic timing and use of antibiotics, better nutrition, less invasive (laparoscopic and endoscopic) surgery, maintenance of normothermia, and surgical resection of even tumors.<sup>354-358</sup> Third, patients with GI disease may have many other associated disorders not directly related to the GI tract. For example, they may be anemic from deficiencies in iron, intrinsic factor, folate, or vitamin B<sub>12</sub>.

They may also manifest neurologic changes from combined-system disease. Respiration may be impaired because of tobacco abuse, peritonitis, abscess, pulmonary obstruction, previous incisions, aspiration, or pulmonary embolism (as occurs with ulcerative colitis or with thrombophlebitis in bedridden patients). These patients may also have hepatitis, cholangitis, side effects from antibiotic drugs or other medications, massive bleeding with anemia and shock, or psychological derangements.

Because GI disease can be accompanied by so many diverse associated disorders, the clinician must clearly search for involvement of other systems and preoperatively assess and treat such disorders appropriately. Discussion of two specific diseases, ulcerative colitis and carcinoid tumor, highlights the importance of involvement of other systems in GI disease.

### **Ulcerative Colitis and Carcinoid Tumors as Examples of Gastrointestinal Disease Affecting Other Systems**

Ulcerative colitis is a chronic inflammatory disease of the colonic mucosa, typically starting in the rectum and extending proximally through the colon. It is often marked with an unpredictable clinical course with periods of remission and exacerbation. Patients with ulcerative colitis may also have the following: phlebitis; deficiencies in iron, folate, or vitamin B<sub>12</sub>; anemia; or clotting disorders caused by malabsorption. They can present as malnourished or dehydrated, or with electrolyte abnormalities. In addition, ulcerative colitis can be accompanied by massive bleeding, bowel obstruction, bowel perforation, toxic megacolon, hepatitis, arthritis, iritis, spondylitis, diabetes, or pancreatitis.

The site of origin of carcinoid tumors in more than 60% of patients is the GI tract.<sup>358a</sup> Within the GI tract, carcinoid tumors have been documented to occur from the esophagus to the rectum. Tumors arising in the ileocecal region have the highest incidence of metastases. Carcinoid tumors originating from sites other than the GI tract, such as the head and neck, lung, gonads, thymus, breast, and urinary tract, have also been reported. Cardiac involvement, although frequently reported, is usually limited to right-sided valvular and myocardial plaque formation.<sup>359</sup>

Not all patients with carcinoid tumors have symptoms attributable to secretion of hormone by the tumor. Some do, however, and unexpected carcinoid can manifest intraoperatively by hypersecretion of gastric fluid. The most comprehensive series in the literature indicates that only 7% of patients have carcinoid syndrome, which typically consists of flushing, diarrhea, and valvular heart disease. Of those patients with the syndrome, approximately 74% have cutaneous flushing, 68% have intestinal hypermotility, 41% have cardiac symptoms, and 18% have wheezing. Factors influencing symptoms include the location of the tumor and the specific hormones produced and secreted. Although it is generally believed that if patients do not exhibit carcinoid syndrome, the tumors are not producing serotonin (5-hydroxytryptamine [5-HT]), such may not be the case. Approximately 50% of patients with carcinoid tumors of the GI tract demonstrate evidence of 5-HT production as manifested by elevated urinary levels of 5-hydroxyindoleacetic acid (5-HIAA), a metabolic product of 5-HT. Carcinoid syndrome is usually associated with ileal carcinoid tumors that have metastasized

to the liver. Presumably, the liver clears mediators released from the tumor. Impairment of this clearing ability by the metastatic tumor results in carcinoid syndrome.

Most patients with carcinoid tumors and increased urinary 5-HIAA levels have typical carcinoid tumors originating from the midgut (ileum or jejunum). These patients excrete only small amounts of 5-hydroxytryptophan (5-HTP). Patients with atypical carcinoid tumors that originate in the foregut (bronchus, stomach, and pancreas) excrete large amounts of 5-HT and 5-HTP, as well as moderately higher amounts of 5-HIAA.

Although it is generally agreed that 5-HT is responsible for the diarrhea experienced by patients with carcinoid tumors, other neurohumoral agents may contribute to the flushing and hypotension, including dopamine, histamine, and some of the neuropeptides such as substance P, neuropeptides, vasoactive intestinal peptide, and somatostatin.

The net physiologic effect of circulating 5-HT represents a composite of both direct action (mediated by 5-HT receptors) and indirect action (mediated through modulation of adrenergic neurotransmission). The existence of several subtypes of 5-HT receptors may account for the different effects of 5-HT on various serotonin-sensitive tissue beds. Indirect actions are effected through alterations in catecholamine release and depend on the level of circulating 5-HT.

5-HT has little, if any, direct effect on the heart. With increased levels, however, positive chronotropic and inotropic myocardial effects may occur, mediated by the release of noradrenaline (norepinephrine). Effects of serotonin on the vasculature include both vasoconstriction and vasodilation.

Alterations in GI function attributed to 5-HT include increased motility and net intestinal secretion of water, sodium chloride, and potassium. 5-HT reportedly causes bronchoconstriction in many animals, but rarely in humans. Patients with asthma are a possible exception. Carcinoid tumors frequently manifest as diarrhea with fluid and electrolyte abnormalities. Because these tumors secrete vasoactive substances, patients can exhibit hypotension or hypertension along with the flush associated with release of vasoactive substances. Vasoactive substances can be released from the tumor by any number of substances, including catecholamines. The anesthesiologist needs to be ready and able to treat hypotension, decreased peripheral vascular resistance, bronchospasm, and hypertension. This difficulty in managing carcinoid syndrome seemed to change with the availability of a somatostatin analogue, octreotide, and lanreotide. In fact, somatostatin is such a powerful inhibitor of the release of peptides from carcinoid tumors and an inhibitor of the peptic effects on receptor cells that it is the therapy of choice for preoperative, intraoperative, and postoperative management of carcinoid symptoms and crises.<sup>360,361</sup> In cardiac surgical patients, mortality has declined over time, and vasopressors have been shown to be safe in conjunction with octreotide.<sup>362</sup> However, the ease of management of most patients<sup>360,361,363-366</sup> should not lull the anesthesiologist into being unprepared—in fact, somatostatin has caused problems of its own and has failed to prevent severe hypotension and bronchospasm.<sup>367,368</sup>

In patients with severe hypotension that is not treatable with somatostatin, the drug of choice is vasopressin; angiotensin has demonstrated benefit but only recently become available in the United States. However, the vasoactive

substances released by carcinoid tumors cause fibrosis of the heart valves that often results in pulmonic stenosis or tricuspid insufficiency. To increase cardiac output in a patient with tricuspid insufficiency, the anesthesiologist should avoid drugs or situations that increase pulmonary vascular resistance. In addition, the production of large amounts of 5-HT (equal to 200 mg/day of 5-HIAA) can lead to the development of niacin deficiency with pellagra (as occurs with diarrhea, dermatitis, and dementia).

Steroids have been effective in treating the symptoms of bronchial carcinoid tumors. Although prophylactic preoperative administration and intraoperative therapeutic use have been described, controlled studies of beneficial effects are lacking. Aprotinin, like steroids, inhibits the kallikrein cascade by blocking the proteinase activity of kallikrein, and some reports have described a dramatic clinical response, though it is not available in the United States.

A subset of patients with symptoms of carcinoid syndrome excretes histamine at increased levels in their urine. Histamine causes vasodilation of small blood vessels, which leads to flushing and decreased total peripheral resistance. Histamine is known to cause bronchoconstriction, particularly in patients with bronchial asthma and other pulmonary diseases. Histamine receptor blocking drugs have been used with some success in alleviating the flushing associated with carcinoid syndrome. H<sub>2</sub> antagonism alone was found to be just as effective as combination therapy in preventing symptoms; pure H<sub>1</sub> antagonism, however, was ineffective. These therapies have been relegated to a second-line defense since the use of somatostatin.

Catecholamines aggravate the symptoms of carcinoid syndrome, presumably by stimulating release of hormone by the tumor. Adrenergic receptors have not been demonstrated in carcinoid tumors, nor do these tumors usually have neural innervation. Perhaps adrenergic stimuli work through their mechanical effects on the gut and vessels to stimulate the release of tumor products. Treatment of patients with carcinoid tumors by means of  $\alpha$ - and  $\beta$ -adrenergic antagonists has been beneficial in ameliorating flushing in some instances but ineffective in others.

The results of prospective studies on somatostatin to ameliorate the symptoms of carcinoid syndrome have been dramatic. Somatostatin appears to have been a major advance in the treatment of carcinoid syndrome, it is now the mainstay of medical treatment perioperatively.

Bronchospasm with or without flushing also develops in many patients when vasoactive substances are released. Thus a patient with a carcinoid tumor may be well or may be severely incapacitated by pulmonary, neurologic, nutritional, fluid, electrolytic, or cardiovascular disturbances.

Therefore, although the GI system in itself may not require extensive preoperative preparation, GI disease can cause disturbances in any or all other systems that require extensive preoperative preparation to optimize the patient's condition in addition to preoperative knowledge of physiology and the effects of diseases to guide patients through the perioperative period smoothly. In addition, the anesthesiologist's understanding of the nature of the surgical procedure aids in determining the system involvement caused by the GI disorder.

Another perioperative consideration is that patients with GI diseases have had to endure the psychosocial trauma of having to live with their disease for long periods or the necessity of

facing such a prospect.<sup>369</sup> They need emotional support, kindness, and empathy as much as, if not more than, other patients without sacrificing scientific rigor in the treatment of their condition. Obtaining relevant psychological data while gathering medical information, sitting while taking the history, and empathizing with the patient about how difficult it must be to accomplish tasks with this disease legitimize the physician's interests in and support of the patient's pain and other psychosocial issues. The time spent sitting and talking with the patient also allows the anesthesiologist to discuss options for pain therapy with the patient, and other issues that show the anesthesiologist to be both a competent physician and particularly concerned with that patient's well-being.

## LIVER DISEASE

What are the risks of giving anesthesia to patients with acute liver disease who require emergency surgery? What are the risks of giving anesthesia to patients with chronic impairment of liver function? What can be done to minimize these risks? Although one may think that the experiences gained from providing anesthesia for liver transplantation would answer many of these questions, a substantial difference exists between optimizing cardiovascular function to meet the needs of a new liver (e.g., supply of nutrients) and maintaining liver function in a diseased liver. Hepatic physiology and pathology are discussed in [Chapter 16](#).

## Hematologic Disorders and Oncologic Disease

### HEMATOLOGIC DISORDERS

#### Sickle Cell Anemia and Related Hemoglobinopathies

The sickle cell syndromes constitute a family of hemoglobinopathies caused by abnormal genetic transformation of amino acids in the heme portion of the hemoglobin molecule. The sickle cell syndromes arise from a mutation in the  $\beta$ -globin gene that changes the sixth amino acid from valine to glutamic acid. A major pathologic feature of sickle cell disease is the aggregation of irreversibly sickled cells in blood vessels. The molecular basis of sickling is the aggregation of deoxygenated hemoglobin B molecules along their longitudinal axis.<sup>370</sup> This abnormal aggregation distorts the cell membrane and thereby produces a sickle shape. Irreversibly sickled cells become dehydrated and rigid and can cause tissue infarcts by impeding blood flow and oxygen to tissues.<sup>370-373</sup> Several studies show enhanced adhesion of sickled erythrocytes to vascular endothelium, as well.<sup>374</sup> Some other abnormal hemoglobins interact with hemoglobin S to various degrees and give rise to symptomatic disease in patients heterozygous for hemoglobin S and one of the other hemoglobins such as the hemoglobin of thalassemia (hemoglobin C).

Three tenths of 1% of the African American population in the United States have sickle cell-thalassemia disease (hemoglobin SC); these patients also have end-organ disease and symptoms suggestive of organ infarction. For these patients, perioperative considerations should be similar to those for patients with sickle cell disease (hemoglobin SS).

Whereas 8% to 10% of African Americans have the sickle cell trait (hemoglobin AS), 0.2% are homozygous for sickle cell hemoglobin and have sickle cell anemia. Sickle cell trait is a heterozygous condition in which the individual has one  $\beta$ S globin gene and one  $\beta$ A globin gene, which results in the production of both hemoglobin S and hemoglobin A, with a predominance of hemoglobin A. Sickle cell trait is not clinically significant because hemoglobin AS cells begin to sickle only when the oxygen saturation of hemoglobin is less than 20%. Minimal difference has been found between physiologically normal persons (i.e., those with hemoglobin AA) and those with hemoglobin AS regarding survival rates, though there is one exception—patients with hemoglobin AS have a 50% increase in pulmonary infarction. However, single case reports of a perioperative death and a perioperative brain infarct in two patients with hemoglobin AS disease do exist, as does a report of death believed to be caused by aortocaval compression during general anesthesia that resulted in a sickling crisis.<sup>375</sup> Frequent measurement of oxygen saturation (pulse oximetry) in multiple areas of the body is recommended when caring these AS patients, including the ear and toe in pregnant patients.<sup>375</sup>

The pathologic end-organ damage that occurs in sickle cell states is attributable to three processes: the sickling or adhesion of cells in blood vessels, which causes infarcts and subsequent tissue destruction secondary to tissue ischemia; hemolytic crisis secondary to hemolysis; and aplastic crises that occur with bone marrow exhaustion, which can rapidly result in severe anemia. Patients currently in crisis should not undergo surgery except for emergencies, and then only after an exchange transfusion.<sup>372,374-378</sup>

Because sickling is increased with lowered oxygen tensions, acidosis, hypothermia, and the presence of more desaturated hemoglobin S; current therapy includes keeping the patient warm and well hydrated, giving supplemental oxygen, maintaining high cardiac output, and avoiding areas of stasis with pressure or tourniquets. Meticulous attention to these practices in periods when we do not usually pay most careful attention (i.e., waiting in the preinduction area) or when gas exchange may be most unmatched to the cardiovascular-metabolic demands (early postoperative period) may be important in lessening morbidity. Following these measures routinely succeeded in reducing mortality to 1% in several series of patients with sickle cell syndromes.<sup>375,378,379</sup> Retrospective review of patients' charts led the authors of those studies to conclude that, at most, a 0.5% mortality rate could be attributed to the interaction between sickle cell anemia and anesthesia.

Several investigators have advocated using partial exchange transfusions perioperatively. In children with sickle cell anemia and acute lung syndromes, partial exchange transfusion improved clinical symptoms and blood oxygenation. In addition, serum bilirubin levels decreased in patients with acute liver injury. Clinical improvement of pneumococcal meningitis and cessation of hematuria in papillary necrosis also accompanied exchange transfusion.<sup>371</sup> The goal of transfusion therapy is to lower the concentration of hemoglobin S to less than 30%, minimize splenic sequestration, treat severe anemia, and avoid acute chest syndrome due to low  $\text{PaO}_2$ .<sup>379a</sup> Exchange transfusion serves to lower the concentration of hemoglobin S, while red blood cell transfusions serve to correct anemia. To date only regular transfusion therapy has been associated with improved mortality in the extended period.<sup>379b,c</sup> Two studies

demonstrated a possible decrease in perioperative morbidity after partial exchange transfusion when compared with the risks of exchange transfusion.<sup>373,380</sup> A retrospective review of 14 patients with sickle cell anemia who were undergoing total hip revision supported the decision to perform a simple transfusion preoperatively only if the patient's hemoglobin is significantly lower than their steady-state hemoglobin level.<sup>381</sup> Transfusion can be used intraoperatively according to hemoglobin level or blood loss volume. Other conditions are common in sickle cell syndromes: pulmonary dysfunction with increased shunting, renal insufficiency, gallstones, small MIs, priapism, stroke, aseptic necrosis of bones and joints, ischemic ulcers, retinal detachment as a result of neovascularization, and complications of repeated transfusions.

In thalassemia, globin structures are normal, but because of gene deletion, the rate of synthesis of either the  $\alpha$  or  $\beta$  chains of hemoglobin ( $\alpha$ - and  $\beta$ -thalassemia, respectively) decreases.<sup>382-384</sup> Two copies of the gene that codes for the  $\alpha$ -globin chain are located on chromosome 16. Deletion of all four of these genes causes cell death in utero, and three deletions cause severe chronic hemolysis and a shortened life span.  $\alpha$ -Thalassemia-1 (trait) occurs when two genes have been deleted and mild anemia results;  $\alpha$ -thalassemia-2 (silent) occurs when the two genes have been deleted but no mild anemia or microcytosis results. In  $\alpha$ -thalassemia trait, the hemoglobin  $A_2$  level is normal.  $\beta$ -Thalassemia is associated with an excess of  $\alpha$  chains, which denature developing erythrocytes, thereby leading to their premature death in marrow or to shortened survival in the circulation. An elevated hemoglobin  $A_2$  level is the hallmark of  $\beta$ -thalassemia trait, a common cause of mild anemia and microcytosis. These syndromes are common in Southeast Asia, India, and the Middle East and in people of African descent.

In thalassemia, facial deformity from erythropoietin-stimulated ineffective erythropoiesis (ineffective because of a genetic inability to produce useful hemoglobin) was reported to make endotracheal intubation difficult.<sup>382,383</sup> The anemia associated with these syndromes often produces compensatory hyperplasia of the erythroid marrow, which in turn is associated with severe skeletal abnormalities.<sup>382-384</sup>

### Cytoskeletal Anemias (Hereditary Spherocytosis and Elliptocytosis), Enzyme-Deficient Anemias, and Autoimmune Hemolytic Anemias

Congenital abnormalities of the erythrocyte membrane are becoming better understood. In elliptocytosis and hereditary spherocytosis, the membrane is more permeable to cations and is more susceptible to lipid loss when cell energy is depleted than is the membrane of a normal red blood cell. Both hereditary spherocytosis (present in 1 in 5000 people) and hereditary elliptocytosis are inherited as autosomal dominant traits. In both disorders, defects in the membrane are thought to result from a mutation of spectrin, a structural protein of the membrane cytoskeleton.<sup>385</sup> Although the therapeutic role of splenectomy in these diseases is not fully defined, in severe disease, splenectomy is known to improve the shortened life span of the red blood cell from 20-30 days to 40-70 days. Because splenectomy predisposes the patient to gram-positive septicemia (particularly pneumococcal), perhaps patients should be given pneumococcal vaccine preoperatively. No specific problems related to anesthesia have been reported for these disorders.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency (a gender-linked recessive trait) has been recognized as the most common enzymopathy worldwide, most often expressed in males, and in patients of African, Asian, Mediterranean, or Middle Eastern descent.<sup>385a</sup> Young cells have normal activity, but older cells are grossly deficient when compared with normal cells. A deficiency in G6PD results in hemolysis of the erythrocyte and the formation of Heinz bodies. Red blood cell hemolysis can also occur with intercurrent infections or after the administration of drugs that produce substances requiring G6PD for detoxification (e.g., methemoglobin, glutathione, and hydrogen peroxide). Drugs to be avoided are sulfa drugs, quinidine, prilocaine, lidocaine, antimalarial drugs, antipyretic drugs, nonnarcotic analgesics, vitamin K analogues, and perhaps sodium nitroprusside.

The autoimmune hemolytic anemias include cold antibody anemia, warm antibody anemia (idiopathic), and drug-induced anemia and occur from antibody-mediated destruction of red blood cells.<sup>386-388</sup> Cold antibody hemolytic anemia is mediated by IgM or IgG antibodies, which at room temperature and lower temperatures cause red blood cells to clump. When these patients are given blood transfusions, the cells and all fluid infusions must be warm, and body temperature must be meticulously maintained at 37°C if hemolysis is to be prevented. Warm antibody (or idiopathic) hemolytic anemia is mediated by IgG and is a difficult management problem characterized by chronic anemia, the presence of antibodies active against red blood cells, a positive Coombs test, and difficulty crossmatching blood. For patients undergoing elective surgery, autologous transfusions, predeposit of blood with or without erythropoietin stimulation,<sup>389</sup> and blood from rare Rh-negative red blood cell donors or the patient's first-degree relatives (or both) can be used. In emergency situations, the possibility of autotransfusion, splenectomy, corticosteroid treatment, rituximab, cyclophosphamide, or azathioprine should be discussed with a hematologist knowledgeable in this area.<sup>389a</sup>

Drug-induced anemias have three mechanisms. In receptor-type hemolysis, a drug (e.g., penicillin) binds to the membrane of the red blood cell, and the complex stimulates the formation of an antibody against the complex. In "innocent bystander" hemolysis, a drug (e.g., quinidine, sulfonamide) binds to a plasma protein, thereby stimulating an antibody (IgM) that cross-reacts with an erythrocyte. In autoimmune hemolysis, the drug stimulates the production of an antibody (IgG) that cross-reacts with the erythrocyte. Drug-induced hemolytic anemias generally cease when therapy with the drug ends.

### Granulocytopenia

Granulocyte mechanisms have undergone experimental elaboration since 2000, partly because of the molecular biologic revolution: in addition to erythropoietin, more than 14 hemolymphopoietic growth factors or cytokines have been characterized biochemically and cloned genetically. These growth factors interact with cell-surface receptors to produce their major actions (Table 32.14).<sup>390</sup> Use of the colony-stimulating factors has permitted more intense oncologic treatment. The few reports related to their perioperative effects detail the unfavorable adverse consequences that such therapies can have on gas exchange when adverse immunologic effects occur.<sup>391</sup>

In patients who have fewer than 500 granulocytes/mL of blood and established sepsis, the use of growth factor and granulocyte transfusion has been shown to prolong

life.<sup>392-394</sup> Although bone marrow transplantation is being used increasingly, complications usually occur after transplantation, not on harvesting of cells. Abnormal results on pulmonary function testing before bone marrow transplantation seem to predict complications after transplantation, but not so strongly as to preclude transplantation.<sup>395</sup>

### Platelet Disorders

Although inherited platelet disorders are rare, acquired disorders are quite common and affect at least 20% of all patients in medical and surgical ICUs, with infections and drug therapies being the leading causes.<sup>396</sup> Both acquired and inherited platelet conditions cause skin and mucosal bleeding, whereas defects in plasma coagulation produce deep tissue bleeding or delayed bleeding. Perioperative treatment of inherited platelet disorders (e.g., Glanzmann thrombasthenia, Bernard-Soulier syndrome, Hermansky-Pudlak syndrome) consists of platelet transfusions. EACA has been used successfully to decrease perioperative bleeding in thrombocytopenic patients. The much more common acquired disorders may respond to one of several therapies. Immune thrombocytopenias, such as those associated with lupus erythematosus, idiopathic thrombocytopenic purpura, uremia, hemolytic-uremic syndrome, platelet transfusions, heparin, and thrombocytosis, may respond to steroids, splenectomy, plateletpheresis, eradication of *Helicobacter pylori*, or alkylating agents, or may require platelet transfusions, plasma exchange, whole blood exchange, or transfusion; sometimes these disorders do not respond to anything.<sup>179,397,398</sup> Traditionally, splenectomy is performed when steroid therapy fails or reaches a dosage that poses unacceptable risks of toxicity. Immunoglobulin infusions and rituximab may induce desirable remissions in idiopathic thrombocytopenic purpura without splenectomy.

Thrombotic thrombocytopenic purpura is a rare immune-mediated thrombotic microangiopathic disorder caused by antibodies to ADAMTS 13 (A Disintegrin AND Metalloproteinase with a Thrombospondin type 1 motif, member 13) that, despite various therapies, still carries a high mortality rate.<sup>398a</sup> The current therapies of plasma exchange, corticosteroids, and rituximab have improved survival rates, though new therapies are under investigation.<sup>398b</sup> One uncontrolled study implies that the benefit lies not only in improvement of the hematologic picture but also in prevention of ARDS, a leading cause of death in these patients.<sup>398</sup> In that study, early institution of plasmapheresis improved oxygenation.

By far the largest number of platelet abnormalities consists of drug-related defects in the aggregation and release of platelets. Aspirin irreversibly acetylates platelet cyclooxygenase, the enzyme that converts arachidonic acid to prostaglandin endoperoxidases. Because cyclooxygenase is not regenerated in the circulation within the life span of the platelet and because this enzyme is essential for the aggregation of platelets, one aspirin tablet may affect platelet function for a week. All other drugs that inhibit platelet function (e.g., vitamin E, indomethacin, sulfapyrazone, dipyridamole, tricyclic antidepressant drugs, phenothiazines, furosemide, steroids) do not inhibit cyclooxygenase function irreversibly; these drugs disturb platelet function for only 24 to 48 hours. If emergency surgery is needed before the customary 8-day period for platelet regeneration after aspirin therapy or if the 2-day period for other drugs has not elapsed, administration of 2 to 5 units of platelet concentrate will return platelet function

**TABLE 32.14** Major Effects of Hemolymphopoietic Growth Factors and Cytokines

Cytokine	Other Names	Biologic Effects
Erythropoietin		Erythrocyte production
Interleukin-3 (IL-3)	Multic colony-stimulating factor Stem cell-activating factor Persisting cell-stimulating factor Hemopoietin-2	Stimulates proliferation and differentiation of granulocyte, macrophage, eosinophil, mast cell, megakaryocyte, and T- and B-cell lineage and early myeloid stem cells Interacts with erythropoietin to stimulate erythroid colony formation, stimulates proliferation of AML blasts, and stimulates histamine release by mast cells
Granulocyte colony-stimulating factor (G-CSF)	Differentiation factor MGI-2	Stimulates granulocyte lineage proliferation and differentiation Acts on early myeloid stem cells, especially in association with other factors; synergizes with IL-3 to stimulate megakaryocyte colony formation Increases neutrophil phagocytosis and antibody-dependent cell-mediated cytotoxicity Releases neutrophils from bone marrow and is chemotactic for neutrophils and monocytes Enhances phagocytosis and antibody-dependent cell-mediated cytotoxicity and oxidative metabolism of neutrophils Stimulates monocyte killing of <i>Mycobacterium avium-intracellulare</i> and <i>Candida</i> species, tumoricidal activity of monocytes, antibody-dependent cell-mediated cytotoxicity, and expression of cell-surface proteins
Granulocyte-macrophage colony-stimulating factor (GM-CSF)		Stimulates granulocyte, macrophage, and megakaryocyte proliferation and differentiation, early myeloid stem cells, and—in the presence of erythropoietin—erythropoiesis Enhances the cytotoxic and phagocytic colony-stimulating factor activity of neutrophils against bacteria, yeast, parasites, and antibody-coated tumor cells Increases surface expression of neutrophil adhesion proteins and enhances eosinophil cytotoxicity, macrophage phagocytosis, and basophil histamine release Amplifies IL-2-stimulated T-cell proliferation and stimulates B-cell lines to proliferate
Colony-stimulating factor-1	Macrophage colony-stimulating factor	Stimulates predominantly macrophage-monocyte proliferation and differentiation with lesser effects on granulocytes Acts synergistically with other factors on earlier myeloid stem cells Stimulates macrophage phagocytosis, killing, migration, antitumor activity, and metabolism Stimulates secretion of plasminogen activator, G-CSF, interferon, IL-3, or tumor necrosis factor by peritoneal macrophages
Interleukin-1 (α and β)	Endogenous pyrogen Hemopoietin-1 Osteoclast-activating factor Lymphocyte-activating factor	Induces synthesis of acute-phase proteins by hepatocytes Activates resting T cells, cofactor for T- and B-cell proliferation Chemotactic for monocytes and neutrophils Induces production of growth factors, including G-CSF, GM-CSF, IL-6, CSF-1, IL-3, and interferon by many cells Radioprotective in mice
Interleukin-2	T-cell growth factor	Growth factor for T cells, activates cytotoxic T lymphocytes, promotes synthesis of other cytokines, enhances natural killer cell function
Interleukin-4	B-cell-stimulating factor-1 (BSF-1) B-cell differentiation factor (BCDF) IgG induction factor	Enhances antibody production (IgG and IgE) and up-regulates class II MHC molecules and Fc receptors on B cells Costimulant with anti-IgM antibodies for induction of DNA synthesis in resting B cells Stimulates growth of activated T cells In the presence of IL-3, enhances mast cell growth; with G-CSF, enhances granulocytes of GM colony formation; and with erythropoietin and/or IL-1, stimulates erythroid and megakaryocyte colony formation
Interleukin-5	Eosinophil differentiation factor (EDF) T-cell-replacing factor (TRF) B-cell growth factor-II (BCGF-II) B-cell differentiation factor (BCDF)	Enhances antibody production (IgA) Promotes proliferation and IgG secretion by B-cell lines and induces hapten-specific IgG secretion in vitro by in vivo-primed B cells Promotes differentiation by normal B cells Stimulates eosinophil production and differentiation (GM-CSF and IL-3 act synergistically with IL-5 to stimulate eosinophil proliferation and differentiation) Enhances synthesis of IL-2 receptors
Interleukin-6	B-cell-stimulating factor-2 (BSF-2) Interferon-β <sub>2</sub> T-cell activation factor Hybridoma growth factor	B-cell differentiation and IgG secretion T cells activated to cytotoxicity Synergizes with IL-3 on early marrow myeloid stem cells and stimulates proliferation and differentiation of granulocytes, macrophages, eosinophils, mast cells, and megakaryocytes, as well as platelet production (may be a thrombopoietin)
Interleukin-7	Lymphopoietin-1	Stimulates pre-B-cell production Stimulates T-cell proliferation
Interleukin-8*	Neutrophil-activating factor T-cell chemotactic factor	Inflammatory mediator; stimulates activation of neutrophils
Interleukin-9		Stimulates erythroid colony formation and proliferation of a megakaryocyte cell line

**TABLE 32.14** Major Effects of Hemolymphopoietic Growth Factors and Cytokines—cont'd

Cytokine	Other Names	Biologic Effects
Interleukin-10	Cytokine synthesis-inhibiting factor	Inhibits cytokine production by $T_{H}1$ cells
Interleukin-11		Stimulates B-cell, megakaryocyte, and mast cell lineages
C-kit ligand	Mast cell factor Stem cell factor Hemolymphopoietic growth factor-1	Acts on relatively early stem cells synergistically with other cytokines Stimulates pre-B cells

\*Not considered a true growth factor but included here for completeness.

AML, Acute myeloblastic leukemia; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; MHC, major histocompatibility complex;  $T_{H}1$ , first of the thymus-derived cells.

in a 70-kg adult to an adequate level and platelet-induced clotting dysfunction to normal. Only 30,000 to 50,000 normally functioning platelets per milliliter are needed for normal clotting. One platelet transfusion will increase the platelet count from 5,000 to 20,000/mL blood; the platelet half-life is approximately 8 hours.

Heparin-induced thrombocytopenia can develop within hours on reexposure to heparin in a previously sensitized patient; prevalence has been shown to be increasing, particularly in ICU populations.<sup>398c</sup> The diagnosis starts with a clinical assessment, most commonly the 4-T score (Thrombocytopenia, Timing of fall, presence of Thrombosis, and other causes for Thrombocytopenia), with enzymatic immunoassays for confirmation.<sup>398d</sup> Treatment can be initiated prior to confirmatory test results, if suspicion is high. Argatroban is a direct thrombin inhibitor effective as therapy for heparin-induced thrombocytopenia.<sup>399</sup>

Major risk factors for thrombosis include factor V Leiden and prothrombin 20210A mutations, elevated plasma homocysteine, and the antiphospholipid antibody syndrome.<sup>400,401</sup> Clinicians facing these challenging patients may seek expert local consultation for help with management. This issue is discussed more fully in [Chapter 50](#).

### Hemophilia and Related Clotting Disorders

Abnormalities in blood coagulation as a result of defects in plasma coagulation factors are either inherited or acquired. Inherited disorders include X-linked hemophilia A (a defect in factor VIII activity), von Willebrand disease (defect in the von Willebrand component of factor VIII), hemophilia B (a sex-linked deficiency of factor IX activity), and other less common disorders. The sex-linked origin of some of these disorders means that hemophilia occurs almost exclusively in the male children of female carriers; men do not transmit the disease to their male children.

In elective surgery, levels of the deficient coagulation factor should be assayed 48 hours preoperatively and the level restored to 40% of normal before the surgical procedure. One unit of factor concentrate per kilogram of body weight normally increases the factor concentration by 2%. Thus, in an individual essentially devoid of activity, administration of 20 units/kg body weight would be required as an initial dose. Because the half-life is 6 to 10 hours for factor VIII and 8 to 16 hours for factor IX, approximately 1.5 units/h/kg of factor VIII or 1.5 units/2 hours/kg of factor IX should be given. Additional administration of factors VIII and IX should be guided by the activity of the clotting factors for approximately 6 to 10 days postoperatively.<sup>402-404</sup>

An antibody that inactivates factor VIII or IX (fresh frozen plasma) fails to increase clotting factor activity after incubation

with the patient's plasma) develops in approximately 10% of patients with either hemophilia A or B. These acquired anti-coagulants are usually composed of IgG, are poorly removed by plasmapheresis, and are variably responsive to immunosuppressive drugs. The use of prothrombin complex concentrates can be lifesaving to bypass the inhibitor.

Patients who come to the operating room after having received many units of blood (as in massive GI bleeding and trauma) may have deficient clotting caused by depletion of platelets and later coagulation factors, which occurs after administration of approximately 10 units of blood. Treatment of these deficiencies can be corrected with platelet concentrates and fresh frozen plasma. In settings of massive hemorrhage requiring large volume transfusion, the approximation of whole blood through a one to one to one ratio of packed red blood cells to plasma to platelets can be advantageous.

Urokinase, streptokinase, and tissue-type plasminogen activator (t-PA) have been used to treat pulmonary embolism, deep vein thrombosis, stroke, and arterial occlusive disease. These drugs accelerate the lysis of thrombi and emboli, in contrast to heparin, which may prevent and slow propagation, but will not dissolve a thrombus. Bleeding complications associated with these fibrinolytic agents are the result of dissolution of hemostatic plugs and can be quickly reversed by discontinuing the medication and replenishing plasma fibrinogen with cryoprecipitate or plasma. However, cryoprecipitate and plasma are seldom needed preoperatively because the fibrinolytic activity of urokinase and streptokinase usually dissipates within 1 hour of discontinuing their administration. Nonetheless, insufficient data have accumulated to prescribe the ideal preoperative preparation and intraoperative management of hemostasis in patients recently treated with urokinase, streptokinase, or t-PA. Postponing surgery for three half-lives of the drug (increases in plasmin activity in blood can be assayed for  $\geq 4$  to 8 hours) may not be possible, and meticulous observation of the operative field for hemostasis may not suffice.<sup>405,406</sup> The process may be even more complex in a patient with a vascular or cardiac condition who requires heparin administration intraoperatively. To correct the fibrinogen deficiency in these patients, some clinicians administer fibrinogen as cryoprecipitate preoperatively, and EACA at heparin administration.

DDAVP has been used in operations associated with high blood loss as a routine measure to decrease bleeding and transfusion requirements. DDAVP therapy began as treatment of platelet dysfunction in von Willebrand disease but has since expanded to routine use in patients undergoing cardiovascular surgery and to frequent use in other high-blood loss operations. A meta-analysis of cardiac surgery concluded that DDAVP was not associated with a clinically significant reduction in exposure to blood transfusion in unselected patients,

and therefore the authors were unable to recommend the routine use of DDAVP in patients exposed to CPB.<sup>407</sup> However, DDAVP may reduce postoperative bleeding in patients who have received preoperative aspirin within 7 days of surgery, patients with CPB times in excess of 140 minutes, and patients with demonstrable platelet dysfunction. The authors suggested that DDAVP could be used selectively in these subgroups.

## ONCOLOGIC DISEASE

Patients with malignant tumors may be otherwise healthy or may be chronically ill with nutritional, neurologic, metabolic, endocrinologic, electrolyte, cardiac, pulmonary, renal, hepatic, hematologic, or pharmacologic disabilities. Thus determining the other morbidities accompanying malignant tumors requires thorough evaluation of all systems. Abnormalities frequently accompanying such tumors include hypercalcemia either by direct bone invasion or by ectopic elaboration of PTH or other bone-dissolving substance, uric acid nephropathy, hyponatremia (especially with small cell, or oat cell, carcinoma of the lung), nausea, vomiting, anorexia and cachexia, fever, tumor-induced hypoglycemia, intracranial metastases (10%-20% of all cancers), peripheral nerve or spinal cord disorders, meningeal carcinomatosis, toxic neuropathies secondary to anticancer therapy, and paraneoplastic neurologic syndromes (dermatomyositis, Eaton-Lambert syndrome, myopathies, and distal neuropathies).

Many patients with malignant tumors are given large doses of analgesics and should be kept comfortable during the perioperative period, it is of particular importance in terminally ill patients.<sup>408</sup> Immunomodulators, stimulating factors or cytokines, gene identification,<sup>409,410</sup> and drugs for treating side effects (e.g., midazolam, ondansetron, and even marijuana) have given new hope for safer, more effective therapy with fewer limiting side effects. The effect of ondansetron in preventing vomiting and the effect of midazolam in preventing memory-stimulated vomiting have been important additions. The neurokinin-1 antagonists have also been approved for treatment in oncologic patients.

The toxicity of cancer chemotherapy is related to the drugs used and the dose. For radiation therapy, damage occurs when the following doses are exceeded: lungs, 1500 rad; kidneys, 2400 rad; heart, 3000 rad; spinal cord, 4000 rad; intestine, 5500 rad; brain, 6000 rad; and bone, 7500 rad. The toxicities of biologic and immunomodulating therapies are related to the change in immune function that they cause. Alkylating agents cause bone marrow depression, including thrombocytopenia, as well as alopecia, hemorrhagic cystitis, nausea, and vomiting. The alkylating agents, including cyclophosphamide and mechlorethamine, can act as an anticholinesterase and prolong neuromuscular blockade.<sup>411</sup> The antineoplastic alkaloid vincristine produces peripheral neuropathy and SIADH, and vinblastine produces myelotoxicity. Cisplatin is also associated with peripheral neuropathy and severe nausea. Nitrosoureas can produce severe hepatic and renal damage, as well as bone marrow toxicity, myalgia, and paresthesia. Folic acid analogues such as methotrexate have been linked to bone marrow depression, ulcerative stomatitis, pulmonary interstitial infiltrates, GI toxicity, and occasionally, severe liver dysfunction. Fluorouracil and floxuridine, both pyrimidine analogues, cause bone marrow toxicity, megaloblastic anemia, nervous system dysfunction, and hepatic and GI alterations. Purine analogues (mercaptopurine, thioguanine) have

bone marrow depression as their primary toxic effect. Anthracycline antibiotics (doxorubicin, daunorubicin, mithramycin, mitomycin C, bleomycin) can all cause pulmonary infiltrates, cardiomyopathy (especially doxorubicin and daunorubicin), myelotoxicity, and GI, hepatic, and renal disturbances. Knowing these expected side effects and complications allow general anesthesia to be safely provided to this patient population with the appropriate preoperative plan.

## Patients Given Drug Therapy for Chronic and Acute Medical Conditions

A steadily increasing number of potent drugs are being used to treat disease, and the average hospitalized patient receives more than 10 drugs. Many drugs have side effects that may make anesthesia challenging and patient management more difficult. Knowing the pharmacologic properties and potential side effects of commonly used drugs helps the anesthesiologist avoid pitfalls during anesthesia and surgery.

### ANTIHYPERTENSIVE DRUGS

ACE inhibitors (e.g., captopril, enalapril, and lisinopril) and angiotensin II receptor blockers (e.g., valsartan, candesartan) are being used increasingly as first-line drugs and appear to improve the quality of life of patients taking antihypertensive drugs. ACE inhibitors and angiotensin II receptor blockers may be associated with more peripheral vasodilation and hypotension on induction of anesthesia than are sympatholytic agents. Both ACE inhibitors and angiotensin II receptor blocking agents are associated with such severe hypotension with standard anesthetic induction that we discontinue or at least consider discontinuing the use of these drugs preoperatively (see earlier).

Catecholamine or sympathetic receptor blocking drugs affect the three major types of catecholamine receptors:  $\alpha$ -adrenergic,  $\beta$ -adrenergic, and dopaminergic. The existence of subdivisions (e.g.,  $\beta_1$  and  $\beta_2$ ) suggested the possibility that some drugs would be found to affect only one set of receptors. For example, terbutaline is used more frequently than isoproterenol because terbutaline is said to exert a preferential effect on  $\beta_2$  receptors (i.e., dilation of bronchial smooth muscle), thereby avoiding the cardiac stimulation produced by drugs that stimulate  $\beta_1$ -receptors. In fact, the selectivity is dose related. At a certain dose, a direct  $\beta_2$ -receptor stimulating drug affects only those receptors but, at a higher dose, stimulates both  $\beta_1$  and  $\beta_2$  receptors. The effect of a given dose varies with each patient. A certain dose may stimulate  $\beta_1$  and  $\beta_2$  receptors in one patient but neither receptor in another patient. More and more selective blocking drugs are being developed in the hope of widening the margin among  $\beta_1$ ,  $\beta_2$ , and  $\alpha$ -adrenergic effects. Ultimately, however, even more selectivity is desired. It would be advantageous to be able to decrease the heart rate without changing myocardial contractility or to increase contractility without changing the heart rate.

Metoprolol, atenolol, propranolol, betaxolol, timolol, esmolol, pindolol, oxprenolol, acebutolol, carteolol, penbutolol, and nadolol are widely available  $\beta$ -adrenergic receptor blocking drugs used for therapy in the United States. Because nadolol has poor lipid solubility, it has a long elimination half-life

(17-24 hours) and does not cross the blood-brain barrier readily. Although selective  $\beta$ -adrenergic receptor blocking drugs should be more appropriate in patients with increased airway resistance or diabetes, this advantage is apparent only when low doses are used. The use of  $\beta$ -adrenergic receptor blocking drugs has become widespread because these drugs treat everything from angina and hypertension to priapism and stage fright. These drugs appear to decrease morbidity and mortality in patients who have initially survived MI, and they may increase perioperative survival in selected patients.<sup>412,413</sup>

When administration of  $\beta$ -adrenergic receptor blocking drugs is terminated, sympathetic stimulation often increases, as though the body had responded to the presence of these drugs by increasing sympathetic neuron activity. Thus propranolol and nadolol withdrawal can be accompanied by a hyper- $\beta$ -adrenergic condition that increases myocardial oxygen demands. Administering propranolol or metoprolol can cause bradycardia, exacerbations of decompensated heart failure, fatigue, dizziness, depression, psychoses, bronchospasm, and Peyronie disease. The POISE study emphasized the concerns that inadequate titration of these agents can lead to stroke or increased mortality.<sup>111</sup> Side effects of dopaminergic receptor blocking drugs are discussed later.

Prazosin, terazosin, and oxazocine are  $\alpha_1$ -adrenergic receptor blocking drugs used to treat hypertension, ischemic cardiomyopathy, receding hairlines, and benign prostatic hypertrophy because they dilate both veins and arteries and reduce sphincter tone. These drugs are associated with vertigo, palpitations, depression, dizziness, weakness, and anticholinergic effects.

Some sympathomimetic drugs stimulate  $\alpha$ -adrenergic receptors in the brainstem. Clonidine, a drug with a half-life of 12 to 24 hours, dexmedetomidine, and guanfacine are  $\alpha_2$ -adrenergic receptor stimulants. Presumably,  $\alpha_2$ -adrenergic agonists, including clonidine, dexmedetomidine, and guanfacine, lower arterial blood pressure on a long-term basis through the central brainstem adrenergic stimulation referred to previously. They may also be used on a long-term basis to treat opiate, cocaine, food, and tobacco withdrawal. Occasionally, withdrawal from clonidine can precipitate a sudden rebound hypertensive crisis. Tricyclic antidepressant drugs and presumably phenothiazines and the butyrophenones interfere with the action of clonidine. Although administration of a butyrophenone (e.g., droperidol) to a patient taking clonidine, dexmedetomidine, or guanfacine on a long-term basis could theoretically precipitate a hypertensive crisis, this has not been reported. Clonidine administration can be accompanied by drowsiness, dry mouth, orthostatic hypotension, bradycardia, and impotence. Acute clonidine or dexmedetomidine administration decreases anesthetic requirements by at least 40% to 60%; long-term administration decreases requirements by 10% to 20%.<sup>414,415</sup> Because of the relative safety of these drugs and their ability to decrease anesthetic requirements, block narcotic-induced muscle rigidity, and provide pain relief, their popularity preoperatively, intraoperatively, and in ICU sedation is increasing dramatically.<sup>414-418</sup>

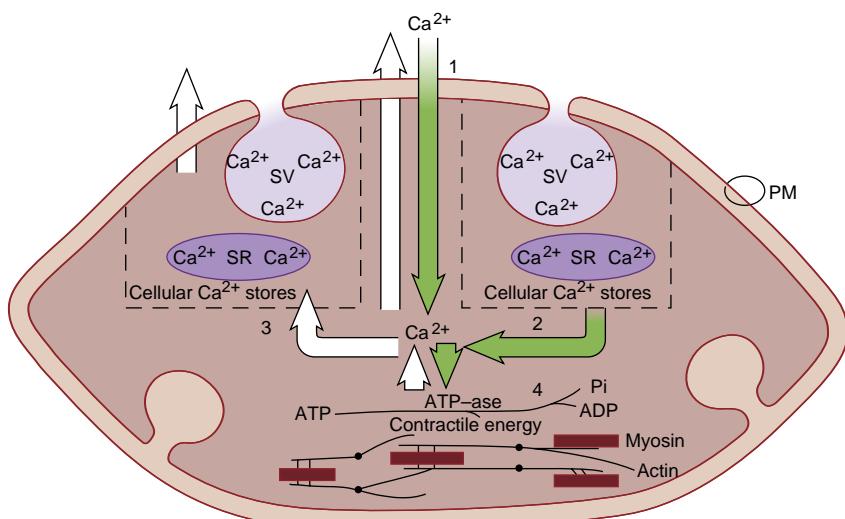
Three other classes of antihypertensive drugs affect the sympathetic nervous system indirectly: diuretics, arteriolar dilators, and calcium channel blocking agents. Thiazide diuretic drugs are associated with hypochloremic alkalosis, hypokalemia, hyperglycemia, hyperuricemia, and hypercalcemia. The potassium-sparing diuretic drug spironolactone is associated with hyperkalemia, hyponatremia,

gynecomastia, and impotence. All diuretic drugs can cause dehydration. The thiazide diuretics and furosemide appear to prolong neuromuscular blockade.

The arteriolar dilator hydralazine can cause a lupus-like condition (usually with renal involvement), nasal congestion, headache, dizziness, CHF, angina, and GI disturbances. Such a syndrome is nonexistent with the other direct vaso-dilator on the U.S. market, minoxidil.

The calcium channel blocking drugs (slow-channel calcium ion antagonists) inhibit the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. Such inhibition reduces the heart rate (negative chronotropy), depresses contractility (negative inotropy), decreases conduction velocity (negative dromotropy), and dilates coronary, cerebral, and systemic arterioles (Fig. 32.7).<sup>419</sup> Verapamil, diltiazem, and nifedipine all produce such effects, but to varying degrees and apparently by similar, but different mechanisms. These mechanisms relate to the three different classes of calcium channel antagonists that they represent: the phenylalkyl amines, the benzothiazepines, and the dihydropyridines, respectively. Nifedipine is the most potent of the three as a smooth muscle dilator, whereas verapamil and diltiazem have negative dromotropic and inotropic effects, and weak vasodilating properties. Diltiazem has weak vasodilating properties when compared with nifedipine and has less of an AV conduction effect than does verapamil. Thus verapamil and diltiazem can increase the PR interval and produce AV block. In fact, reflex activation of the sympathetic nervous system may be necessary during the administration of diltiazem, and especially during verapamil therapy, to maintain normal conduction. Clearly, verapamil and diltiazem must be titrated very carefully when a patient is already taking a  $\beta$ -adrenergic receptor blocking drug or when adding  $\beta$ -blocking drugs to a patient already taking verapamil or diltiazem.

The use of calcium channel blocking drugs has several important implications for anesthetic management.<sup>419-421</sup> First, the effects of inhaled and narcotic anesthetics and nifedipine in decreasing systemic vascular resistance, arterial blood pressure, and contractility may be additive. Similarly, verapamil and anesthetics (inhaled anesthetics, nitrous oxide, and narcotics) increase AV conduction times and additively decrease arterial blood pressure, systemic vascular resistance, and contractility. Second, verapamil and presumably the other calcium channel blocking drugs have been found to decrease anesthetic requirements by up to 25%. These drugs can produce neuromuscular blockade, and potentiate both depolarizing and nondepolarizing neuromuscular blocking drugs. Finally, because slow-channel activation of calcium is necessary to cause spasms of cerebral and coronary vessels, bronchoconstriction, and normal platelet aggregation, these drugs may have a role in treating cerebral vasospasm (nimodipine), coronary artery graft vasospasm (nicardipine), bronchoconstriction, and unwanted clotting disorders perioperatively. These drugs are highly protein bound and may displace or be displaced by other drugs that are also highly protein bound (e.g., lidocaine, bupivacaine, diazepam, disopyramide, and propranolol). Adverse consequences can be minimized by titrating the inhaled or narcotic drug to the hemodynamic and anesthetic effects. Hemodynamic, but not electrophysiologic, changes can usually be reversed by administering calcium. Reversal of the electrophysiologic effects may occur if high doses of  $\beta$ -adrenergic agonists are given.



**Fig. 32.7** Schematic drawing of a smooth muscle cell showing calcium ( $\text{Ca}^{2+}$ ) flux and possible sites of interference by halothane and nifedipine. The concentration of calcium in the cytoplasm increases (green arrows) because of entry through the plasma membrane (PM) and release from surface vesicles (SV) or the sarcoplasmic reticulum (SR). When the concentration of cytoplasmic  $\text{Ca}^{2+}$  is sufficiently high, adenosine triphosphate (ATP) is activated. Splitting of ATP by adenosine triphosphatase (ATPase) into inositol ( $\text{Pi}$ ) and adenosine diphosphate (ADP) provides the interaction and contraction of actin filaments and myosin particles constituting muscle fibers. The concentration of cytoplasmic  $\text{Ca}^{2+}$  decreases (white arrows) with the return of  $\text{Ca}^{2+}$  to cellular stores and the extracellular transport of  $\text{Ca}^{2+}$ . Both halothane and nifedipine probably (1) inhibit the entry of  $\text{Ca}^{2+}$  and (2) may also interfere with cytoplasmic  $\text{Ca}^{2+}$  flux by reducing the release of  $\text{Ca}^{2+}$  by the SR, by (3) reducing storage and reuptake, or by (4) blocking ATPase or the contractile mechanism (or both). (Redrawn from Tosone SR, Reves JG, Kissin I, et al. Hemodynamic responses to nifedipine in dogs anesthetized with halothane. *Anesth Analg*. 1983;62:903-908.)

## MOOD-ALTERING DRUGS

Mood-altering drugs are the most frequently prescribed medications in the United States.<sup>422,423</sup> They include MAOIs, SSRIs, phenothiazines, tricyclic antidepressant drugs, other antidepressants that do not fall into previous drug category classifications such as bupropion, and drugs of abuse such as cocaine. MAOIs, which include isocarboxazid, phenelzine, pargyline, tranylcypromine, and deprenyl, bind irreversibly to the enzyme MAO, thereby increasing intraneuronal levels of amine neurotransmitters (serotonin, norepinephrine, dopamine, epinephrine). This increase is associated with an antidepressant effect, an antihypertensive effect, an antinarcoleptic effect, elevation of liver enzymes, and delayed onset of Parkinson disease. Because two forms of the enzyme (MAO-A and MAO-B) are selective in vitro for substrate (MAO-A is selective for serotonin, dopamine, and norepinephrine; MAO-B for tyramine and phenylethylamine), presumably MAOIs selective for MAO-A or MAO-B would have different effects.<sup>424</sup>

Interactions between MAOIs and a variety of foods and drugs containing indirect-acting sympathomimetic substances such as ephedrine or tyramine (found in aged hard cheeses) can occur for as long as 2 weeks after the last dose of MAOI is given. The most serious effects of this interaction are convulsions and hyperpyrexic coma (particularly after narcotics).

Anesthetic management of a patient given an MAOI can be challenging; for this reason it is widely accepted practice to discontinue MAOIs at least 2 to 3 weeks before any planned operation, further MAOIs are seen quite infrequently.<sup>422-428</sup> Severe reactions have occurred when too short an interval existed between the administration of MAOIs and tricyclic antidepressants. Emergency surgery in patients given MAOIs can be punctuated by hemodynamic instability. A regional block can be attempted as treatment of postoperative pain to avoid having to give narcotics. Cases of hyperpyrexic coma

after the administration of most narcotics have been reported in humans, and animal studies document a 10% to 50% incidence of hyperpyrexic coma in animals pretreated with MAOIs and then given a variety of narcotics.<sup>422-428</sup> These reactions appear to be treated best by supportive care.

Alternative drugs for the treatment of severe depression include the tricyclic antidepressant drugs: amitriptyline, imipramine, desipramine, doxepin, nortriptyline, trazodone, and others.<sup>422,423</sup> Tricyclic antidepressant drugs also block the reuptake of neurotransmitters and cause their acute release. Given on a long-term basis, these drugs decrease stores of noradrenergic catecholamines. Tricyclic antidepressant drugs also produce side effects similar to those of atropine (dry mouth, tachycardia, delirium, urinary retention) and can cause changes on the ECG (changes in the T wave, prolongation of the QRS complex, bundle branch block or other conduction abnormalities, or PVCs). Although arrhythmias induced by tricyclic antidepressants have been treated successfully with physostigmine, bradycardia has sometimes occurred.<sup>422,423</sup> Drug interactions with tricyclic antidepressants include those related to blockade of the reuptake of norepinephrine. Such interactions, although predictable for a population of patients, may not alter a patient's threshold for arrhythmias. The selective serotonin reuptake inhibitors have gained popularity and include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, though these can also have serious side effects. For instance, fluoxetine causes nausea, vomiting, headaches, nervousness, and possibly paranoia and ideas of suicide more commonly than do the tricyclics<sup>422,423</sup>; however, it is less likely to cause systemic anticholinergic effects or orthostatic hypotension. Bupropion, which is fundamentally different than the SSRIs, may cause nausea, vomiting, seizures, agitation, tremor, excitement, and increased motor activity, but it only rarely

causes anticholinergic effects or orthostatic hypotension. Discontinuing drugs can cause withdrawal symptoms or precipitate recurrence of psychiatric illness. Switching among drugs for depression can cause hyperpyrexia and coma; thus switching drugs preoperatively should not be requested casually.<sup>422,423</sup>

The effectiveness of phenothiazines and butyrophenones in schizophrenia suggests a dopamine receptor blocking action. In addition, these drugs possess varying degrees of parasympathetic stimulation and ability to block  $\alpha$ -adrenergic receptors. The phenothiazines include chlorpromazine, promazine, triflupromazine, fluphenazine, trifluoperazine, prochlorperazine, and many others. The butyrophenones include droperidol and haloperidol. Both the phenothiazines and butyrophenones produce sedation, depression, and antihistaminic, antiemetic, and hypothermic responses. They are also associated with cholestatic jaundice, impotence, dystonia, and photosensitivity. Other side effects associated with phenothiazines include orthostatic hypotension (partly as a result of  $\alpha$ -adrenergic blockade) and abnormalities on the ECG such as prolongation of the QT or PR intervals, blunting of T waves, depression of the ST segment, and on rare occasion, PVCs and torsades de pointes.<sup>422,423,429,430</sup>

Several important drug interactions are noteworthy for the phenothiazine derivatives. The effects of CNS depressants (especially narcotics and barbiturates) are enhanced by the concomitant administration of phenothiazines. In addition, the CNS seizure threshold is lowered by the administration of phenothiazines, which should be avoided in patients who are epileptic or withdrawing from any drug that depresses the CNS. Lithium carbonate is used to treat manic depression, but it is more effective in preventing mania than in relieving depression. In excitable cells, lithium mimics sodium and decreases the release of neurotransmitters both centrally and peripherally. Lithium prolongs neuromuscular blockade and may decrease anesthetic requirements because it blocks brainstem release of norepinephrine, epinephrine, and dopamine.

Psychoactive drugs such as the amphetamines (including methamphetamines, and crystal methamphetamine) and cocaine acutely release norepinephrine, epinephrine, and dopamine and block their reuptake. Taken on a long-term basis, they deplete nerve endings of these neurotransmitters.

Drugs that appear to increase central  $\alpha$ -adrenergic release increase anesthetic requirements, whereas drugs that appear to decrease central  $\alpha$ -adrenergic release decrease anesthetic requirements. (This may not be the mechanism by which they alter anesthetic requirements, but it is a convenient way of remembering the alteration.) Drugs that affect only the  $\beta$ -adrenergic receptors do not alter anesthetic requirements.

## ANTIARRHYTHMIC DRUGS

Antiarrhythmic drugs include local anesthetics (lidocaine, procaine), anticonvulsant (phenytoin),  $\beta$ -adrenergic blocking agents, calcium channel blocking drugs, or primary antiarrhythmic drugs. These drugs are classified into five major categories: local anesthetics that alter phase 0 and phase 4 depolarization (quinidine, procainamide, and flecainide), local anesthetics that affect only phase 4 depolarization

(lidocaine, mexiletine, tocainide, phenytoin, encainide),  $\beta$ -adrenergic receptor antagonists, antiadrenergic drugs (bretlyium, disopyramide, amiodarone), and calcium entry blockers. A lack of adverse reports does not imply that all these drugs should be continued through the time of surgery.

The pharmacologic characteristics of the various antiarrhythmic drugs can affect anesthetic management. Disopyramide is similar to quinidine and procainamide in its antiarrhythmic effectiveness. Disopyramide is excreted mainly by the kidneys, but hepatic disease increases its half-life. This drug often produces anticholinergic effects, including tachycardia, urinary retention, and psychosis. Hepatitis has also been reported to have occurred after its use.<sup>431</sup> Little is known of the interaction of bretlyium with anesthetic agents; however, since it blocks the release of catecholamines, long-term therapy with this drug has been associated with hypersensitivity to vasopressors.<sup>431</sup> Quinidine depends on the kidneys for excretion, can produce vagolytic effects that can decrease AV block, and is associated with blood dyscrasias and GI disturbances.<sup>431</sup> Most of the antiarrhythmic drugs enhance nondepolarizing neuromuscular blockade. Reports have confirmed this enhancement for quinidine, phenytoin, lidocaine, procainamide, and propranolol.<sup>432-440</sup> No data document such an effect for depolarizing muscle relaxants. Amiodarone, an antiadrenergic drug used to treat recurrent supraventricular and ventricular tachycardia, causes thyroid dysfunction as a result of the large amount of iodine in its structure, as well as peripheral neuropathy, and has been associated with hypertension, bradycardias, and reduced cardiac output during anesthesia.<sup>441</sup> The drug has a half-life of 29 days, and its pharmacologic effects persist for more than 45 days after discontinuance.<sup>442</sup>

## ANTIBIOTICS

Many antibacterial drugs are nephrotoxic or neurotoxic, or both, and many prolong neuromuscular blockade.<sup>434-443</sup> The only antibiotics devoid of neuromuscular effects appear to be penicillin G and the cephalosporins.<sup>439</sup> Most enzyme-inducing drugs do not increase the metabolism of the volatile agents. Appropriate antibiotic prophylaxis for surgery requires a knowledge of the probability of infection for that type of surgical procedure and, if the incidence of infection warrants, the use of a drug regimen directed against the most likely infecting organisms.<sup>443</sup>

## MEDICATIONS FOR GLAUCOMA

Medications for glaucoma include two organophosphates: echothiophate and isoflurophate. These drugs inhibit serum cholinesterase, which is responsible for the hydrolysis and inactivation of succinylcholine and ester-type local anesthetics such as procaine, chloroprocaine, and tetracaine.<sup>444,445</sup> These ester-type local anesthetics should be avoided in patients treated with eye drops containing organophosphate. Table 32.15 lists other medications related to anesthesia and their side effects (from the National Registry for Drug-Induced Ocular Side Effects, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, OR 97201; 503-279-8456).

**TABLE 32.15** Common Ophthalmologic Drugs and Their Anesthetically Important Interactions

Drug (Trade Name)	Toxicities and Specific Treatments
<b>GLAUCOMA: PRIMARY GOAL IS TO REDUCE IOP BY</b>	
Miotics and epinephrine: increase outflow of aqueous humor β-Blockade and carbonic anhydrase inhibitors: reduce production of aqueous humor Osmotic drugs: transiently decrease volume	
<b>MIOTICS</b>	
Parasympathomimetics Pilocarpine (Adsorbocarpine, Isopto Carpine, Pilocar, Pilocel) Carbachol	
<b>ACETYLCHOLINESTERASE INHIBITORS</b>	Tox: Hypersalivation, sweating, N/V, bradycardia, hypotension, bronchospasm, CNS effects, coma, respiratory arrest, death Rx: Atropine, pralidoxime (Protopam) Ix: Succinylcholine—prolonged apnea (drugs must be discontinued 4 weeks before)
<b>EPINEPHRINE (EPITRATE, MUROCOLL, MYTRATE, EPIFRIN, GLAUCON, EPINAL, EPPY)</b>	Tox: (rare) Tachycardia, PVCs, HTN, headache, tremors Ix: Avoid drugs that sensitize to catecholamines (e.g., halothane)
<b>β-BLOCKERS</b>	Tox: β-Blockade with bradycardia, exacerbation of asthma, CNS depression, lethargy, confusion Synergy noted with systemic drugs
Timolol (Timoptic) Betaxolol (Betoptic) Levobunolol (Betagan)	
<b>CARBONIC ANHYDRASE INHIBITORS</b>	Tox: Anorexia, GI disturbances, “general miserable feeling” and malaise, paresthesias, diuresis, hypokalemia (transient), renal colic and calculi, hyperuricemia, thrombocytopenia, aplastic anemia, acute respiratory failure in patients with COPD
Acetazolamide (Diamox) Dichlorphenamide (Daranide, Oratrol) Ethoxzolamide (Cardrase, Ethamide) Methazolamide (Neptazane)	
<b>OSMOTIC DRUGS</b>	Tox: Dehydration, hyperglycemia, nonketotic hyperosmolar coma (rare); fatalities with mannitol secondary to CHF or intracranial bleeding; urea may cause thrombosis Tox: Hypotension, bradycardia Rx: Atropine
<b>MYDRIATICS AND CYCLOPLEGICS: PROVIDE PUPILLARY DILATATION AND PARALYSIS OF ACCOMMODATION</b>	
Anticholinergics block muscarinic receptors; paralyzing in iris α-Adrenergics contract the dilator of the iris	
<b>ANTICHOLINERGICS</b>	Tox: Dry mouth, flushing, thirst, tachycardia, seizure, hyperactivity, transient psychosis, rare coma, and death Rx: Physostigmine
Atropine (Atropisol, Bufopto, Isopto Atropine) Cyclopentolate, alone (Cyclogyl) or with phenylephrine-homatropine (Cyclomydril) Homatropine (Homatrocel, Isopto Homatropine) Scopolamine (Isopto Hyoscine, Murocoll 19) Tropicamide (Mydriacyl)	
<b>β-ADRENERGICS</b>	Tox: Tachycardia, HTN, PVCs, myocardial ischemia, agitation
Phenylephrine (Efricel, Mydfrin, Neo-Synephrine) Hydroxyamphetamine (Paredrine)	

CHF, Congestive heart failure; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; HTN, hypertension; IOP, intraocular pressure; Ix, interaction; N/V, nausea and vomiting; PVCs, premature ventricular contractions; Rx, treatment; Tox, toxicity.

Modified from the National Registry for Drug-Induced Ocular Side Effects, University of Oregon Health Sciences Center, Portland, OR.

Complete references available online at [expertconsult.com](http://expertconsult.com).

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## KEY POINTS

- Herbal medication use has increased dramatically in the overall population and particularly in preoperative patients.
- Patients might not volunteer information unless they are queried specifically about herbal medication use.
- Although many commonly used herbs have side effects that affect drug metabolism, bleeding, and neuronal function, they are not subject to regulations on purity, safety, and efficacy.
- Knowledge of specific interactions and metabolism of herbs can provide practical guidelines to facilitate perioperative management.
- Other complementary therapies, including acupuncture and music therapy, have become increasingly popular and have shown positive results for certain pain conditions, albeit high-quality data are still lacking.
- Dietary supplements may influence gut microbiota, a consortium of diverse microorganisms residing in the gastrointestinal tract, which represents a new research frontier in perioperative medicine.

Complementary and alternative medicine (CAM) has implications for physicians in general, but has particular importance for the perioperative period because of specific complications associated with certain therapies. Complementary medicine is defined as the addition of nonconventional therapies to accepted treatments; alternative medicine describes the use of nonconventional therapies in lieu of accepted treatments. They have become an important part of contemporary health care. The more popular term of “integrative health or integrative medicine” is used when complementary approaches are incorporated into mainstream health care.

According to a 2012 U.S. National Health Interview Survey (NHIS), 33.2% of adults and 11.6% of children (4–17 years of age) have used CAM.<sup>1,1a</sup> Visits to CAM practitioners exceed those to American primary care physicians,<sup>2</sup> and CAM is even more widely used in Europe, where herbal medicines are prescribed more frequently than conventional drugs are. Furthermore, patients undergoing surgery appear to use CAM more than the general population does.<sup>3</sup> Aside from the widespread use of CAM, perioperative physicians have a special interest in CAM therapies for several reasons. First, several commonly used herbal medications exhibit direct effects on the cardiovascular and coagulation systems. Second, some CAMs can interfere with conventional medications that are commonly given in the postoperative period. Finally, the therapeutic potential of CAM in the perioperative period is increasingly being described

in the literature for reducing postoperative nausea, vomiting, and pain.

Despite the public enthusiasm for CAM, scientific knowledge in this area is still incomplete and often confusing for practitioners and patients. One recent study confirmed poor knowledge of this subject among physicians.<sup>4</sup> Recommendations for clinicians are often based on small clinical trials, case reports, animal studies, predictions derived from known pharmacology, and expert opinion. Research is essential because CAM therapies are often widely adopted by the public before adequate data are available to support their safety and efficacy. In 1991, Congress established the Office of Alternative Medicine, which is now known as the National Center for Complementary and Integrative Health. It operates within the National Institutes of Health.

Based on the 2012 NHIS study, the most commonly used CAMs were natural products, deep breathing exercises, meditation, chiropractic or osteopathic manipulation, massage, and yoga. Interestingly, a 2017 NHIS survey noted increases in the use of yoga and meditation by both adults and children (<https://nccih.nih.gov/research/statistics/NHIS>, Accessed 11/13/2018/tg). CAM practices can be classified into three general categories (Box 33.1).<sup>5</sup> This chapter is not intended as a comprehensive review of CAM. Specific therapies relevant to anesthesia are discussed, with a focus primarily on herbal medicines. Nonherbal dietary supplements, acupuncture, and music are also considered because they are relevant to perioperative care.

### BOX 33.1 Three Major Categories of Complementary and Alternative Medicine

1. Natural products: this group includes a variety of products, such as herbs (also known as botanicals), vitamins and minerals, and probiotics. They are widely marketed, readily available to consumers, and often sold as dietary supplements.
2. Mind-body practices: yoga, chiropractic and osteopathic manipulation, meditation, and massage therapy are among the most popular mind and body practices used by adults. Other mind and body practices include acupuncture, relaxation techniques (such as breathing exercises, guided imagery, and progressive muscle relaxation), tai chi, qi gong, and hypnotherapy.
3. Others: traditional healers, Ayurvedic medicine, traditional Chinese medicine, homeopathy, naturopathy, and functional medicine.

Modified from the National Center for Complementary and Integrative Health. <https://nccih.nih.gov/health/integrative-health>. Accessed April 11, 2018.

## Herbal Medicines

Preoperative use of herbal medicines has been associated with adverse perioperative events.<sup>6</sup> Surveys estimate that 22% to 32% of patients undergoing surgery use herbal medications.<sup>7-9</sup> In a recent retrospective review, 23% of surgery patients indicated the use of natural products, and older patients preferred dietary supplements.<sup>10</sup>

Herbal medicines can affect the perioperative period through several classic mechanisms: direct effects (i.e., intrinsic pharmacologic effects), pharmacodynamic interactions (i.e., alteration of the action of conventional drugs at effector sites), and pharmacokinetic interactions (e.g., alteration of the absorption, distribution, metabolism, and elimination of conventional drugs). Because approximately 50% of herbal medicine users take multiple herbs concomitantly<sup>7</sup> and 25% of herbal medicine users take prescription drugs,<sup>11</sup> adverse effects are difficult to predict and attribute.

Herbal medicines are associated with unique problems not usually found with conventional drugs.<sup>12</sup> Many of the issues complicating the understanding of herbal medications derive from the fact that they are classified as dietary supplements under the Dietary Supplement Health and Education Act of 1994. As such, the introduction of herbal medications does not require animal studies, clinical trials, or postmarketing surveillance. Under current law, the burden is shifted to the U.S. Food and Drug Administration (FDA) to prove products unsafe before they can be withdrawn from the market, such as the withdrawal of intranasal Zicam (cold medicine) after more than 130 reports of persistent anosmia.<sup>13</sup> Commercial herbal medicine preparations can have unpredictable pharmacologic effects resulting from inaccurate labeling, misidentified plants, adulterants, variations in natural potency, and unstandardized processing methods.

Two of the major problems confronting herbal medicine research involve quality control and added adulterants. In a recent clinical trial to treat human H1N1 influenza, an herbal formulation containing 12 different Chinese herbal

medicines including licorice (genus *Glycyrrhiza*) was used.<sup>14</sup> Some of the other botanicals in the formula were not accurately identified. There are three *Glycyrrhiza* species on the market that may show a twofold difference when the three species are compared.<sup>15</sup>

Labeled active ingredients can vary tenfold in different commercial preparations.<sup>16</sup> In June 2007, the FDA issued regulations for current good manufacturing practices (GMPs) for dietary supplements.<sup>17</sup> This rule requires that proper controls be in place so that dietary supplements are processed in a consistent manner and meet quality standards. Especially emphasized are the identity, purity, strength, and composition of the products. Dietary products adhering to GMPs undoubtedly reduce the potential risk in the use of herbal medicines. Because this rule is somewhat similar to that for prescription drug GMPs, many supplement manufacturers believe that it is not practical for botanicals.<sup>18</sup>

Beyond quality control is the inclusion of biologically active pharmacologic adulterants in herbal medications and supplements. There are clinical consequences when quality control is lacking or herbal preparations are adulterated, as found in a weight-loss remedy study that revealed one manufacturer's incorrect substitution of an herb for another when the carcinogen aristolochic acid led to an outbreak of nephropathy and urothelial carcinoma.<sup>19</sup> In another event, more than 14 million capsules of asexual enhancement supplement were recalled because the compound on the label did not actually exist and the supplement did contain an analogue of sildenafil, which has not been tested in humans.<sup>20</sup> In light of these events, in August 2016, the FDA proposed a new guidance to evaluate the safety of supplements based on their history of use, formulation, proposed daily dose, and recommended duration of use. Although the guidance represents only a fraction of what is necessary for a new drug application, it requires some testing for tolerability in animals, but not in humans,<sup>21</sup> when products are marketed for consumption at doses substantively greater than those historically ingested. Any ingredient formulated or prepared in a novel manner is considered a new ingredient.

In this section, we discuss the preoperative assessment and management of patients who use herbal medicines and examine 11 herbal medicines that have the greatest effect on perioperative patient care: *Echinacea*, *ephedra*, *garlic*, *ginger*, *Ginkgo biloba*, *ginseng*, *green tea*, *kava*, *saw palmetto*, *St. John's wort*, and *valerian* (Table 33.1).

## Preoperative Assessment and Management

Preoperative assessment should address the use of herbal medicines (see Table 33.1). One study found that 90% of anesthesia providers do not routinely ask about herbal medicine use.<sup>22</sup> Moreover, more than 70% of patients are not forthcoming about their herbal medicine use during routine preoperative assessment.<sup>7</sup> When a positive history of herbal medicine use is elicited, one in five patients is unable to properly identify the preparation being taken.<sup>23</sup> Asking patients to bring their herbal medicines

**TABLE 33.1** Clinically Important Effects, Perioperative Concerns, and Recommendations for Perioperative Discontinuation of 11 Commonly Used Herbal Medicines

Herbs (Common Names)	Pharmacologic Effects	Perioperative Concerns	Discontinue Before Surgery
<i>Echinacea</i> (purple cone-flower root)	Activation of cell-mediated immunity	Allergic reactions Decreases effectiveness of immunosuppressants Potential for immunosuppression with long-term use	No data
<i>Ephedra</i> (ma huang)	Increases heart rate and blood pressure through direct and indirect sympathomimetic effects	Risk of myocardial ischemia and stroke from tachycardia and hypertension Ventricular arrhythmias with halothane Long-term use depletes endogenous catecholamines and may cause intraoperative hemodynamic instability Life-threatening interaction with MAO inhibitors	24 h
<i>Garlic</i> (ajo)	Inhibits platelet aggregation (may be irreversible) Increases fibrinolysis Equivocal antihypertensive activity	May increase risk of bleeding, especially when combined with other medications that inhibit platelet aggregation	7 days
Ginger	Antiemetic Antiplatelet aggregation	May increase risk of bleeding	No data
<i>Ginkgo</i> (duck-foot tree, maidenhair tree, silver apricot)	Inhibits platelet-activating factor	May increase risk of bleeding, especially when combined with other medications that inhibit platelet aggregation	36 h
<i>Ginseng</i> (American ginseng, Asian ginseng, Chinese ginseng, Korean ginseng)	Lowers blood glucose Inhibits platelet aggregation (may be irreversible) Increased PT/PTT in animals	Hypoglycemia May increase risk of bleeding May decrease anticoagulant effect of warfarin	7 days
Green tea	Inhibits platelet aggregation Inhibits thromboxane A2 formation	May increase risk of bleeding May decrease anticoagulant effect of warfarin	7 days
<i>Kava</i> (awa, intoxicating pepper, kawa)	Sedation Anxiolysis	May increase sedative effect of anesthetics Increase in anesthetic requirements with long-term use unstudied	24 h
<i>Saw palmetto</i> (dwarf palm, <i>Sabal</i> )	Inhibits 5 $\alpha$ -reductase Inhibits cyclooxygenase	May increase risk of bleeding	No data
<i>St. John's wort</i> (amber, goat weed, hardhay, hypericum, Klamath weed)	Inhibits neurotransmitter reuptake MAO inhibition unlikely	Induction of cytochrome P450 enzymes; affects cyclosporine, warfarin, steroids, and protease inhibitors; may affect benzodiazepines, calcium channel blockers, and many other drugs Decreased serum digoxin levels Delayed emergence	5 days
<i>Valerian</i> (all heal, garden heliotrope, vandal root)	Sedation	May increase sedative effect of anesthetics Benzodiazepine-like acute withdrawal May increase anesthetic requirements with long-term use	No data

MAO, Monoamine oxidase; PT, prothrombin time; PTT, partial thromboplastin time.

and other dietary supplements with them at the time of the preoperative evaluation would be helpful. A positive history of herbal medicine use should alert one to the presence of undiagnosed disorders causing symptoms leading to self-medication. Patients who use herbal medicines may be more likely to avoid conventional diagnosis and therapy.<sup>24</sup>

In general, herbal medicines should be discontinued preoperatively. Patients who require nonelective surgery are not evaluated until the day of surgery or are noncompliant with instructions to discontinue herbal medications preoperatively. In this situation, anesthesia can usually proceed safely at the discretion of the anesthesia provider, who should be familiar with commonly used herbal medicines. For example, recent use of herbal medicines that inhibit platelet function (e.g., garlic, ginseng,

*G. biloba*) may warrant specific strategies for procedures with substantial intraoperative blood loss (e.g., platelet transfusion) and those that alter the risk-benefit ratio of using certain anesthetic techniques (e.g., neuraxial blockade).

Preoperative discontinuation of all herbal medicines might not eliminate complications related to their use. Withdrawal of some of the herbal medicines can increase morbidity and mortality after surgery similar to regular medications.<sup>25,26</sup> The danger of abstinence after long-term use may be similar with herbal medicines such as valerian, which can produce acute withdrawal after long-term use.

Although the American Society of Anesthesiologists has no official standard or guideline for the preoperative use of herbal medications, public and professional educational

information released by this organization suggests that herbals be discontinued at least 2 weeks before surgery.<sup>25</sup> Our review of the literature favors a more targeted approach. When pharmacokinetic data for the active constituents in an herbal medication are available, the timeframe for preoperative discontinuation can be tailored. Some herbal medications are eliminated quickly and may be discontinued near the time of surgery. For other herbal medicines, 2 weeks is recommended.<sup>27</sup>

Evidence-based estimates of herbal safety in the perioperative period are limited. One study of 601 patients who used traditional Chinese herbal medications suggested an infrequent rate of potential serious complications.<sup>28</sup> Clinicians should be familiar with commonly used herbal medications to recognize and treat any complications that might arise. Table 33.1 summarizes the clinically important effects, perioperative concerns, and recommendations for preoperative discontinuation of the 11 herbal medications that account for 30% of the dietary supplements sold in the United States.<sup>29</sup> The type of surgery and potential perioperative course should be considered in these clinical recommendations.

## ECHINACEA

Three species of *Echinacea*, a member of the daisy family, are used for the prophylaxis and treatment of viral (decreasing the incidence and duration of the common cold), bacterial, and fungal infections, particularly those of upper respiratory origin, although its efficacy in fungal infections is doubtful.<sup>30,31</sup> The biological activity of *Echinacea* could be immunostimulatory, immunosuppressive, or antiinflammatory.<sup>32</sup> Although studies have not specifically addressed interactions between *Echinacea* and immunosuppressive drugs, experts generally warn against the concomitant use of *Echinacea* and these drugs because of the probability of diminished effectiveness.<sup>33,34</sup> In contrast to its immunostimulatory effects with short-term use, long-term use of more than 8 weeks is accompanied by the potential for immunosuppression<sup>34</sup> and a theoretically increased risk for postsurgical poor wound healing and opportunistic infections. A recent phytochemical study identified a potential immunosuppressant compound from *Echinacea*—cynarine.<sup>35</sup>

Information about *Echinacea*'s pharmacokinetics is still limited.<sup>36</sup> *Echinacea* significantly reduced plasma concentrations of S-warfarin, but did not significantly affect warfarin pharmacodynamics and platelet aggregation in healthy subjects.<sup>37</sup> However, this herb should be discontinued as far in advance of surgery as possible when compromises in hepatic function or blood flow are anticipated.<sup>38</sup> In the absence of definitive information, patients with preexisting liver dysfunction should be cautious in using *Echinacea*.

## EPHEDRA

*Ephedra*, known as *ma huang* in Chinese medicine, is a shrub native to central Asia. It is used to promote weight loss, increase energy, and treat respiratory conditions such as asthma and bronchitis. *Ephedra* contains alkaloids,

including ephedrine, pseudoephedrine, norephedrine, methylephedrine, and norpseudoephedrine.<sup>25</sup> Commercial preparations can be standardized to a fixed ephedrine content. Publicity about adverse reactions to this herb prompted the FDA to bar its sale in 2004, but ephedra is still widely available via the Internet.

*Ephedra* causes dose-dependent increases in arterial blood pressure and heart rate. Ephedrine, the predominant active compound, is a noncatecholamine sympathomimetic that exhibits  $\alpha_1$ ,  $\beta_1$ , and  $\beta_2$  activity indirectly by releasing endogenous norepinephrine (noradrenaline). These sympathomimetic effects have been associated with more than 1070 reported adverse events, including fatal cardiac and central nervous system complications.<sup>39</sup> Vasoconstriction and, in some cases, vasospasm of coronary and cerebral arteries can cause myocardial infarction and thrombotic stroke.<sup>40</sup> *Ephedra* can also affect cardiovascular function by causing hypersensitivity myocarditis, characterized by cardiomyopathy with myocardial lymphocyte and eosinophil infiltration.<sup>41</sup> Long-term use results in tachyphylaxis from depletion of endogenous catecholamine stores and can contribute to perioperative hemodynamic instability. In these situations, direct-acting sympathomimetics may be preferred as first-line therapy for intraoperative hypotension and bradycardia. Concomitant use of ephedra and monoamine oxidase inhibitors can result in life-threatening hyperpyrexia, hypertension, and coma. Finally, continuous ephedra is a rare cause of radiolucent kidney stones.<sup>42</sup> Recently, there was a case report describing acute angle-closure glaucoma caused by ephedra.<sup>42a</sup>

The pharmacokinetics of ephedrine have been studied in humans.<sup>43,44</sup> Ephedrine has an elimination half-life of 5.2 hours, with 70% to 80% of the compound excreted unchanged in urine. Based on the pharmacokinetic data and the known cardiovascular risks associated with ephedra, including myocardial infarction, stroke, and cardiovascular collapse from catecholamine depletion, this herb should be discontinued at least 24 hours before surgery.

## GARLIC

Garlic is one of the most extensively researched medicinal plants. It has the potential to modify the risk for atherosclerosis by reducing arterial blood pressure, thrombus formation, and serum lipid and cholesterol concentrations.<sup>45</sup> These effects are primarily attributed to its sulfur-containing compounds, particularly allicin and its transformation products. Commercial garlic preparations can be standardized to a fixed alliin and allicin content.

Garlic inhibits platelet aggregation in vivo in a concentration-dependent fashion. The effect of one of its constituents, ajoene, is irreversible and can enhance the effect of other platelet inhibitors such as prostacyclin, forskolin, indomethacin, and dipyridamole.<sup>46</sup> Although the effects are not consistently demonstrated in volunteers, there is one case described in an 80 year old who had a spontaneous epidural hematoma develop that was attributed to continuous garlic use.<sup>47</sup> Garlic has interacted with warfarin, resulting in an increased international normalized ratio (INR).<sup>48</sup>

In addition to bleeding concerns, garlic can decrease systemic and pulmonary vascular resistance in laboratory animals, but this effect is marginal in humans.<sup>49</sup> Although there are insufficient pharmacokinetic data on garlic's constituents, the potential for irreversible inhibition of platelet function may warrant discontinuation of garlic at least 7 days before surgery, especially if postoperative bleeding is a particular concern or other anticoagulants are given. Additionally, garlic's pharmacokinetics should be considered when a risk-benefit analysis is made for neuraxial techniques.

## GINGER

Ginger (*Zingiber officinale*) is a popular spice with a long history of use in Chinese, Indian, Arabic, and Greco-Roman herbal medicines. Ginger has a wide range of reported health benefits for those with arthritis, rheumatism, sprains, muscular aches, pains, sore throats, cramps, constipation, indigestion, nausea, vomiting, hypertension, dementia, fever, infectious diseases, and helminthiasis.<sup>50</sup> Ginger contains up to 3% volatile oil, mostly monoterpenoids and sesquiterpenoids.<sup>51</sup> Gingerols are representative compounds in ginger.<sup>52</sup>

Ginger is an antiemetic and has been used to treat motion sickness and to prevent nausea after laparoscopy.<sup>53</sup> The number of postoperative antiemetic medications was significantly reduced after aromatherapy with essential oil of ginger.<sup>54</sup> In another recent trial, ginger supplementation reduced the severity of acute chemotherapy-induced nausea in adult cancer patients and compared favorably to conventional antiemetics.<sup>55</sup>

In an in vitro study, gingerols and related analogues inhibited arachidonic acid-induced human platelet serotonin release and aggregation, with a potency similar to that of aspirin.<sup>52</sup> In another in vitro study, the antiplatelet effects of 20 ginger constituents were evaluated. Five constituents showed antiplatelet activities at relatively low concentrations. One of the ginger compounds (8-paradol) was the most potent cyclooxygenase-1 inhibitor and antiplatelet aggregation drug.<sup>56</sup> In a case report, a ginger-phenprocoumon combination resulted in an increased INR and epistaxis.<sup>57</sup> Although the sample size was relatively small, the platelet inhibition potential of ginger has been suggested in a pilot clinical study.<sup>58</sup> This result may warrant the discontinuation of ginger at least 2 weeks before surgery.

## GINKGO

Ginkgo is derived from the leaf of *G. biloba* and has been used for cognitive disorders, peripheral vascular disease, age-related macular degeneration, vertigo, tinnitus, erectile dysfunction, and altitude sickness. Studies have suggested that ginkgo can stabilize or improve cognitive performance in patients with Alzheimer disease and multiinfarct dementia,<sup>59</sup> but not in healthy geriatric patients.<sup>60</sup> The compounds that might be responsible for its pharmacologic effects are the terpenoids and flavonoids. The two ginkgo extracts used in clinical trials are standardized to ginkgo-flavone glycosides and terpenoids.

Ginkgo alters vasoregulation, acts as an antioxidant, modulates neurotransmitter and receptor activity, and inhibits platelet-activating factor. Of these effects, inhibition of platelet-activating factor is of primary concern for the perioperative period. Although bleeding complications have not occurred in clinical trials, four cases of spontaneous intracranial bleeding,<sup>61-63</sup> one case of spontaneous hyphema,<sup>64</sup> and one case of postoperative bleeding after laparoscopic cholecystectomy<sup>65</sup> have been described when ginkgo was being taken.

Terpene trilactones are highly bioavailable when administered orally. The elimination half-lives of the terpene trilactones after oral administration are between 3 and 10 hours. For ginkgolide B, a dosage of 40 mg twice daily resulted in a higher area under the curve, and a longer half-life and residence time, than after a single 80-mg dose. A once daily dose of 80 mg guaranteed a larger maximum concentration peak ( $T_{max}$ ) that was reached 2 to 3 hours after administration.<sup>66</sup> The pharmacokinetics of terpene trilactones in three different ginkgo preparations in human plasma<sup>67</sup> indicate that ginkgo should be discontinued at least 2 weeks before surgery to avoid bleeding.<sup>38</sup>

## GINSENG

Among the several species of ginseng used for their pharmacologic effects, Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*) are the most commonly described.<sup>68</sup> Ginseng has been labeled an "adaptogen" because it reputedly protects the body against stress and restores homeostasis.<sup>69</sup> Because its pharmacologic actions are attributed to the ginsenosides, a group of compounds known as *steroidal saponins*, many commercially available ginseng preparations have been standardized to ginsenoside content.<sup>68,70</sup>

The many heterogeneous and sometimes opposing effects of different ginsenosides<sup>71,72</sup> give ginseng a broad but incompletely understood pharmacologic profile including general health, fatigue, immune function, cancer, cardiovascular disease, diabetes mellitus, cognitive function, viral infections, sexual function, and athletic performance.<sup>69</sup> The underlying mechanism is similar to that classically described for steroid hormones. This herb decreases postprandial blood glucose in both healthy and type 2 diabetes patients,<sup>73</sup> an effect that can create unintended hypoglycemia in patients who have fasted before surgery.

Ginseng can alter coagulation pathways. The antiplatelet activity of panaxynol, a constituent of ginseng, may be irreversible in humans.<sup>74</sup> Ginseng extract and ginsenosides inhibit platelet aggregation in vitro<sup>75,76</sup> and prolong thrombin time and activated partial thromboplastin time in *in vivo* animal models.<sup>77,78</sup>

The clinical evidence implicating ginseng as a cause of bleeding is weak and based on only a few case reports.<sup>79</sup> Although ginseng may inhibit the coagulation cascade, one case associated its use with a significant decrease in warfarin anticoagulation.<sup>80</sup> Subsequently, a study in volunteers showed that American ginseng interfered with warfarin-induced anticoagulation,<sup>81</sup> reducing its anti-coagulant effect. When prescribing warfarin, clinicians

should specifically ask about ginseng use. In another clinical trial, warfarin's clearance was moderately increased with Asian ginseng.<sup>82</sup> Because warfarin is often used after orthopedic or vascular procedures, this herbal drug interaction can affect perioperative management in many patients.

In rats, the elimination half-lives are different after an intravenous infusion of ginseng, with ginsenosides Re and Rg1 between 0.7 and 4 hours, and ginsenosides Rb1 and Rd between 19 and 22 hours.<sup>83</sup> After oral administration of ginseng, ginsenoside Rb1 reached the maximum plasma concentration at approximately 4 hours with a prolonged half-life.<sup>84,85</sup> These data suggest that ginseng should be discontinued at least 48 hours before surgery. Because platelet inhibition by ginseng may be irreversible, ginseng use should be stopped at least 2 weeks before surgery.<sup>38</sup>

## GREEN TEA

Tea from the *Camellia sinensis* is one of the most ancient and the second most widely consumed beverage in the world.<sup>86,87</sup> Tea can be classified into different types, such as green, oolong, and black. Green tea, which is not fermented and is derived directly from drying and steaming fresh tea leaves, contains polyphenolic compounds. Catechins in green tea account for 16% to 30% of its dry weight. Epigallocatechin-3-gallate (EGCG), the most predominant catechin in green tea, is responsible for much of the biologic activity mediated by green tea.<sup>86</sup>

In an early in vitro and in vivo study, both green tea and EGCG significantly prolonged mouse tail bleeding time in conscious mice. They inhibited adenosine diphosphate- and collagen-induced rat platelet aggregation in a dose-dependent manner.<sup>88</sup> The antiplatelet activity can result from the inhibition of thromboxane A2 formation by preventing arachidonic acid liberation and thromboxane A2 synthase.<sup>89,90</sup> Regarding a possible adverse effect of green tea on platelets, one case reported thrombotic thrombocytopenic purpura developed after a patient consumed a weight-loss product containing green tea.<sup>91</sup> On the other hand, drinking green tea could antagonize the anticoagulant effects of warfarin because green tea contains vitamin K.<sup>92</sup>

The half-life for EGCG in one study was between 1.9 and 4.6 hours<sup>93</sup> and in another study was observed to be between 2.2 and 3.4 hours.<sup>94</sup> Based on pharmacokinetic data and possible antiplatelet activity, green tea should be discontinued at least 7 days before surgery.

## KAVA

Kava is derived from the dried root of the pepper plant *Piper methysticum*. Kava has gained widespread popularity as an anxiolytic and sedative. The kavalactones appear to be the source of kava's pharmacologic activity.<sup>95</sup>

Because of its psychomotor effects, kava was one of the first herbal medications expected to interact with anesthetics. The kavalactones can have many effects such as: (1) dose-dependent effects on the central nervous system, including antiepileptic, neuroprotective, and local anesthetic properties; (2) act as a sedative-hypnotic by potentiating inhibitory

neurotransmission of  $\gamma$ -aminobutyric acid (GABA); (3) increased barbiturate sleep time in laboratory animals,<sup>96</sup> which might explain the mechanism of a coma attributed to an alprazolam-kava interaction<sup>97</sup>; (4) abuse potential, whether long-term use can result in addiction, tolerance, and acute withdrawal after abstinence is unknown; (5) increased  $\gamma$ -glutamyl transpeptidase levels with potential risk of hepatotoxicity<sup>98</sup>; and (6) produces "kava dermatopathy," characterized by reversible scaly cutaneous eruptions.<sup>99</sup>

In an in vitro investigation, a kava compound (+)-kavalactone suppressed the aggregation of human platelets. Kava inhibits cyclooxygenase with the potential to decrease renal blood flow and to interfere with platelet aggregation. Consumption of kava has potential cardiovascular effects that could manifest in the perioperative period.<sup>100,101</sup> Although kava has been banned in Europe since 2002, it is available in North America and many countries in the Pacific region. A concentration-based response relationship can occur with hepatotoxicity, even leading to numerous cases of liver transplantation.<sup>102-104</sup>

Peak plasma levels occur 1.8 hours after an oral dose, and the elimination half-life of kavalactones is 9 hours.<sup>105</sup> Unchanged kavalactones and their metabolites undergo renal and fecal elimination.<sup>106</sup> Pharmacokinetic data and the possibility for enhancement of the sedative effects from anesthetics suggest that kava should be discontinued at least 24 hours before surgery. Earlier discontinuation probably should be considered when surgical procedures are expected to compromise hepatic function or blood flow.

## SAW PALMETTO

Saw palmetto, which is used by more than 2 million men in the United States to treat symptoms associated with benign prostatic hypertrophy, is of questionable efficacy for this purpose.<sup>107</sup> The major constituents of saw palmetto are fatty acids and their glycerides (i.e., triacylglycerides and monoacylglycerides), carbohydrates, steroids, flavonoids, resin, pigment, tannin, and volatile oil. The pharmacologic activity of saw palmetto has not been attributed to a single compound.

Although the mechanism of action of saw palmetto is not known, multiple mechanisms have been proposed.<sup>108</sup> Saw palmetto extract, like finasteride, inhibits  $5\alpha$ -reductase in vitro; however, results of in vivo studies have been inconsistent.<sup>109</sup> Other proposed mechanisms are inhibition of estrogen and androgen receptors, binding of autonomic receptors, blocking of prolactin receptor signal transduction, interference with fibroblast proliferation, induction of apoptosis, inhibition of  $\alpha_1$ -adrenergic receptors, and antiinflammatory effects.

In a patient undergoing craniotomy, saw palmetto was associated with excessive intraoperative bleeding that required termination of the procedure.<sup>109</sup> Another case of hematuria and coagulopathy in a patient who used saw palmetto was reported.<sup>110</sup> This complication was attributed to saw palmetto's antiinflammatory effects, specifically the inhibition of cyclooxygenase and subsequent platelet dysfunction. Because there are no pharmacokinetic or clinical data for saw palmetto, specific recommendations for preoperative discontinuation cannot be made.

## ST. JOHN'S WORT

St. John's wort is the common name for *Hypericum perforatum*, and has been used for mental health and depression conditions. A multicenter clinical trial concluded that St. John's wort is not effective in the treatment of major depression.<sup>111</sup> The compounds believed to be responsible for its pharmacologic activity are hypericin and hyperforin.<sup>112</sup> Commercial preparations are often standardized to a fixed hypericin content of 0.3%.

St. John's wort exerts its effects by inhibiting reuptake of serotonin, norepinephrine, and dopamine.<sup>113</sup> Concomitant use of this herb with or without serotonin reuptake inhibitors can create a syndrome of central serotonin excess.<sup>114</sup> Although early in vitro data implicated monoamine oxidase inhibition as a possible mechanism of action, a number of later investigations have demonstrated that monoamine oxidase inhibition is insignificant in vivo.<sup>115</sup>

Use of St. John's wort can significantly increase the metabolism of many concomitantly administered drugs, some of which are vital to the perioperative care of certain patients. There is induction of the cytochrome P450 3A4 isoform,<sup>116</sup> and interactions with substrates of the 3A4 isoform, including indinavir sulfate,<sup>117</sup> ethinylestradiol,<sup>118</sup> and cyclosporine,<sup>119</sup> have been documented. There are important clinical consequences of this metabolic effect, particularly in transplant patients. In two case reports of heart transplant patients, after taking St. John's wort the patients' plasma cyclosporine concentrations became subtherapeutic and acute transplant rejection resulted. After stopping St. John's wort, plasma cyclosporine remained within the therapeutic range with no further episodes of rejection (Fig. 33.1).<sup>120</sup> In one series of 45 organ transplant patients, St. John's wort was associated with an average 49% decrease in blood cyclosporine levels.<sup>121</sup> Other P450 3A4 substrates commonly used in the perioperative period include alfentanil, midazolam, lidocaine, calcium channel blockers, and 5-hydroxytryptamine receptor antagonists. In addition, the cytochrome P450 2C9 isoform also may be induced, which results in decreased anticoagulant effect of warfarin, a substrate of the 2C9 isoform, in seven reported cases.<sup>118</sup> Other 2C9 substrates include the nonsteroidal

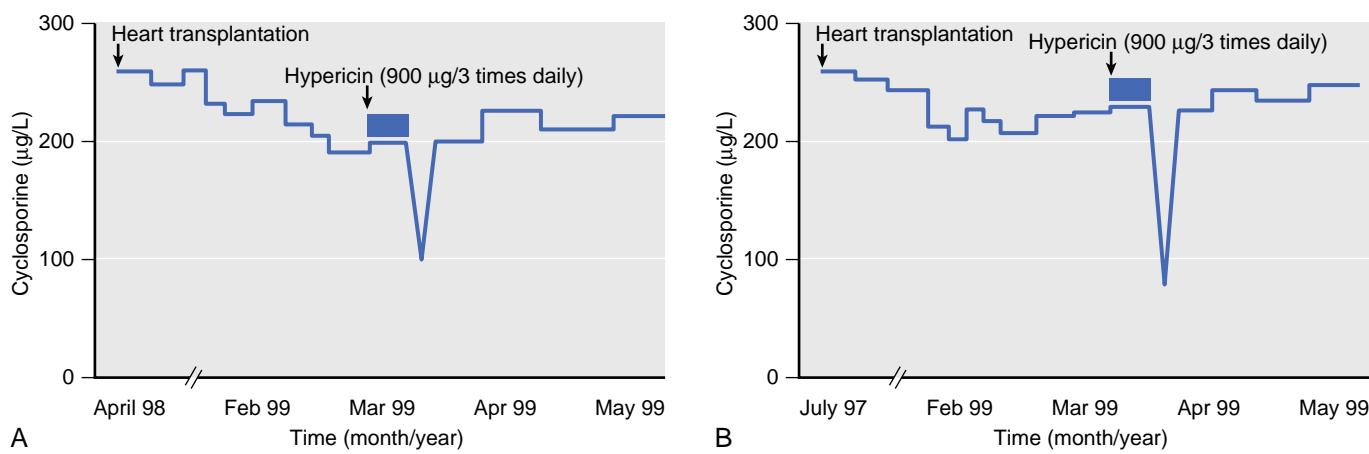
antiinflammatory drugs. Furthermore, the enzyme induction caused by St. John's wort may be more pronounced when other enzyme inducers, which could include other herbal medications, are taken concomitantly. St. John's wort also affects digoxin pharmacokinetics.<sup>115</sup>

The single-dose and steady-state pharmacokinetics of hypericin, pseudohypericin, and hyperforin have been determined in humans.<sup>122,123</sup> After oral administration, peak plasma levels of hypericin and hyperforin are achieved in 6.0 and 3.5 hours, respectively, and their median elimination half-lives are 43.1 and 9.0 hours, respectively. Long half-life and altered metabolism of many drugs make concomitant use of St. John's wort a particular risk in the perioperative setting. Pharmacokinetic data suggest that this herbal medication should be discontinued at least 5 days before surgery. Discontinuation is especially important in patients awaiting organ transplantation or in those who might require oral anticoagulation postoperatively. Moreover, these patients should be advised to avoid taking St. John's wort postoperatively.

## VALERIAN

Valerian (*Valeriana officinalis*) is an herb that is native to temperate regions of the Americas, Europe, and Asia. It is used as a sedative, particularly in the treatment of insomnia, and virtually all herbal sleep aids contain valerian.<sup>124</sup> Valerian contains many compounds acting synergistically, but the sesquiterpenes are the primary source of valerian's pharmacologic effects. Commercially available preparations may be standardized to valerenic acid.

Valerian produces dose-dependent sedation and hypnosis.<sup>125</sup> These effects are probably mediated through modulation of GABA neurotransmission and receptor function.<sup>126</sup> Valerian increased barbiturate sleep time in experimental animals.<sup>127</sup> In several randomized, placebo-controlled trials in humans, there was a mild subjective improvement in sleep with valerian, especially when used for 2 weeks or more.<sup>128,129</sup> Objective tests have had less consistent results, with little or no improvement in sleep noted.<sup>130</sup> In one patient, valerian withdrawal appeared to mimic an acute benzodiazepine withdrawal syndrome characterized by



**Fig. 33.1** Cyclosporine concentrations in two patients (A and B) after heart transplantation. Treatment with St. John's wort extract containing 900 µg of hypericin was associated with a drop in cyclosporine values below the therapeutic range and acute transplant rejection. (From Breidenbach T, Hoffmann MW, Becker T, et al. Drug interaction of St John's wort with cyclosporine. *Lancet*. 2000;355:1912.)

delirium, cardiac complications after surgery, and attenuation of the symptoms by administration of a benzodiazepine.<sup>131</sup> Based on these findings, valerian should potentiate the sedative effects of anesthetics and adjuvants that act at the GABA receptor, such as midazolam.

The pharmacokinetics of valerian's constituents have not been studied, although their effects may be short-lived. Abrupt discontinuation in patients who may be physically dependent on valerian risks benzodiazepine-like withdrawal. In these individuals, this herbal medication should be gradually decreased with close medical supervision over the course of several weeks before surgery. If such tapering is not feasible, physicians can advise patients to continue taking valerian until the day of surgery. Based on the mechanism of action and a reported case of efficacy,<sup>131</sup> benzodiazepines can treat withdrawal symptoms should they develop in the postoperative period.

## OTHER HERBAL MEDICINES

In a survey conducted in 2007,<sup>1</sup> the top 10 herbal medicines also included soy isoflavones, grape seed extract, and milk thistle. There are no reports of adverse effects or perioperative risks from these herbs.

Although boldo (*Peumus boldus*), Danshen (*Salvia miltiorrhiza*), Dong quai (*Angelica sinensis*), and papaya (*Carica papaya*) are encountered less frequently, it may be prudent to discontinue their use 2 weeks before surgery because they have shown antiplatelet aggregation activity and herb-drug interactions.<sup>132</sup>

## COMMON DIETARY SUPPLEMENTS

Herbal medicines fall into the broader category of dietary supplements that also includes vitamins, minerals, amino acids, enzymes, animal extracts, prebiotics, and probiotics. Data on the safety of these agents in the perioperative period are scant. High-dose vitamin use, particularly of the fat-soluble vitamins (i.e., A, D, E, and K), can be associated with acute and chronic toxicity. Drug interactions for coenzyme Q<sub>10</sub>, glucosamine, chondroitin, sulphate, and fish oil have been sufficiently documented to merit inclusion in this chapter. Prebiotics and probiotics have become increasingly popular in research, in the context of the rapidly evolving field of gut microbiome, adding to the current knowledge of perioperative medicine.

## Coenzyme Q<sub>10</sub>

Coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>), or ubidecarenone, is a single-constituent antioxidant compound that is structurally related to vitamin K. It is widely promoted as an antioxidant. Endogenous CoQ<sub>10</sub> can prevent the membrane transition pore from opening, because it counteracts several apoptotic events, such as DNA fragmentation, cytochrome c release, and membrane potential depolarization.<sup>52</sup>

Of importance, this compound interacts with warfarin and was investigated in rats.<sup>133</sup> Following oral administration of 1.5 mg/kg of racemic warfarin to rats during an 8-day oral regimen of CoQ<sub>10</sub> (10 mg/kg daily), no apparent effect was observed on serum protein binding of

warfarin enantiomers. Treatment with CoQ<sub>10</sub> did not affect the absorption and distribution of the S- and R-enantiomers of warfarin, but it increased total serum clearance of both R- and S-warfarin. The increased clearance values are likely due to acceleration of certain metabolic pathways and renal excretion of the warfarin enantiomers.

An in vitro study showed a predicted 32% and 17% increase in the total clearance of S- and R-warfarin respectively with co-administration of 100 mg CoQ<sub>10</sub>.<sup>134</sup> CoQ<sub>10</sub> may decrease the effects of warfarin,<sup>135</sup> but results were inconsistent in another controlled, clinical trial.<sup>136</sup> In 171 patients, co-administration of CoQ<sub>10</sub> with warfarin appeared to increase the risk of bleeding.<sup>137</sup> Based on the clinical information regarding drug interaction and reported prolonged elimination half-life (38-92 hours) after a single oral dose,<sup>138</sup> CoQ<sub>10</sub> should be discontinued at least 2 weeks before surgery.

## GLUCOSAMINE AND CHONDROITIN SULFATE

Glucosamine and chondroitin sulfate are widely used for joint disorders by many patients undergoing orthopedic procedures. Although their mode of action may be complex, glucosamine and chondroitin sulfate have been widely accepted as supplements in the management of osteoarthritis (OA) because they are the essential components of proteoglycan in normal cartilage.<sup>139</sup> When a large-scale trial evaluated glucosamine and chondroitin sulfate alone or in combination, pain was not reduced in a group of patients with OA of the knee. Exploratory analyses suggested that the two in combination might be effective in a subgroup of patients with moderate-to-severe knee pain.<sup>140</sup>

Long-term clinical data regarding the safety of glucosamine and chondroitin sulfate alone or in combination are limited. Use of chondroitin sulfate alone is well tolerated and without significant adverse drug interaction.<sup>139</sup> One concern regarding the use of glucosamine is its potential to cause or worsen diabetes in animal models<sup>141</sup>; this effect is supported by clinical studies.<sup>142</sup> In a report from the FDA MedWatch database, there were 20 cases of complications involving glucosamine or glucosamine-chondroitin sulfate use with warfarin. Coagulation was altered as manifested by increased INR or increased bleeding or bruising.<sup>143</sup>

When glucosamine is taken orally, 90% is absorbed. Because of extensive first-pass metabolism, only 25% bioavailability is achieved by oral administration compared with bioactivity of 96% with intravenous administration.<sup>144</sup> Peak plasma levels occurred 4 hours after an oral dose and declined to baseline after about 48 hours.<sup>145</sup> Chondroitin sulfate was absorbed slowly after oral ingestion with a plasma peak at 8.7 hours and decline to baseline at about 24 hours.<sup>146</sup> Considering the reported interaction between glucosamine-chondroitin and warfarin, these supplements should be discontinued 2 weeks before surgery, especially if warfarin will be given during the perioperative period.

## FISH OIL

Intake of fish oil supplements containing omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) reduces the incidence of many chronic diseases that involve

inflammatory processes, including cardiovascular diseases, inflammatory bowel disease, cancer, rheumatoid arthritis, and neurodegenerative illnesses.<sup>147</sup> However, omega-3 fatty acid did not reduce the rate of death in patients with cardiovascular risk in one study.<sup>148</sup> A metaanalysis of efficacy also concluded that omega-3 polyunsaturated fatty acid supplementation does not decrease the risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke based on relative and absolute measures of association.<sup>149</sup> This article included many studies of patients with complex risk factors.

Omega-3 fatty acids, however, can inhibit platelet aggregation and increase bleeding risk by the following studies: (1) In vitro experiments have demonstrated an antiplatelet aggregate effect,<sup>150</sup> and inhibition correlated with platelet cyclic adenosine monophosphate levels.<sup>151</sup> (2) In vivo studies have showed decreased platelet aggregation but do not influence bleeding time.<sup>152,153</sup> (3) The inhibition of platelet aggregation was gender specific in a clinical study.<sup>154</sup>

Although evidence for significant bleeding concerns is not found in clinical trials,<sup>155,156</sup> several case reports have illustrated a possible interaction between warfarin and omega-3 fatty acids.<sup>157</sup> Extremely elevated INR associated with warfarin in combination with omega-3 fatty acids was found in two cases.<sup>158,159</sup> These reports suggest that fish oil be discontinued 2 weeks before surgery, especially for patients taking large doses.

## PREBIOTICS AND PROBIOTICS

A prebiotic is a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and activity of one or a limited number of bacteria in the colon that has the potential to improve host health. A probiotic is a live microbial feed supplement that beneficially affects the host by improving its intestinal microbial balance.<sup>159a</sup> Both prebiotics and probiotics can perturbate the gut microbiota, a consortium of diverse microorganisms residing in the gastrointestinal tract, with significant influence in energy metabolism, immune system development, neurologic function, and behaviors. Research on gut microbiota has made significant progress in recent years owing to the technological advancement of next-generation DNA sequencing and high-throughput data processing.

Targeting gut microbiota using fecal transplantation or fecal capsules to treat recurrent *Clostridium difficile* infection is under intense investigation, with a few trials indicating promising results.<sup>159b</sup> However, a recent trial comparing oral probiotics with oral antibiotics for elective colorectal surgery showed that conventional oral antibiotics preparation in addition to mechanical bowel preparation is better than oral probiotics with mechanical bowel preparation.<sup>159c</sup> Studies have implicated gut microbiota in visceral hypersensitivity (irritable bowel syndrome), inflammatory pain, and more recently, neuropathic pain.<sup>159d-159f</sup> Moreover, gut microbiota have been shown to modulate the central nervous system function, including anxiety/depression and cognition. Despite the rapidly evolving field of gut microbiome, data on perioperative use of prebiotics and probiotics are scarce. Future research is warranted to investigate potential roles of prebiotics and probiotics in the

perioperative setting, particularly in volatile anesthetics sensitivity, postoperative pain control, and postoperative cognitive dysfunction.

## Other Dietary Supplements

Other top 10 dietary supplements include flaxseed oil, fiber or psyllium, cranberry, melatonin, methylsulfonylmethane, and lutein.<sup>1</sup> No special concerns have been published associated with bleeding or other perioperative risks from the use of these supplements.

## Summary

Commonly used herbal medications can have direct and indirect effects in the perioperative period. Although there is little direct evidence for discontinuation timing, emerging knowledge of the underlying biology of these medications and review of case reports suggest that herbal medications should be considered in the perioperative plan.

## Acupuncture

### MECHANISM AND GENERAL PRACTICE

Although acupuncture can reduce preoperative anxiolysis, intraoperative anesthetic requirements, and postoperative ileus, and can support cardiovascular function, it has been most widely studied to control postoperative pain and to prevent or treat nausea and vomiting.<sup>160</sup>

Acupuncture has been used in China for more than 3000 years, and in the 1970s, it gained international attention as a treatment for a variety of diseases. In 1974, Dr. Bonica became the first pain physician invited by the Chinese government as a member of an American medical delegation to assess the utility of acupuncture in surgical procedures. He witnessed more than 28 surgeries personally and spoke with a large number of surgeons as well as anesthesia providers. In the report subsequently published in JAMA,<sup>160a</sup> he pointed out, "it (acupuncture) may prove extremely useful in relieving postoperative pain thus obviating the depressant effects of narcotics usually employed for this purpose." Traditional Chinese medicine (TCM) is the basis for acupuncture practice. According to TCM, the human body operates on 12 bilaterally distributed channels (6 yin channels and 6 yang channels) in conjunction with two midline channels in the ventral and dorsal aspects of the body, respectively. Acupuncture is the stimulation of anatomic locations on the skin by a variety of techniques that can be classified as invasive (e.g., needles, injections) or noninvasive (e.g., transcutaneous electrical stimulation, pressure, laser). Needles inserted into the skin can be stimulated by manual manipulation, moxibustion (i.e., burning a substance to produce heat), pressure, laser, and electricity. A scientific basis may exist for acupuncture. Acupuncture stimulates high-threshold, small-diameter nerves that activate the spinal cord, brainstem (i.e., periaqueductal gray area), and hypothalamic (i.e., arcuate) neurons, which trigger endogenous opioid mechanisms.<sup>161</sup> The effect of

acupuncture analgesia can be reversed by administration of naloxone.<sup>162</sup> Other mechanisms such as modulation of immune function,<sup>163</sup> inhibition of the inflammatory response,<sup>164</sup> regulation of neuropeptide gene expression,<sup>165</sup> and alteration in hormonal levels<sup>166</sup> have been proposed. The development of neuroimaging tools, such as positron emission tomography<sup>167</sup> and functional magnetic resonance imaging (fMRI),<sup>168,169</sup> make noninvasive studies of acupuncture's effects on human brain activity possible. Studies using positron emission tomography have demonstrated that the thalamic asymmetry present in patients suffering from chronic pain was reduced after acupuncture treatment. Other studies using fMRI have pointed to relationships between particular acupoints and activation of the visual cortex.<sup>170</sup> Using a noninvasive imaging technique called Bi-Digital O-Ring Test, researchers found that each meridian is connected to a representative area in the cerebral cortex, suggesting that the meridian system defined in the theories of Chinese medicine may overlap with distinct supraspinal regions.<sup>170a</sup> Electroacupuncture, particularly at low frequency, is associated with widespread fMRI signal increases in the anterior insula area, limb, and paralimbic structures. These humoral and neuronal changes induced by acupuncture form the basis for its clinical use.

According to the Centers for Disease Control and Prevention, more than 50 million procedures are performed each year in the United States, including more than 1 million hip and knee replacements. Most surgical procedures are associated with postoperative pain, for which opioids are the mainstay of treatment. However, opioid usage is associated with a high incidence of side effects including respiratory depression, reduced gastrointestinal motility, sedation, and itching. Chronic exposure to high-dose opioids can also induce opioid tolerance and dependence. It is therefore highly desirable to develop alternative therapies that provide adequate postoperative pain relief with minimal side effects. In this context, acupuncture for acute postoperative pain control has gained significant interest, including its use for oral-maxillofacial and neck surgeries, sternotomy/thoracotomy, abdominal/pelvic surgeries, and orthopedic and spine surgeries. Studies have shown that acupuncture can lead to improved pain scores or reduced opioid requirements postoperatively. Lao and associates carried out a randomized, double-blinded, and placebo-controlled trial on postoperative dental pain ( $N = 39$ ).<sup>170b</sup> The acupuncture group received acupuncture for about 20 minutes with intermittent manual manipulation to trigger "De Qi" sensation—a sensation of numbness, distension, or electrical tingling at the needling site. The control group underwent placebo acupuncture treatment at the identical acupuncture points to the acupuncture group but without needle insertion into the skin. Mean pain-free postoperative time was significantly longer in the acupuncture group (172.9 minutes) than in the placebo group (93.8 minutes). Pain medication requirements were significantly less in the acupuncture group than in the control group. Of note, this study also ruled out psychological variables as confounders for their observed benefits of acupuncture.

It is important to note that many of the studies on clinical applications of acupuncture have insufficient sample size, high dropout rates, inadequate follow-up, and poorly

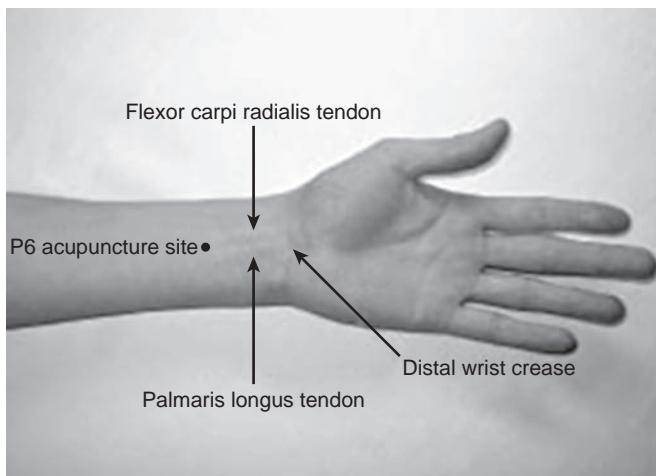
defined illnesses, enrollment criteria, and outcome measures.<sup>161</sup> Additionally, many of the clinical trials are single center studies, which could potentially demonstrate larger treatment effects than multicenter studies.<sup>170c</sup>

Side effects of acupuncture treatments include bruising or bleeding at the needle insertion site, transient vasovagal response, infection, dermatitis, and retained needle fragments. The occurrence of adverse events during acupuncture treatment is considered extremely low. In a survey that included 34,407 acupuncture treatments, there were no reported events of serious side effects and only 43 cases of significant mild side effects were noted, such as nausea, fainting, and bruising.<sup>170d,e</sup> Recently, the safety of acupuncture was confirmed in a cohort of cancer patients with thrombocytopenia.<sup>170f</sup>

## ACUPUNCTURE FOR POSTOPERATIVE NAUSEA AND VOMITING

One of the most promising indications for acupuncture is to prevent postoperative nausea and vomiting (PONV). PONV results in patient dissatisfaction, delayed discharge, unanticipated hospital admission, and the use of resources. Drugs have been the mainstay of management, however these have limited effectiveness, are associated with adverse effects, and can be costly. Acupuncture prevents PONV compared with sham acupuncture or no treatment.<sup>160</sup> In two early controlled trials, acupuncture prevented PONV in the pediatric population<sup>171,172</sup>; however, one literature review of 10 research studies examining the use of acupressure and acupuncture in adults concluded that it is not effective in preventing and managing PONV.<sup>173</sup> Other clinical studies have found that acupuncture prevents PONV and results in a greater degree of adult patient satisfaction.<sup>174,175</sup> For many of the trials in both adults and children, the PONV acupuncture point was P6 or PC6 (i.e., Nei guan or Pericardium 6).<sup>173,176</sup> The P6 acupuncture point is located between the palmaris longus and flexor carpi radialis muscle tendons, 4 cm proximal to the distal wrist crease and 1 cm below the skin (Fig. 33.2). Intraoperative stimulation of the P6 acupuncture point reduced the incidence of PONV, and its efficacy was similar to that of antiemetic drugs.<sup>177</sup> Stimulation of the acupuncture point should be initiated before induction of anesthesia.<sup>178</sup> Postoperative stimulation may be just as or more effective.<sup>179</sup> In children, stimulation immediately before emergence and in the recovery room has been effective. A recent metaanalysis for pediatric tonsillectomy indicated that acupuncture at the P6 acupuncture point is effective in preventing PONV.<sup>179a</sup> Some anesthesiologists anecdotally report tapping a small needle cap or other piece of smooth plastic over the P6 point as an effective means of acupressure stimulation.

Studies often differ in acupuncture method: duration and timing of stimulation, unilateral versus bilateral stimulation, and type of stimulation (i.e., needles with or without additional stimulation, acupressure, transcutaneous electrical stimulation, cutaneous laser stimulation, injection of a 50% dextrose solution, or capsicum plaster). Data to compare the effectiveness, safety, and costs of different methods of stimulation are inadequate.



**Fig. 33.2** The P6 acupuncture point is located between the palmaris longus and flexor carpi radialis muscle tendons, 4 cm proximal to the distal wrist crease and 1 cm below the skin.

## DEEP BREATHING

Deep breathing exercises are performed as part of a relaxation technique. With this method, a subject consciously slows breathing and focuses on taking deep breaths.<sup>180</sup> Deep breathing can help reduce abdominal and surgical pain.<sup>181,182</sup>

Studies of postoperative pain relief with breath control were reported in the 1970s.<sup>183,184</sup> Since then, many studies have reported its efficacy against postoperative pain in adult patients<sup>181,185</sup>; prevented postoperative pulmonary complications<sup>186</sup>; and decreased pain in pediatric patients.<sup>199</sup>

Fast or forced deep breathing can also increase postoperative pain.<sup>187</sup> Thus, those who assist patients in postoperative pain management should encourage deep breathing exercises that are performed slowly, smoothly, and gently. Slow, deep breathing relaxation exercises have been used successfully as an adjunct to opioids for postoperative pain management in patients who had coronary bypass surgery<sup>188</sup>; however, after abdominal surgery, deep breathing was ineffective for pain reduction in older patients because pulmonary complications developed postoperatively.<sup>189</sup> Most patients who receive deep breathing education think it is useful, and the exercise was effective in increasing their feelings of rapport with staff and intention to follow their doctor's directives.<sup>190</sup> Results from a recent trial demonstrated that slow, deep breathing had analgesic effects with increased vagal cardiac activity.<sup>191</sup> Slow, deep breathing relaxation can also decrease the sensation of postoperative nausea.<sup>192,193</sup>

## Music Therapy

Music therapy is the clinical, evidence-based use of music interventions to accomplish individualized therapeutic goals. Because music can be used for diverse applications, music therapists practice in a variety of healthcare and education settings.<sup>194</sup> Music for pain relief benefits individuals experiencing a low to moderate amount of pain more than

those experiencing a high degree of pain.<sup>195</sup> A patient's preferred music should be considered when it is used for pain relief. The increase of endogenous opioids through music may be the reason for pain relief.<sup>194</sup>

Perioperatively, music can decrease preoperative anxiety, reduce intraoperative sedative and analgesic requirements, and increase patient satisfaction. Patient-selected music can reduce patient-controlled sedative requirements during spinal anesthesia and analgesic requirements during lithotripsy.<sup>196</sup> Music in the preoperative setting can reduce anxiety without affecting physiologic measures of stress.<sup>197,198</sup> Music can also increase patient satisfaction and reduce systolic blood pressure during cataract surgery after retrobulbar block.<sup>199</sup> Perioperative music can reduce arterial pressure, anxiety, and pain among women undergoing mastectomy for breast cancer.<sup>200</sup> As a noninvasive intervention, the low sensory stimulation of music reduced anxiety and increased cooperation in children undergoing induction of anesthesia.<sup>201</sup>

Music therapy interventions that have targeted nausea, both anticipatory or after treatment, have had conflicting results.<sup>194</sup> One study showed that a patient's preferred music for listening during chemotherapy infusion was effective in decreasing the onset and occasion of nausea.<sup>202</sup> In another study, listening to music with a personal message from the physician yielded no difference in chemotherapy-induced side effects compared with not listening to music during chemotherapy.<sup>203</sup> Some studies have found no effect on PONV from music therapy,<sup>204,205</sup> yet PONV was reduced in hospitalized transplant patients postoperatively.<sup>206</sup> Although the exact mechanism is not well understood, music therapy has been an alternative option to mainstream therapies in healthcare settings to reduce patient pain, anxiety, and perioperative stress.<sup>207</sup> Another use of music is in the intensive care unit. A recent clinical trial observed that among patients in the intensive care unit who received acute ventilator support for respiratory failure, patient-directed music intervention resulted in more reduction in anxiety and sedation frequency and intensity compared with usual care.<sup>208</sup> In addition, music can attenuate cardiovascular variability and nociceptive effects.<sup>209,210</sup>

## Conclusion

One of the fastest changing aspects of health care is the growing public and scientific interest in CAM. An increasing number of patients and physicians have combined integrative medicine into their treatment plans. Because of the significant increase in demand for CAM therapies, most U.S. medical schools have added coursework on integrative medicine. Anesthesiologists are the physicians to manage these patients perioperatively, and therefore should have updated knowledge for the modalities of complementary and integrative medicine. To manage herbal medications in the perioperative period, their possible direct and indirect effects should be recognized based on an understanding of the underlying pharmacology. Surgery and anesthesia can usually proceed safely if potential complications are anticipated and can be minimized. As CAM therapies

**TABLE 33.2** Printed and World Wide Web Sources of Herbal Medicine Information

Source	Comments
Physicians' Desk Reference for Herbal Medicines	
Encyclopedia of Dietary Supplements	
Commission E Monographs	Safety and efficacy information on herbs and phyto-medicinals; published in German, translated to English, 1998
Center for Food Safety and Applied Nutrition, Food and Drug Administration: <a href="https://www.fda.gov/AboutFDA/CentersOffices/OfficeofFoods/CFSAN/default.htm">https://www.fda.gov/AboutFDA/CentersOffices/OfficeofFoods/CFSAN/default.htm</a>	Clinicians should use this site to report adverse events associated with herbal medicines and other dietary supplements. Sections also contain safety, industry, and regulatory information
National Center for Complementary and Alternative Medicine, National Institutes of Health: <a href="http://nccam.nih.gov/">http://nccam.nih.gov/</a>	This site contains fact sheets about alternative therapies, consensus reports, and databases
Agricultural Research Service, U.S. Department of Agriculture <a href="https://www.ars.usda.gov/">https://www.ars.usda.gov/</a>	The site contains an extensive phytochemical database with search capabilities
Quackwatch: <a href="http://www.quackwatch.com">http://www.quackwatch.com</a>	Although this site addresses all aspects of health care, there is a considerable amount of information covering complementary and herbal therapies
National Council Against Health Fraud: <a href="http://www.ncahf.org">http://www.ncahf.org</a>	This site focuses on health fraud with a position paper on over-the-counter herbal remedies
HerbMed: <a href="http://www.herbmed.org">http://www.herbmed.org</a>	This site contains information on numerous herbal medications, with evidence for activity, warnings, preparations, mixtures, and mechanisms of action. There are short summaries of important research publications with Medline links.
ConsumerLab: <a href="http://www.consumerlab.com">http://www.consumerlab.com</a>	This site is maintained by a corporation that conducts independent laboratory investigations of dietary supplements and other health products

gain popularity in the United States, patients are likely to accept some alternative modalities during the perioperative period, such as acupuncture, deep breathing, and musical intervention. These modalities are easy to administer, have a rapid onset of action, are cost effective, and produce minimal side effects. Based on preliminary studies, perioperative use of CAM therapies may be an adjunct for management of multiple symptoms including pain, anxiety, and nausea and vomiting, among others. Additional large, well-designed trials are required to verify current observations on the effectiveness of CAM and to answer the concerns of possible side effects. Although medical schools are beginning to incorporate CAM into their curricula, it is important for anesthesiologists to stay informed about CAM therapies (Table 33.2).

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## KEY POINTS

- Patient positioning is a major responsibility that requires the cooperation of the entire surgical team.
- Many patient positions that are used for surgery result in undesirable physiologic consequences including significant cardiovascular and respiratory compromise. Anesthetic agents blunt natural compensatory mechanisms, rendering surgical patients vulnerable to positional changes.
- Peripheral nerve injuries, although rare, represent 22% of cases in the 1990 to 2007 American Society of Anesthesiologists' Closed Claims Project. The mechanisms of injury are stretching, compression, and ischemia. Patient positioning is often a suspected contributory factor, although precautions have usually been taken and no specific cause for the injury is known.
- The American Society of Anesthesiologists first issued a Practice Advisory in 2000 for the prevention of perioperative peripheral neuropathies that was updated in 2019. However, very few of the studies reviewed met the standard for a scientifically proven relationship between intervention and outcome.
- Anesthesia administered outside the operating room presents special challenges with regard to patient positioning because of monitoring and equipment limitations and differences in the work environment and culture.
- Perioperative visual loss (POVL) is a rare but serious injury that appears more frequently after cardiac, spine, and orthopedic joint surgery.
- Causes of POVL include central or branch retinal artery occlusion, anterior and posterior ischemic optic neuropathy, cortical blindness, acute glaucoma, and acute expansion of gas bubbles placed in the eye in retinal surgery.
- Signs and symptoms of visual loss in the postoperative period may be subtle and can be incorrectly attributed to the residual effects of anesthetic drugs. Any patient reporting eye pain, an inability to perceive light or motion, complete or partial loss of visual fields, decreased visual acuity, or loss of pupil reactivity must be evaluated immediately by an ophthalmologist.
- The most common cause of perioperative central and branch retinal artery occlusion is compression of the eye. During cardiac surgery, emboli may occlude the retinal arteries.
- Patients who undergo prolonged operative procedures in the prone position with large blood loss are at increased risk for development of ischemic optic neuropathy. Other factors conferring a risk during spine surgery include male sex, obesity, the use of a Wilson frame, and intravascular fluids administered perioperatively.
- Patients should be informed of the risk for visual loss accompanying lengthy surgical procedures with the patient positioned prone and with anticipated large blood loss. Both anesthesia and surgery personnel, together, should develop a plan by which informed consent for this complication may be facilitated.
- POVL in the presence of focal neurologic signs or the loss of accommodation reflexes or abnormal eye movements suggests a diagnosis of cortical blindness. Neurologic consultation should be obtained.

## Introduction

The purpose of patient positioning in the operating room is to facilitate the surgical procedure, however, optimal surgical positioning may put patients at risk of injury or significantly alter intraoperative physiology. Peripheral nerve injuries, pressure injuries, and eye injuries are significant sources of perioperative morbidity.<sup>1-3</sup> Proper patient positioning is imperative and requires the cooperation of the entire surgical team. For this reason the

American Society of Anesthesiologists (ASA) requires intraoperative documentation of "patient positioning and actions to reduce the chance of adverse patient effects or complications related to positioning."<sup>4</sup> Preventing positioning complications requires clinical judgement, vigilance, and a cooperative team approach. This chapter will review the most commonly utilized surgical positions, physiologic alterations from positioning, and specific risks and injuries associated with different surgical positions.

## Physiologic Considerations of Positioning

Complex physiologic responses have evolved to blunt the hemodynamic effects of positional changes in order to maintain blood pressure within a narrow range. These essential mechanisms maintain perfusion to the brain and vital organs, regardless of posture and position—for example, as a person reclines from an upright to a supine position venous return to the heart increases and initially the increased preload causes an increase in stroke volume and cardiac output. This causes an increase in arterial blood pressure, which activates afferent baroreceptors from the aorta (via the vagus nerve) and within the walls of the carotid sinuses (via the glossopharyngeal nerve). Mechanoreceptors from the atria and ventricles are also activated to decrease sympathetic outflow to muscle and splanchnic vascular beds. Lastly, atrial reflexes are activated to regulate renal sympathetic nerve activity, plasma renin, atrial natriuretic peptide, and arginine vasopressin levels.<sup>5</sup> Ultimately, heart rate and cardiac output are decreased to reach homeostasis in the new position.

Different types of anesthesia and anesthetic agents can blunt these compensatory pathways. Most current inhaled anesthetics, and many intravenous anesthetics, induce vasodilation. The use of spinal or epidural anesthesia causes a significant sympathectomy across all anesthetized dermatomes, independent of the presence of general anesthesia, reducing preload and potentially blunting cardiac response. Therefore, under anesthesia, changes in patient position may cause a more exaggerated hemodynamic response compared with position changes in unanesthetized patients. This can be particularly important for positions that would normally elicit a sympathetic response and vasoconstriction in order to maintain cardiac and cerebral perfusion, such as the sitting position. Interruptions in monitoring to facilitate positioning or turning of the surgical table should be minimized during position changes in order to monitor hemodynamic outcomes. Being aware of the physiologic consequences will help the anesthesiologist anticipate changes in hemodynamics with patient position changes.

Positive-pressure ventilation increases mean intrathoracic pressure, diminishing the venous pressure gradient from peripheral capillaries to the right atrium. This can affect cardiac output as the normal pressure gradients for venous circulation and cardiac preload are relatively low.<sup>6</sup> Positive end-expiratory pressure further increases mean intrathoracic pressure, and possibly further compromises venous return and cardiac output, as do conditions associated with low lung compliance, such as airways disease, obesity, ascites, and light anesthesia.<sup>7</sup> The anesthesia provider needs to anticipate, monitor, and treat these effects, as well as assess the safety of positional changes for each patient.

Normal spontaneous ventilation results from relatively small negative intrathoracic pressure shifts because of diaphragmatic displacement and chest wall movement. Resultant negative intrathoracic pressure also promotes venous return to the heart by reducing the pressure in the great veins and right atrium.<sup>8</sup> With spontaneous ventilation, diaphragmatic movement is greatest adjacent to the most dependent portions of the lung, helping bring new ventilation to the

zones of the lung that are preferentially perfused. When a person shifts from standing to a supine position, functional residual capacity decreases in part due to cephalad displacement of the diaphragm. The chest wall contributes less to ventilation in the supine position causing more reliance on diaphragm contribution. Although gravity has some effect on the perfusion and ventilation of the lung, new evidence points to the importance of other factors as well.<sup>9-13</sup>

Under general anesthesia spontaneously breathing patients have reduced tidal volumes, reduced functional residual capacity, and increased closing volumes. This leads to more ventilation perfusion mismatching due to increased atelectasis and a reduced minute ventilation. Using positive-pressure ventilation with muscle relaxation may counter some of the ventilation-perfusion mismatch by ensuring adequate minute ventilation and limiting atelectasis by use of positive end-expiratory pressure.<sup>9</sup> In addition to these effects of anesthesia, patient position has distinct effects on pulmonary function. In particular, any position that limits the movement of the diaphragm, chest wall, or abdomen may increase atelectasis and therefore increase intrapulmonary shunt.

Newer investigations using high-resolution imaging have shown the prone position to provide superior ventilation-perfusion matching in the posterior segments of the lung near the diaphragm when compared with the supine position. Ventilation of these posterior segments is enhanced, while blood flow is maintained, despite their nondependent position.<sup>8,14</sup>

## General Positioning Considerations

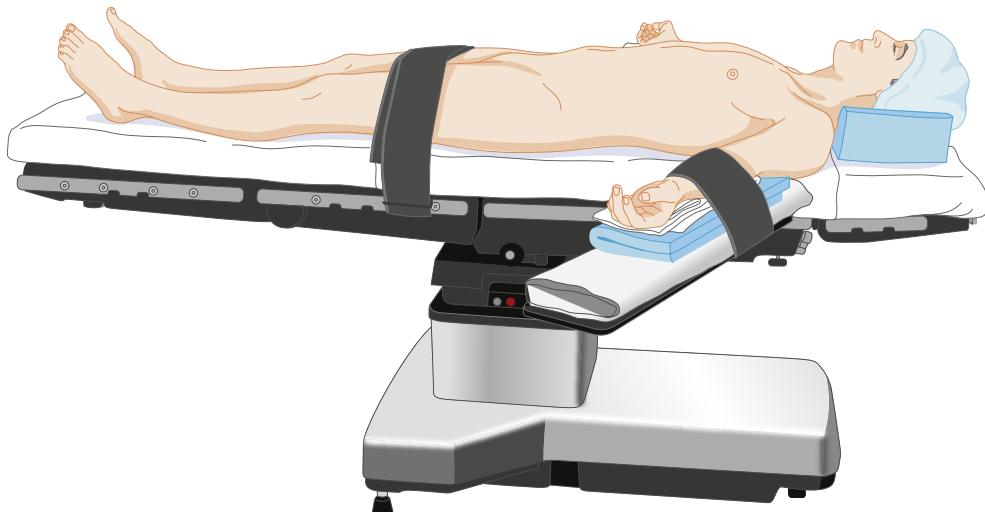
Coordination of the multidisciplinary surgical team is required in order to achieve proper and safe positioning of patients. Principles include maintaining spine and extremity neutrality as much as possible. The patient should lie on a padded surface, and additional padding should be placed around bony prominences and hard objects, such as intravenous fluid lines, monitoring equipment, and poles.

People who are awake and not sedated change position if they become uncomfortable. Even during normal sleep, some movement is normal in order to prevent pressure or stretch injuries. Anesthetized patients are unable to change position if pressure or stretch causes nociception. Therefore, whenever possible, patients should be placed in a natural position that would be well tolerated if the patient were awake or not sedated. When more extreme positions cannot be avoided, their duration should be limited as much as possible. It is reasonable to ask patients what positions they can tolerate comfortably.

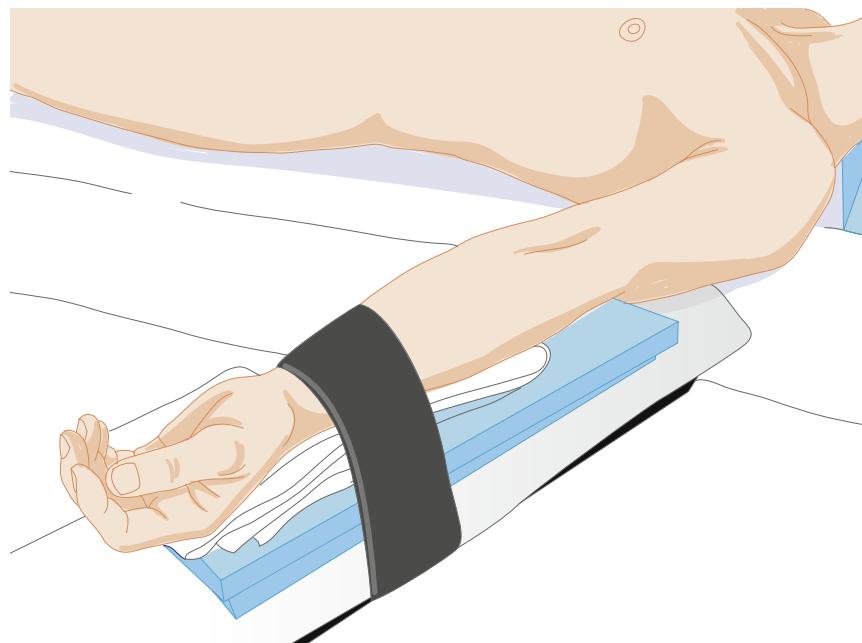
## Specific Positions

### SUPINE

The most common position for surgery is the supine or dorsal decubitus position (Fig. 34.1). Classically, the head, neck, and spine all retain neutrality. Because the entire body is close to the level of the heart, hemodynamic reserve is well maintained. Tissues overlying all bony prominences,



**Fig. 34.1 Supine position.** The base of the table is asymmetrical. When positioned in the usual direction, the patient's center of gravity is over the base. Weight limits decrease when in reverse orientation to the base.



**Fig. 34.2 Arm position using the arm board.** Abduction of the arm is limited to less than 90 degrees whenever possible. The arm is supinated, and the elbow is padded.

such as the heels and sacrum, must be padded to prevent soft tissue ischemia as a result of pressure, especially during prolonged surgery.<sup>15</sup>

The arms can be abducted, adducted, or one arm abducted and one arm adducted. In any variation, the arms should be placed in as neutral a position as possible, minimizing stretch and over extension.<sup>4</sup> When the arms are adducted, they must remain securely placed next to the body. For abducted arm position, abduction should be limited to less than 90 degrees to minimize the likelihood of brachial plexus injury.<sup>4,16</sup> Hands and forearms can be supinated or kept in a neutral position with the palm toward the body. This also reduces external pressure on the spiral groove of the humerus and the ulnar nerve (Fig. 34.2).<sup>4,17,18</sup> Particular attention should be paid to pad bony prominences, like the elbows, and any

protruding objects, such as intravenous fluid lines, monitoring equipment, and poles (Fig. 34.3).

### Variations of the Supine Position

Several variations of the supine position are frequently used. These include the lawn (or beach) chair position, frog-leg position, and Trendelenburg and reverse Trendelenburg positions. The lawn chair position (Fig. 34.4) reduces stress on the back, hips, and knees by placing the patient's hips and knees in mild flexion. This position is often better tolerated by patients who are awake or undergoing monitored anesthesia care than the full supine position. The lawn chair position also facilitates lower extremity venous drainage because the legs are placed slightly above the level of the heart. Abdominal wall tension is also reduced because

the xiphoid to pubic distance is decreased. Proper positioning involves positioning the patient's hips at the break of the surgical table and avoiding venous pooling in the legs.

The frog-leg position allows procedural access to the perineum, medial thighs, genitalia, and rectum. The patient is positioned supine and then the hips and knees are flexed and the hips are externally rotated with the soles of the feet facing each other. Support of the patient's knees to minimize stress and postoperative pain in the hips is required.

The Trendelenburg position, achieved by tilting a supine patient head down (Fig. 34.5), is linked by name to a 19th-century German surgeon, Friedrich Trendelenburg, who described its use for abdominal surgery. Walter Cannon, a Harvard physiologist, is credited with popularizing the use of Trendelenburg positioning to improve hemodynamics for patients in shock during World War I. Today the Trendelenburg position is frequently utilized to improve exposure during abdominal and laparoscopic surgery, during central line placement to prevent



**Fig. 34.3 Arm tucked at patient side.** The arm is in the neutral position with the palm to the hip. The elbow is padded, and the arm is well supported by the mattress.

air embolism and distention of the central vein, and to offset hypotension by temporarily increasing venous return. A steep (30-45 degrees) head-down position is now frequently used for robotic prostate and gynecologic surgeries.

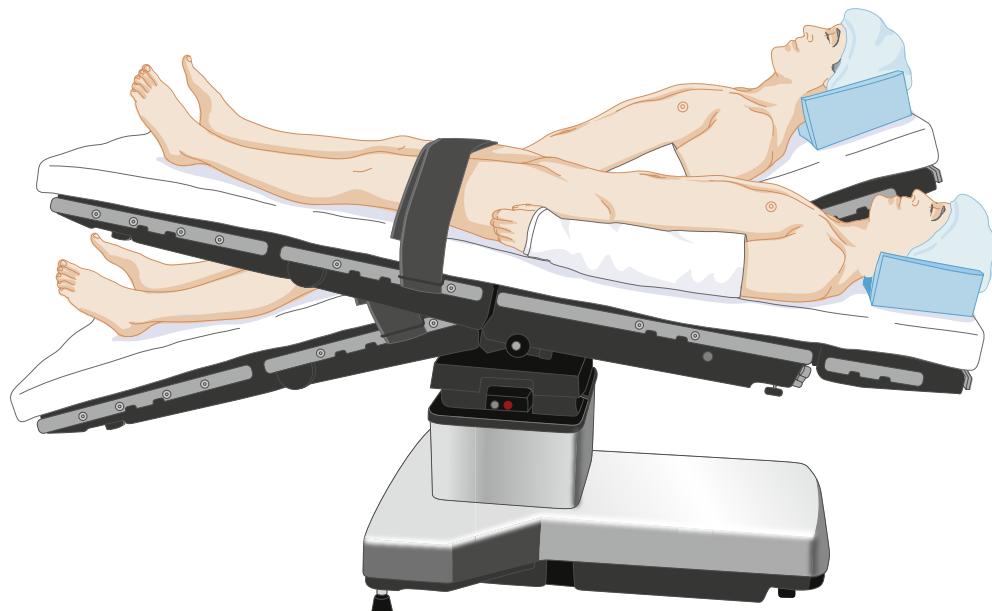
For all positions in which the head is at a different level than the heart, the effect of the hydrostatic gradient on cerebral arterial and venous pressures should be considered when estimating cerebral perfusion pressure. Careful documentation of any potential arterial pressure gradient is especially prudent.

The Trendelenburg position does produce hemodynamic and respiratory changes; however, the hemodynamic changes are not as long-lasting as often thought. Initial placement of the patient in head-down supine position will increase cardiac output approximately 9% in less than 1 minute via an autotransfusion from the lower extremities. This effect is not sustained and within approximately 10 minutes the cardiac output begins to return to baseline. Nevertheless, the Trendelenburg position is still considered an essential part of initial resuscitation efforts to treat hypotension and acute hypovolemia.<sup>19</sup> Functional residual capacity is decreased due to gravitational pull of the diaphragm cephalad. Pulmonary compliance is increased by decreased functional residual capacity and is often further decreased in the Trendelenburg position, due to patient-positioning straps across the chest. In a spontaneously breathing patient, the work of breathing increases. In patients under general anesthesia, these pulmonary changes result in higher airway pressures. Changes to the mechanical ventilator settings can compensate for some of the respiratory changes. However, with patient body habitus and variations in positioning, the higher airway pressures, and changes to minute ventilation are too great to safely continue in the steep Trendelenburg position. Testing the position for patient tolerance after anesthetic induction and completed positioning, prior to the initiation of the surgical procedure, is recommended.

Intracranial and intraocular pressures (IOCs) also increase in Trendelenburg position. Trendelenburg is contraindicated in patients with increased intracranial pressures. In fact, for some patients with severe intracranial hypertension, even



**Fig. 34.4 Lawn or beach chair position.** Flexion of the hips and knees decreases tension on the back.



**Fig. 34.5** Head-down tilt (Trendelenburg) position and head-up tilt (reverse Trendelenburg) position. Shoulder braces should be avoided to prevent brachial plexus compression injuries.

supine position is not tolerated. Consideration of the impact of positioning on intracranial pressure is important, as it may not only affect intraoperative positioning but also may have consequences on site selection for central line placement. Frequently, femoral vein site selection is preferred in patients with severely elevated intracranial pressure in order to avoid exacerbating intracranial hypertension with patient position changes during line placement.

Prolonged head-down positioning can also lead to swelling of the face, conjunctiva, larynx, and tongue, with an increased potential for postoperative upper airway obstruction. The Trendelenburg position increases intraabdominal pressure and displaces the stomach placing the patient at a higher risk for aspiration. Endotracheal intubation is often preferred in order to prevent aspiration of gastric contents.

Care must be taken to prevent patients in steep head-down positions from slipping cephalad on the surgical instruments.<sup>20,21</sup> Techniques to restrain the patient include antiskid bedding, knee flexion, shoulder braces, beanbag cradling, and padded cross-torso straps.<sup>22</sup> Shoulder braces are specifically not recommended because of the risk of compression injury to the brachial plexus. Beanbag pads become rigid when suction is applied to set the shape, and their use in the Trendelenburg position has been associated with brachial plexus injuries.<sup>23-25</sup> If either shoulder braces or beanbag shoulder immobilization is used to prevent sliding, additional caution is recommended regarding abducting the arm; brachial plexus injuries on the side of the abducted arm have been reported in conjunction with beanbag shoulder immobilization and steep Trendelenburg positioning.<sup>26</sup> These injuries may be due to stretch of the upper and middle trunks of the brachial plexus, as they course around the head of the humerus (Fig. 34.6).

The reverse Trendelenburg position (head-up tilt; see Fig. 34.2) is often used to facilitate upper abdominal surgery by shifting the abdominal contents caudad. This position is increasingly popular because of the growing number of laparoscopic surgeries requiring this position. Again, caution

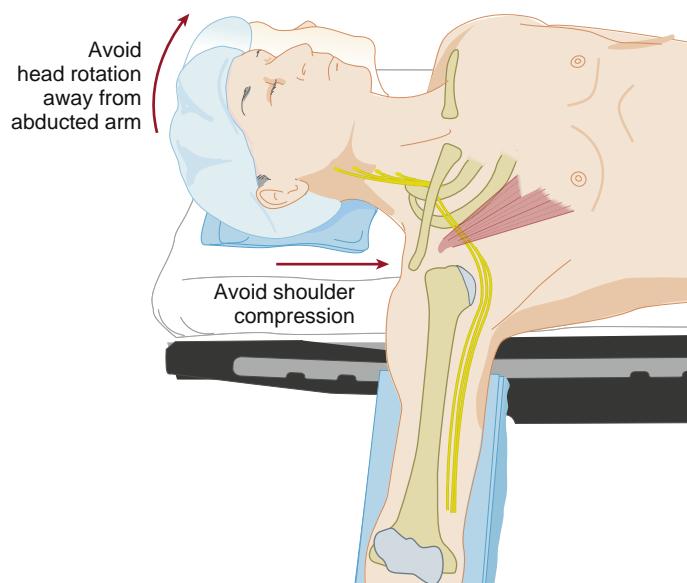
is advised to prevent patients from slipping on the table. As mentioned earlier, any position where the head is above the heart reduces cerebral perfusion pressure and may also cause systemic hypotension. If invasive arterial pressure monitoring is used then the arterial pressure transducer should be zeroed at the level of the Circle of Willis.

### Complications of the Supine Position

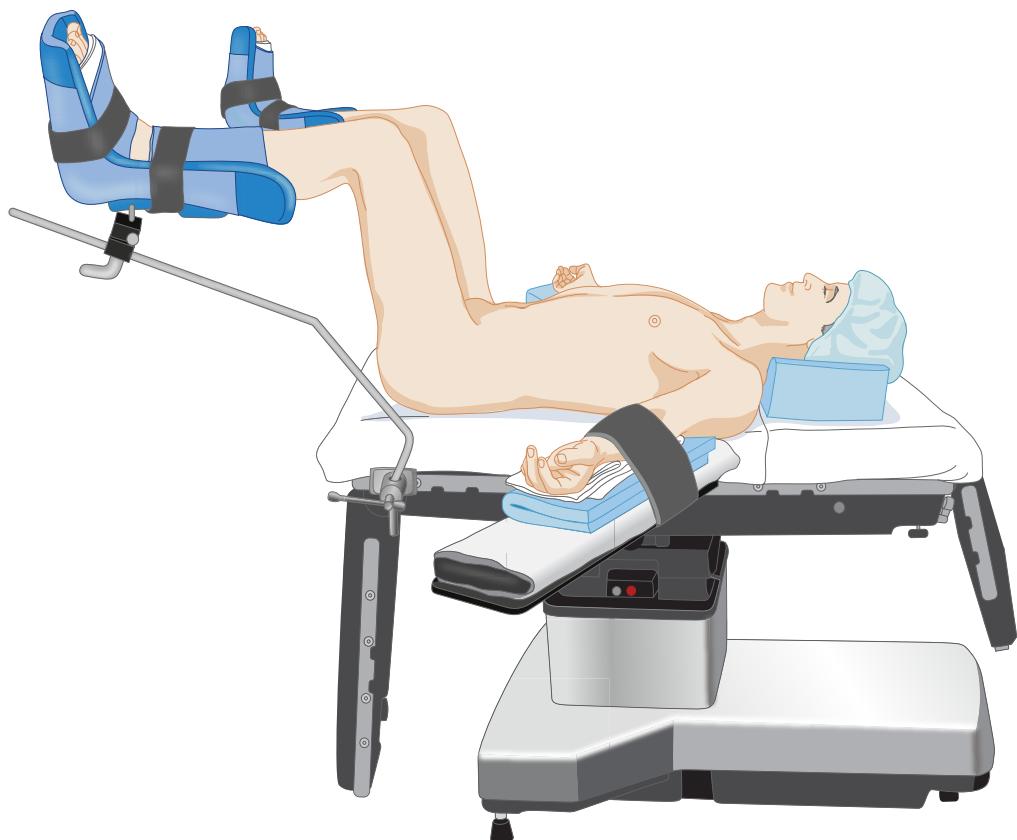
The base of the surgical table is asymmetric. Classically, the base of the table is directly underneath the patient's torso (see Fig. 34.1). However, sometimes the patient's torso overlies the end of the table without the base underneath it in order to improve surgical access or to facilitate the use of specific equipment such as the C-arm for x-ray. Without the table base under the torso of the patient's body, the table is at risk of tilting or tipping over. This risk is higher with obese patients and when the table is in the Trendelenburg position. The surgical table weight limits are significantly different when the table is reversed and should be strictly observed.

Back pain is common in the supine position because the normal lumbar lordotic curvature is often lost. General anesthesia with muscle relaxation and neuraxial block increases the risk of back pain further due to loss of tone in the paraspinal muscles. Patients with extensive kyphosis, scoliosis, or a history of back pain may require extra padding of the spine or slight flexion at the hip and knee.

Peripheral nerve injury (discussed later in this chapter) is a complex phenomenon with multifactorial causes. The ASA has published several revisions of a practice advisory to help prevent perioperative peripheral neuropathies.<sup>4</sup> Ulnar neuropathy has historically been the most common lesion, although brachial plexus injuries have overtaken ulnar neuropathies in more recent closed claims data associated with general anesthesia.<sup>1,3</sup> Regardless of the position of the upper extremities, maintaining the head in a relatively midline position can help minimize the risk of stretch injury to the brachial plexus.<sup>23</sup> Although no direct evidence suggests



**Fig. 34.6** The brachial plexus, shown in yellow, is vulnerable to stretch and compression due to its long course. Arm abduction is limited to less than 90 degrees when supine because when the arm is raised the head of the humerus rotates caudad and stretches the plexus. Shoulder braces should be avoided; they may cause direct compression of the plexus medially between the clavicle and first rib or laterally below the head of the humerus. Excessive head rotation should be avoided, especially away from an abducted arm. Abduction of the arm should be avoided when in a steep head-down position if shoulder braces or a beanbag holds the shoulders.



**Fig. 34.7 Lithotomy position.** Hips are flexed 80 to 100 degrees with the lower leg parallel to the body. Pressure near the fibular head is absent. Arms are on armrests away from the hinge point of the foot section.

that positioning or padding alone can prevent perioperative ulnar neuropathies, the ASA practice advisory recommends limiting arm abduction in the supine patient to less than 90 degrees at the shoulder, with the hand and forearm either supinated or kept in a neutral position.<sup>4</sup>

## LITHOTOMY

The classic lithotomy position (Figs. 34.7–34.9) is frequently used during gynecologic, rectal, and urologic surgeries. The patient's hips are flexed 80 to 100 degrees from

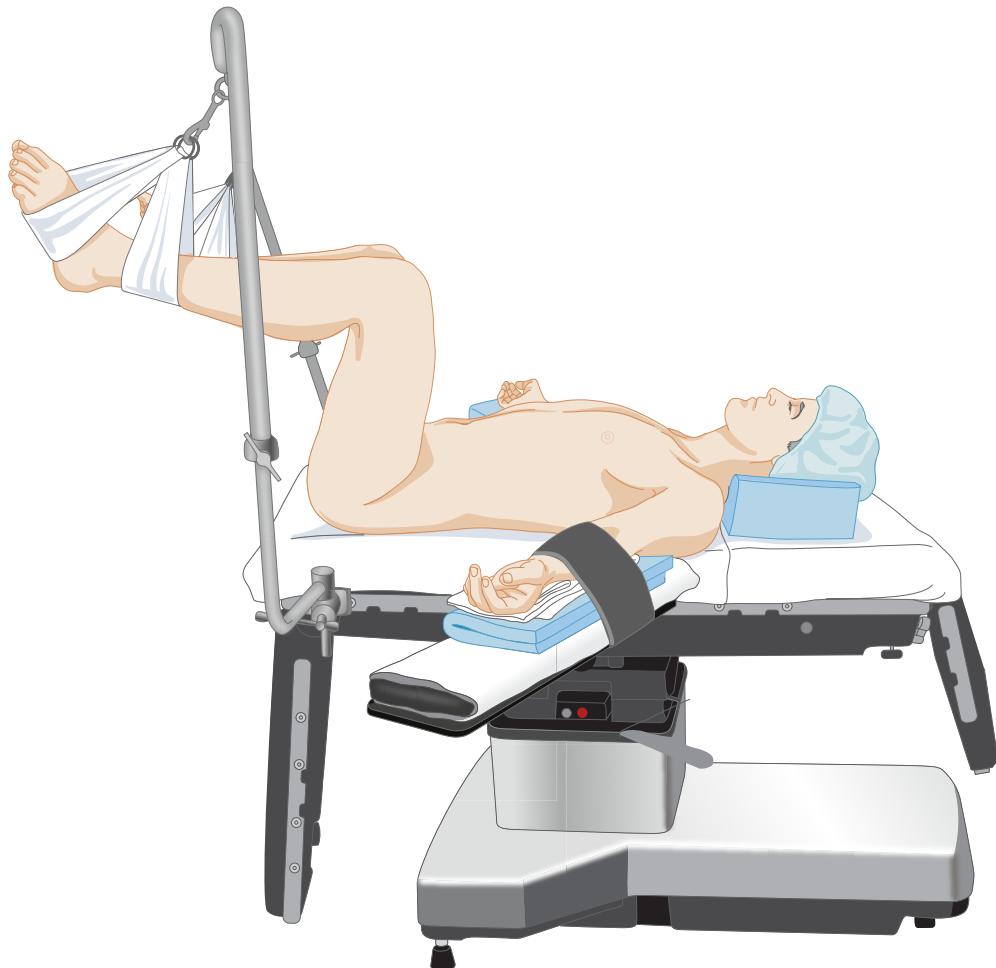


Fig. 34.8 Lithotomy position with "candy cane" stirrup leg holders.

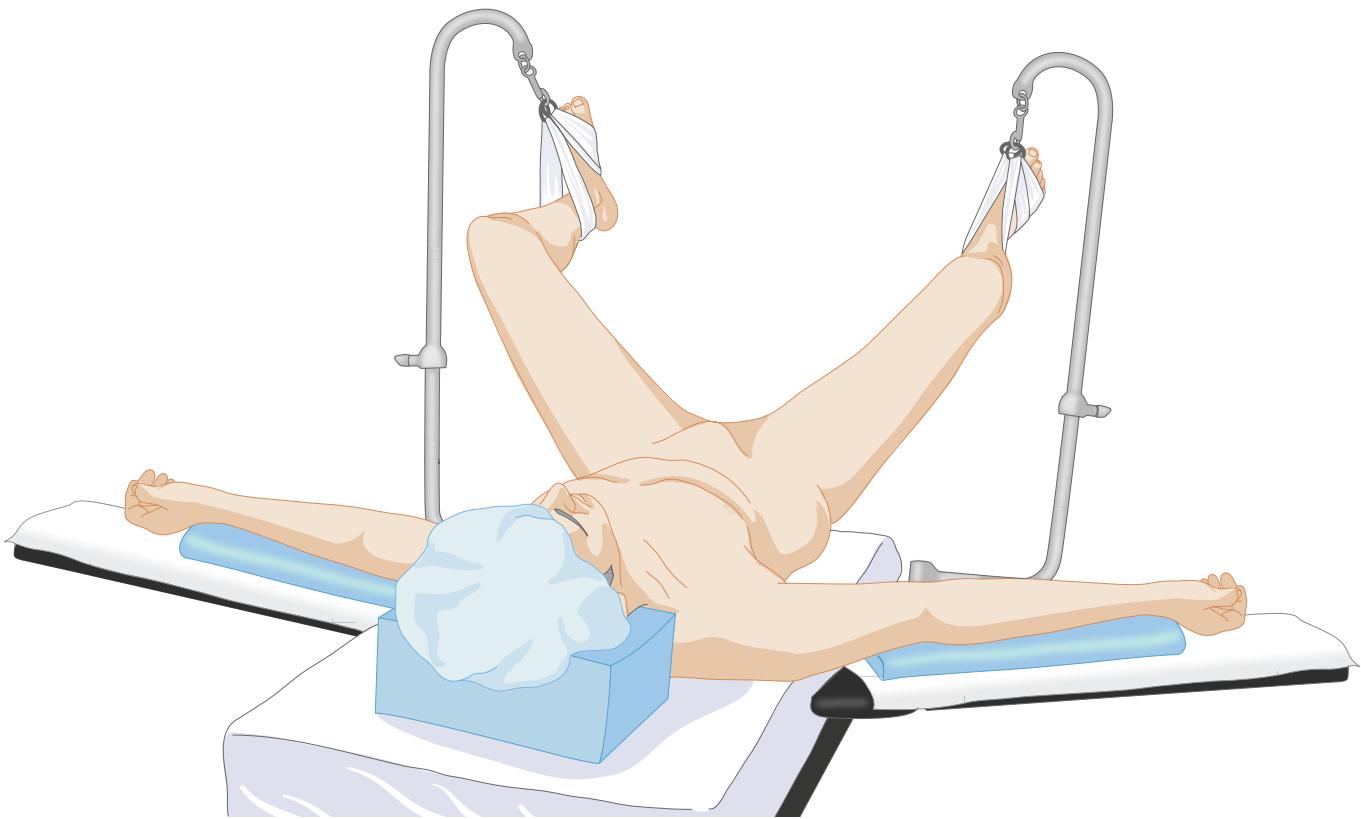
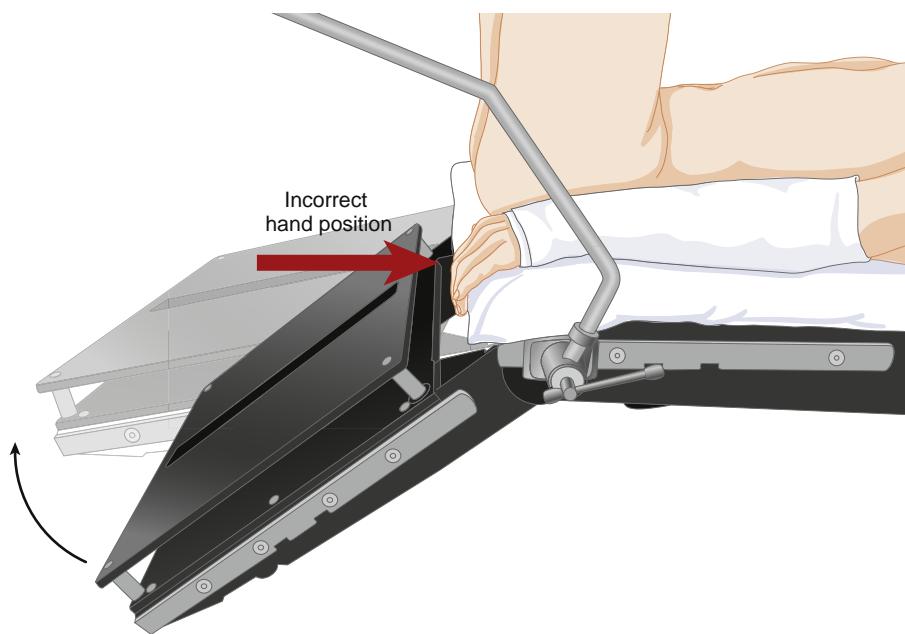


Fig. 34.9 Lithotomy position. The correct position of "candy cane" supports is well away from the lateral fibular head.



**Fig. 34.10 Improper position of arms in lithotomy position.** The fingers are at risk for compression when the lower section of the bed is raised.

the trunk, and the legs are abducted 30 to 45 degrees from the midline. The knees are flexed until the lower legs are parallel to the torso. The legs are then placed in supports or stirrups. The foot section of the surgical table is lowered and sometimes removed from the end of the table.

Positioning a patient into and out of lithotomy requires a coordinated team. The legs should be raised together; simultaneously, the knees and hips are flexed. This prevents torsion and injury to the lumbar spine. Padding of the lower extremities is critical, particularly over bony prominences, to prevent compression against the leg supports. The peroneal nerve is particularly prone to injury as it lies between the fibular head and compression from the leg support (see the peripheral nerve injury section of this chapter).

If the arms are tucked or placed alongside the patient, then the patient's hands and fingers are at risk of injury if they lie near the open edge of the lowered section of the table. When the foot of the table is raised at the end of the procedure the fingers near the open edge can get crushed. Strict attention must be paid to the position of the hands to avoid a potentially disastrous crush injury to the fingers (Fig. 34.10). For this reason, the recommended position of the arms is on armrests far from the table hinge point. If the arms must be tucked at the patient's side, then the hands need to be visualized and confirmed to be safe whenever the leg section of the surgical table is manipulated.

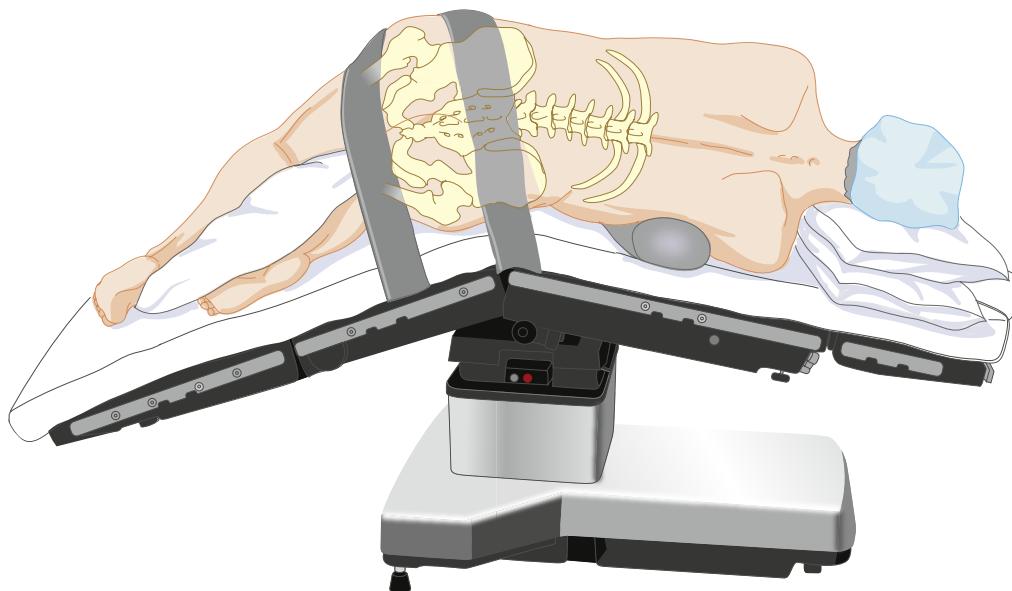
The lithotomy position may also cause significant physiologic changes. When the legs are elevated, venous return increases, causing a transient increase in cardiac output and, to a lesser extent, cerebral venous and intracranial pressure in otherwise healthy patients. In addition, the lithotomy position increases intraabdominal pressure and causes the abdominal viscera to displace the diaphragm cephalad, reducing lung compliance and potentially resulting in a decreased tidal volume. In obese patients, or when large abdominal mass is present (e.g., tumor, gravid uterus), abdominal pressure may increase enough to obstruct venous return to the heart. As with the supine position, the

curvature of the lumbar spine is lost in lithotomy and can put the patient at risk of back pain.<sup>27</sup>

Lower extremity compartment syndrome is a rare but potentially devastating complication of the lithotomy position. Compartment syndrome is caused by increased tissue pressure within a fascial compartment due to tissue ischemia, edema, and rhabdomyolysis. Inadequate arterial inflow (from lower extremity elevation) and decreased venous outflow (due to direct compression or excessive hip flexion) elevates the risk of compartment syndrome for patients in lithotomy.<sup>28,29</sup> Local arterial pressure decreases 0.78 mm Hg for each centimeter the leg is raised above the right atrium.<sup>30</sup> Reperfusion after ischemic injury further increases edema, exacerbating the problem. In a large retrospective review of 572,498 surgeries, the incidence of compartment syndromes was higher in the lithotomy (1 in 8720) and lateral decubitus (1 in 9711) positions, as compared with the supine (1 in 92,441) position. Long procedure time was the only distinguishing characteristic of the surgeries during which patients developed lower extremity compartment syndromes.<sup>28</sup> A survey of urologists in the United Kingdom suggested that compartment syndrome after surgery in the lithotomy position is under-reported and more common than appreciated. Affected patients in this study all had surgical durations greater than 3.5 hours.<sup>31</sup> In a retrospective multicenter review of 185 urologic patients who were placed in high lithotomy position, two patients suffered from compartment syndrome. For both of these patients, operative times exceeded 5 hours.<sup>32</sup> If surgical time extends beyond 2 to 3 hours, periodically lowering the legs is recommended.<sup>32-34</sup> Additional risk includes factors known to compromise tissue oxygenation, such as blood loss, peripheral vascular disease, hypotension, and reduced cardiac output. Elevated body mass index is also a risk factor for compartment syndrome. Intermittent leg compression devices remain controversial.<sup>30,35</sup>



**Fig. 34.11 Lateral decubitus position.** The lower leg is flexed with padding between the legs, and both arms are supported and padded.



**Fig. 34.12 Flexed lateral decubitus position.** The point of flexion should lie under the iliac crest, rather than under the flank or lower ribs to optimize ventilation of the dependent lung.

## LATERAL DECUBITUS

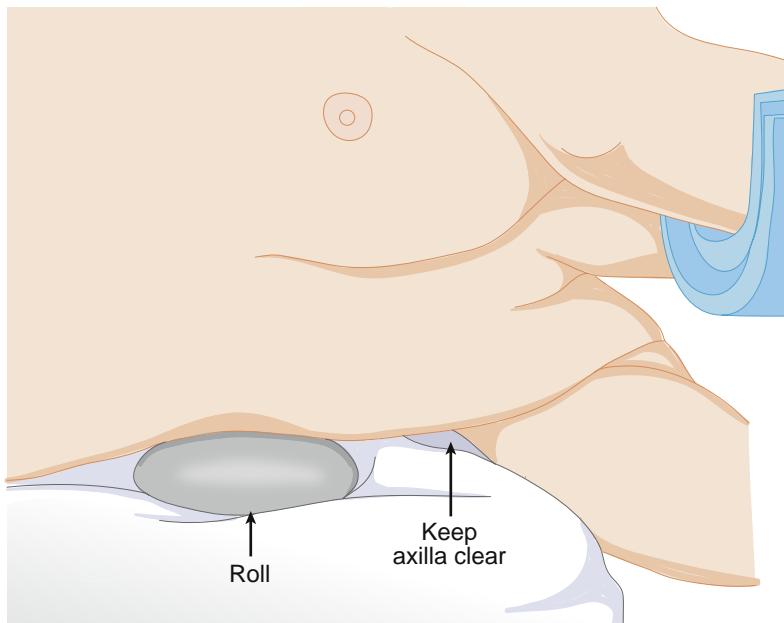
The lateral decubitus position (Fig. 34.11) is most frequently used for surgery involving the thorax, retroperitoneal structures, and hip. Positioning a patient in the lateral decubitus position requires the cooperation of the entire surgical staff. The nonoperative side is dependent and the dependent leg is flexed to minimize stretch of lower extremity nerves. Padding is placed between the knees to minimize excessive pressure on bony prominences. The torso must be balanced and supported both anteriorly and posteriorly. When a kidney rest is used for this purpose, it must be properly placed under the dependent iliac crest to prevent inadvertent compression of the inferior vena cava.

Patients may be laterally flexed while in the lateral position in order to gain better access to the thoracic cavity or

retroperitoneum during renal surgeries. The point of flexion and the kidney rest should lie under the iliac crest rather than the flank or ribcage to minimize compression of the dependent lung (Fig. 34.12). The dependent arm should be placed on a padded arm board perpendicular to the torso. The nondependent arm needs to be carefully supported (Fig. 34.13). Neither arm should be abducted more than 90 degrees. For some high thoracotomies, the nondependent arm may need to be elevated above the shoulder plane for exposure; however, vigilance is warranted to prevent neurovascular compromise. The patient's head must be kept in a neutral position to prevent excessive lateral rotation of the neck and to avoid stretch injuries to the brachial plexus. Often additional head support is required (Fig. 34.14). The dependent ear and eye may be at risk of injury and should be checked regularly.



**Fig. 34.13 Lateral decubitus position showing placement of arms and head.** Additional padding is under the headrest to ensure the alignment of the head with the spine. The headrest is kept away from the dependent eye.



**Fig. 34.14 Use of chest roll in the lateral decubitus position.** The roll, in this case, is a bag of intravenous fluid and is placed well away from the axilla to prevent compression of the axillary artery and brachial plexus.

The dependent brachial plexus and axillary vascular structures are at particular risk of pressure injury in the lateral decubitus position. In order to avoid compression, an axillary roll is frequently placed between the chest wall and the table just caudal to the dependent axilla (see Fig. 34.13). The purpose of the axillary roll is to protect the dependent shoulder and the axillary contents from the weight of the thorax. The axillary roll should never be placed in the axilla. Sometimes a beanbag is used for positioning without an axillary roll. In this scenario, the axilla should be checked to ensure that it is

free from compression. Regardless of the technique, the pulse should be monitored in the dependent arm for early detection of compression to axillary neurovascular structures. Vascular compression and venous outflow obstruction in the dependent arm are risks of the lateral decubitus position. Low pulse oximeter readings can be an early sign of compromised circulation. Similarly, hypotension measured in the dependent arm may be due to axillary arterial compression.

Pulmonary mechanics change in the lateral decubitus position.<sup>36</sup> In a patient who is mechanically ventilated, the



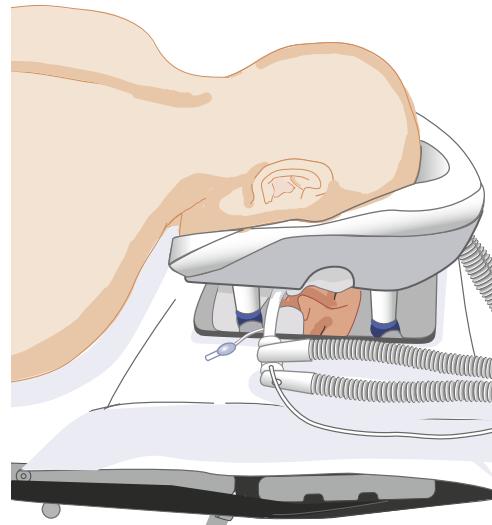
**Fig. 34.15 Prone position with Wilson frame.** Arms are abducted less than 90 degrees whenever possible, although greater abduction may be better tolerated while prone. Pressure points are padded, and the chest and abdomen are supported away from the bed to minimize abdominal pressure and to preserve pulmonary compliance. Soft head pillow has cutouts for eyes and nose and a slot to permit endotracheal tube exit. Eyes must be checked frequently.

combination of the lateral weight of the mediastinum and the disproportionate cephalad pressure of abdominal contents on the dependent lung favors overventilation of the nondependent lung. At the same time, the effect of gravity causes the pulmonary blood flow to the underventilated, dependent lung to increase. Consequently, ventilation-perfusion matching worsens, potentially affecting gas exchange and ventilation.

The lateral decubitus position is preferred during pulmonary surgery and one-lung ventilation. When the nondependent lung is collapsed, the minute ventilation is allocated to the dependent lung. This, combined with decreased compliance as a result of positioning, may further exacerbate the airway pressure required to achieve adequate ventilation. Head-down tilt in the lateral position worsens pulmonary function yet further, increasing shunt fraction.<sup>37</sup>

## PRONE

The prone or ventral decubitus position (Fig. 34.15) is primarily used for surgical access to the posterior fossa of the skull, the posterior spine, the buttocks and perirectal area, and the posterior lower extremities. The patient may receive either monitored anesthesia care or general anesthesia depending on the type of surgery and the patient's body habitus and comorbidities. When general anesthesia is planned, the airway is usually secured via an endotracheal tube while the patient is still supine. Special attention should be paid to securing and taping the endotracheal tube to prevent dislodgement while the patient is prone or during changes in position. Placing an anesthetized patient in the prone position requires the coordination of the entire surgical staff. The anesthesiologist is primarily responsible for coordinating the move while maintaining inline stabilization of the cervical spine and monitoring the endotracheal tube. An exception might be the patient in whom rigid pin fixation is used when the surgeon often holds the pin frame. The endotracheal tube should be disconnected from the circuit during the move from supine to prone in order to prevent dislodgement. Which, and how many, monitors and lines are disconnected during the move is up to the clinical



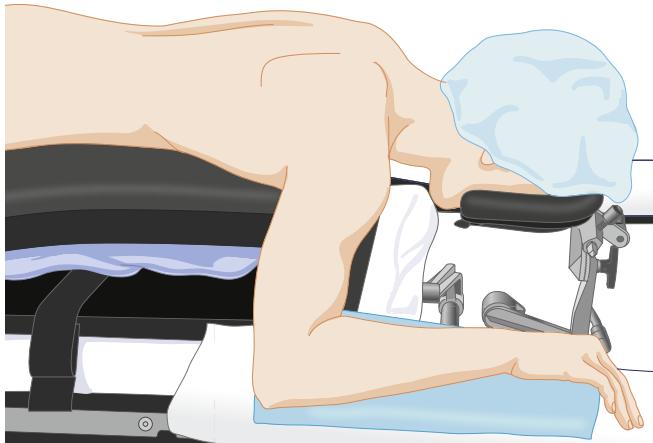
**Fig. 34.16 Mirror system for prone position.** Bony structures of head and face are supported, and monitoring of the eyes and airway is facilitated with a plastic mirror. Although not illustrated, the eyes should be taped closed.

judgement of the anesthesiologist for an individual patient. Lines and monitors connected to the inside arm (the arm moving the least during the move) can often be easily maintained without disconnecting. Ventilation and monitoring should be reestablished as rapidly as possible.

Prone head position is critical. For patients under sedation, the head may be turned to the side if neck mobility is adequate. During general anesthesia, the head is usually kept neutral using a surgical pillow, horseshoe headrest, or head pins. Weight should be on the bony facial prominences and not soft tissue and especially not on the eyes. The face is not always visible. Mirror systems are available to facilitate intermittent visual confirmation that the eyes are not compressed, although direct visualization or tactile confirmation is prudent (Fig. 34.16). Several commercially available pillows are specially designed for the prone position. Most pillows support the

forehead, malar regions, and chin, with a cutout for the eyes, nose, and mouth (see **Fig. 34.15**). The forehead and malar regions are supported by the horseshoe headrest and allow for reasonable access to the airway (**Figs. 34.17 and 34.18**). Pin fixation, which is most used in cranial and cervical surgery, is advantageous because there is no direct pressure on the face (**Fig. 34.19**). Patient movement must be prevented when the head is held in pins; movement in pins can result in scalp lacerations or a cervical spine injury. Both horseshoe and pin headrests attach to the operating room table with adjustable articulating supports. All articulating supports must be fully locked as failure of this bracketing device may lead to complications if the head suddenly drops.

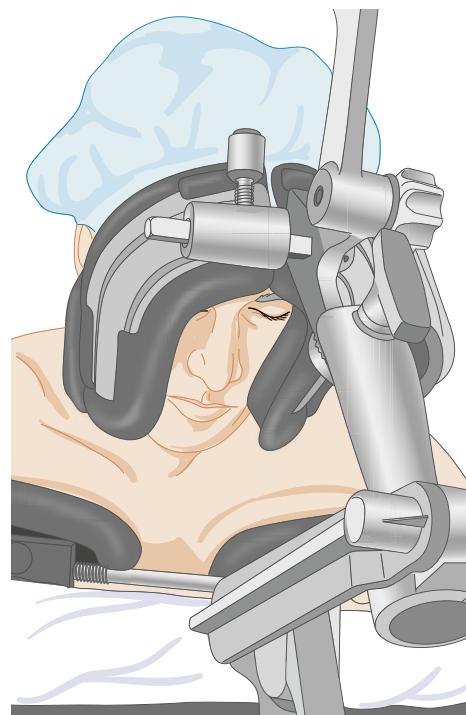
Regardless of the type of head-support technique, proper positioning must be frequently verified during the surgery, checking that there is no pressure on the eyes, that the airway is secure, and that the head weight lies on the bony facial prominences only. The prone position is a risk factor for perioperative visual loss (POVL), which is discussed separately in this chapter. If motor-evoked potentials are



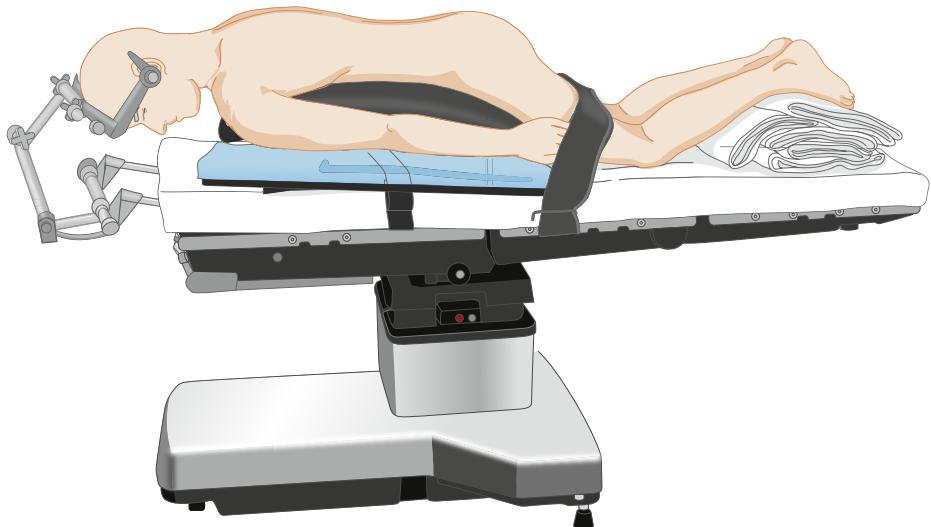
**Fig. 34.17 Prone position with horseshoe adapter.** Head height is adjusted to position the neck in a natural position without undue extension or flexion.

used during spine or neurosurgery, then the position of the tongue and placement of bite blocks must be frequently checked; bite injuries can be severe.<sup>38</sup>

A prone patient's legs should be padded and flexed slightly at the knees and hips. The arms may be positioned to the patient's sides or placed outstretched above the head. If the arms are at the patient's sides then they should be tucked in the neutral position. If the arms are outstretched above the head, the arms should be placed on arm boards with slight flexion at the elbows to prevent undue stretch on



**Fig. 34.18 Prone position with horseshoe adapter.** The face is seen from below. The horseshoe adapter permits superior access to the airway and visualization of eyes. The width may be adjusted to ensure proper support by facial bones.



**Fig. 34.19 Prone position with Mayfield head pins.** Rigid fixation is provided for the cervical spine and posterior intracranial surgeries. The head position may include neck torsion or flexion that affects the depth of the endotracheal tube, and extreme head positions may increase the risk of cervical cord injury.

the peripheral nerves. Extra padding under the elbow may be needed to prevent compression of the ulnar nerve. The arms should not be abducted greater than 90 degrees.

If the legs are in plane with the torso, then hemodynamic reserve is relatively maintained; however, if any significant lowering of the legs or tilting of the entire table occurs, then venous return may increase or decrease accordingly. The prone position does not alter the ability of pulse pressure variation to predict fluid responsiveness. However, the variation has been shown to be augmented at baseline; therefore, fluid responsiveness is observed at a slightly greater level of variation than when supine.<sup>39</sup>

When patients are in the prone position, weight should be distributed to the thoracic cage and bony pelvis, the abdomen should hang freely in order to prevent increases in intraabdominal and intrathoracic pressure. This is accomplished with specific types of prone beds or with gel or foam bolsters. The prone beds and bolsters all place support along each side of the patient from the clavicles to the iliac crests. Placement beyond the iliac crests can cause compression on the femoral vessels and femoral nerve. Some prone beds include the Wilson frame (see Fig. 34.15), Jackson table, Relton frame, and Mouradian/Simmons modification of the Relton frame. Breasts should be placed medially to the prone torso supports (or bolsters), and genitalia should be clear of compression.<sup>40</sup> During posterior spinal surgery, relatively low venous pressure is desirable to minimize bleeding and to facilitate surgical exposure. Elevated abdominal pressure can transmit elevated venous pressures to the abdominal and spine vessels, including the epidural veins, which lack valves. Increased abdominal pressure may also impede venous return through compression of the inferior vena cava, decreasing cardiac output.

Pulmonary function is usually better in the prone position than in the supine position.<sup>41,42</sup> The prone position has been used to improve respiratory function in patients with adult respiratory distress syndrome.<sup>43-45</sup> Under anesthesia, the prone position has advantages over the supine position with regard to lung volumes and oxygenation without adverse effects on lung mechanics,<sup>46,47</sup> including patients who are obese<sup>48</sup> (see also Chapter 58) and pediatric patients (see also Chapter 77).<sup>49</sup> Newer investigations using high-resolution imaging have shown the prone position to provide superior ventilation-perfusion matching in the posterior segments of the lung near the diaphragm when compared with the supine position. The aeration and ventilation of these posterior segments are better, while blood flow is maintained, despite their nondependent position.<sup>8,14</sup>

Other complications of the prone position include airway edema, eye injury, pressure injury, and inadvertent loss of the endotracheal tube, monitoring, and intravenous lines. For long cases, or cases with large intravascular volume shifts, consider checking and documenting an endotracheal cuff leak at the start and end of the case. Lines and tubes need to be placed and should be well secured prior to turning the patient prone.

## SITTING

The sitting position offers excellent surgical exposure to the upper posterior cervical spine and posterior fossa. Gravitational venous drainage of blood in the sitting position does

decrease blood in the operative field and therefore possibly reduces surgical blood loss.<sup>50</sup> The lawn or beach chair position is a variation of the sitting position and is commonly used for shoulder surgeries (Fig. 34.20). The lawn chair position is really a semi-sitting position, with the head of the patient more reclined than in the traditional sitting position. For the surgeon, its advantages versus the lateral decubitus position are superior access to the shoulder from both the anterior and posterior aspect and the potential for great mobility of the arm at the shoulder joint.<sup>51</sup> Access to the airway is generally excellent in the sitting position, facial swelling is minimized, and pulmonary mechanics are reasonably preserved (Chapter 57).

There are unique risks to the sitting position that require much vigilance. One of the most concerning risks is for venous air embolism (VAE). The veins lie above the level of the heart in this position; therefore, air entrainment through the veins to the heart is a real danger. Furthermore, dural veins are valveless and tented open by the cranium (Fig. 34.21; see also Chapter 57). Other complications from the sitting position include quadriplegia, spinal cord infarction, hemodynamic instability pneumocephalus, macroglossia, and peripheral nerve injuries.<sup>52,53</sup>

Placing an anesthetized patient in the sitting position requires flexion at the torso. Hip flexion should be less than 90 degrees in order to minimize stretch on lower extremity nerves (including the sciatic nerve). Arms are supported so that the shoulders are slightly elevated in order to ensure avoidance of traction on the shoulder muscles and potential stretching of upper extremity neurovascular structures. The knees are also usually slightly flexed for balance and to reduce stretching of the sciatic nerve, and the feet are supported and padded.<sup>54</sup> The patient's head must be specially fixed in the sitting position with either rigid pins or taped into a special headrest.

The head and neck position while in the sitting position has been associated with complications. Surgery in the sitting position was found to be a risk factor for cervical spinal cord injury in a review of the ASA Closed Claims Project database from 1970 to 2007.<sup>55</sup> Although the exact mechanism for cervical spinal cord injury is unknown, cervical hyperextension, cervical hyperflexion, or excessive cervical rotation have been implicated as risk factors. Extreme neck positions can impede both arterial and venous blood flow, causing hypoperfusion or venous congestion of the brain. The patient's cervical range of motion should be examined in the preoperative assessment, and adequate distance should be maintained between the mandible and the sternum when the cervical spine is flexed in order to provide for adequate arterial and venous blood flow.<sup>52,56,57</sup>

VAE is a constant concern in the sitting position due to the position of the surgical field above the level of the heart and the tented open dural venous sinuses. The reported incidence of VAE varies greatly in the literature due to a lack of standardization of measurement and grading scale for VAE. VAE can cause arrhythmias, oxygen ( $O_2$ ) desaturation, acute pulmonary hypertension, circulatory compromise, and cardiac arrest. If there is a patent foramen ovale (PFO), then the patient is at risk for a paradoxical arterial embolism causing stroke or myocardial infarction. Traditionally, preoperative contrast echocardiography is recommended to evaluate for a PFO. However, failure to detect a PFO on



**Fig. 34.20 Sitting position adapted for shoulder surgery, often called the lawn or beach chair position.** The arms must be supported to prevent stretching of the brachial plexus without pressure on the ulnar area of the elbow. As with all head-up positions, blood pressure should be regulated with the height of the brain in mind.



**Fig. 34.21 Sitting position with Mayfield head pins.** The patient is typically semi-recumbent rather than sitting; the legs are kept as high as possible to promote venous return. Arms must be supported to prevent shoulder traction and stretching of the brachial plexus. In a commonly used variation, the arms are placed on the abdomen and supported. The head support is preferably attached to the back section of the table to allow the back to be adjusted or lowered emergently without first detaching the head holder.

echocardiography does not ensure that the intraatrial septum is intact.<sup>58</sup> The presence of a PFO has generally been considered a contraindication to the sitting position. A recent review suggested that paradoxical VAE is so rare that the presence of a PFO should not necessarily preclude placing the patient in the sitting position. This study found that a VAE was detected in 40% of patients with a known PFO and that no paradoxical embolism was detected.<sup>59</sup> The decision to proceed should be made with patient informed consent and with a discussion between the surgeon and anesthesiologist.

Continuous monitoring for VAE during surgery in the sitting position is essential. There is no standard for type of VAE monitor. Clinical severity of VAE depends on the amount of air and the speed of entrainment. Extrapolation from animal studies suggests that 3 to 5 mL/kg is a lethal amount of air for an adult human, but in reality much less could be required. Transesophageal echocardiography (TEE) is the most sensitive monitor, able to detect as little as 0.02 mL/kg of air. In fact, TEE is so sensitive that some degree of entrained air can be demonstrated in a large majority of patients during neurosurgery in the sitting position.<sup>58,60</sup> Transthoracic Doppler (TTD) is the most sensitive noninvasive monitor with detection rates of approximately 0.05 mL/kg of air. The TTD probe is placed on either the left or right sternal border between the second to fourth intercostal spaces. Transcranial Doppler (TCD) is a monitor of the middle cerebral artery and is nearly as sensitive as TEE. Pulmonary artery catheters, esophageal stethoscopes, and end-tidal carbon dioxide monitors are all much less sensitive monitors. Electrocardiographic and pulse oximeter changes are later findings.<sup>61,62</sup>

Treatment for VAE includes first stopping further air entrainment. The surgeon is asked to stop operating, to flood the field with normal saline, and possibly apply bone wax. The inspired percent of O<sub>2</sub> is changed to 100%. This will aid in treatment during hypoxemia or hypotension and may help reduce the volume of the air embolism via denitrogenation. Hemodynamic compromise is treated with intravenous fluids and vasoactive agents. Consideration is given to placing the patient in left side down and Trendelenburg in order to move an air lock in the right ventricular outflow track (although this can be difficult or impossible in some surgeries).<sup>61</sup> A central venous catheter is often placed preoperatively in order to aspirate entrained air.<sup>58</sup> An ex-vivo study examining different central venous catheter types and positions found that a multiorifice catheter and single orifice catheter both aspirated 50% to 60% of experimentally introduced air.<sup>63</sup>

Pneumocephalus, quadriplegia, spinal cord infarction, cerebral ischemia, and peripheral nerve injuries are all risks of sitting positions. Pneumocephalus is almost universally found on postoperative imaging from cervical or posterior fossa surgery performed in the sitting position. Tension pneumocephalus, which is accumulation of air in the subdural or ventricular space causing pressure on intracranial structures, is very rare but reported after neurosurgery in the sitting position. Prompt diagnosis and surgical evacuation of air is the treatment. Positioning complications causing quadriplegia or spinal cord infarction are thought to be caused by impaired arterial perfusion with hyperextension, hyperflexion, or excessive rotation of the neck.

Theories relating the sitting positions to cerebral ischemia include reduced cerebral perfusion caused by reduced cardiac output, deliberate or permissive hypotension, loss of compensatory mechanisms caused by anesthesia, failure to compensate for the height of the head in the regulation of the blood pressure, dynamic vertebral artery narrowing or occlusion with the rotation of the head, and air emboli. Investigators have demonstrated positional effects on cerebral oxygen saturation,<sup>64</sup> as well as transient reductions in cerebral oxygen saturation associated with hypotensive periods during shoulder surgeries in the sitting position that reversed after use of ephedrine and phenylephrine to restore cerebral perfusion pressure.<sup>64-66</sup> One observational study of 124 patients undergoing shoulder arthroscopy demonstrated cerebral desaturation by oximetry in 80% of those who were in the lawn or beach chair position and none in the lateral decubitus position.<sup>67</sup> Cerebral oxygen saturation monitoring may be helpful; however, no gold standard limits exist, and values may change along with alterations in patient position and carbon dioxide concentration. Therefore, if measured, trends in cerebral oxygen saturation are best interpreted during periods of constant ventilation and patient position.<sup>68,69</sup> Reasonable recommendations for patients undergoing surgery in the sitting position are to monitor blood pressure carefully in reference to the level of the brain, avoid and rapidly treat any hypotension or bradycardia, and position the head carefully to avoid extreme positions that may compromise cerebral vessels.<sup>70</sup>

Hypotension is a known and very common problem for anesthetized patients in the sitting position. Pooling of blood in the lower body places anesthetized patients in the sitting position at particular risk to hypotensive episodes. Studies reveal that mean arterial pressure, systolic blood pressure, and cardiac index all decrease in the sitting position.<sup>52</sup> Therefore, placement of the patient into the sitting position should be incremental in order to adjust for hemodynamic changes. Intravenous fluids and vasopressors should be in-line and ready.

## ROBOTIC SURGERY

Since its introduction approximately 30 years ago, the use and scope of robotic surgery has expanded greatly. Robotic surgery is now the norm for many types of urologic and gynecologic operations,<sup>71,72</sup> and is extending to other abdominal operations, thoracic surgery, and head and neck operations. Robotic surgery offers technical advantages for surgeons regarding range of motion and accuracy of laparoscopic instrumentation. Once the robot is docked, direct access to the patient is limited. It is therefore imperative that all monitors, lines, and invasive lines are placed prior to docking the robot, and that proper padding and positioning are completed.

Most of the literature about robotic positioning involves urologic and gynecologic operations, which are generally performed with the patient in steep Trendelenburg (30-45 degrees) and lithotomy with arms tucked in neutral position to the sides. The patient must be very well secured in order to avoid slipping in steep Trendelenburg. Non-slip mattresses, chest straps, and shoulder braces may be useful, but shoulder braces are also reported to cause brachial plexus injuries due to stretch between the shoulder and neck. If

shoulder braces are employed, monitoring for excessive stretch at the patient's neck is essential. The endotracheal tube should be well secured to avoid migration. Often a tray or table is placed above the patient's face in order to provide protection from laparoscopic equipment.<sup>73-75</sup> It may be prudent to trial the steep Trendelenburg prior to docking the robot to ensure that the patient is properly positioned, does not slip, and can tolerate steep Trendelenburg from a physiologic standpoint.

Physiologic changes during robotic surgery are due to both laparoscopic insufflation as well as positioning. Hemodynamic changes are largely due to laparoscopic insufflation, whereas changes in respiratory mechanics are also affected by positioning. Functional residual capacity is decreased with both laparoscopy and further decreased with the addition of steep Trendelenburg. This is due to a combination of pressure of abdominal contents from laparoscopy and Trendelenburg pushing up on the diaphragm, and can also be worsened by chest fixation that is applied to prevent the patient from slipping off the table. Peak and plateau airway pressures have been shown to rise as much as 50%. Between changes in pulmonary compliance, decreased functional residual capacity, and the need for increased minute ventilation with carbon dioxide insufflation, intraoperative mechanical ventilation can be quite challenging during these cases.<sup>73-76</sup>

The incidence of positioning complications from robotic surgery vary substantially from 0.8% to 6.6%; most studies indicate an incidence of less than 1%.<sup>77-79</sup> One study found longer operative times, higher ASA physical status, and increased intravenous fluid administration to be risk factors for intraoperative positioning complications.<sup>77</sup> A history of prior abdominal surgery was the only associated risk factor found in a study of gynecologic robotic surgeries.<sup>78</sup> Eye injury, peripheral nerve injuries, rhabdomyolysis, and compartment syndrome were the most frequent positioning complications found in patients with robotic assisted radical prostatectomies. Incidence of injury in this study was not different between robotic versus traditional open prostatectomy.<sup>79</sup> In a recent survey of ASA members, 21.7% of responders answered "yes" that they have experienced a "complication related to Trendelenburg positioning (during robotic surgery)." Airway and facial edema, as well as brachial plexus injuries, were the most common recalled complications in this survey.<sup>80</sup> When steep Trendelenburg is used, consideration should be given to documenting the endotracheal tube airway leak at the start and at the end of the surgical procedure prior to extubation.

## Peripheral Nerve Injury

Peripheral nerve injury remains a serious perioperative complication and a significant source of professional liability despite its infrequent incidence. The ASA states that "postoperative signs and symptoms related to peripheral nerve injury...may include but are not limited to paresthesias, muscle weakness, tingling, or pain in the extremities."<sup>4</sup> Studies of the ASA Closed Claims Project database (in 1990 and 1999) brought awareness of the incidence of perioperative peripheral nerve injury, which was found to be between 0.03% and 0.11%. However, according to

this database, peripheral nerve injuries represented 22% of all claims. In fact, peripheral nerve injury has been second only to death as the leading cause of claims against anesthesiologists.

The overall incidence of peripheral nerve injury claims had increased from 15% in the 1970s.<sup>1,2,81,82</sup> According to a review of 5280 closed claims (from 1990 to 2007), most patients with nerve injuries do recover, however, up to 23% of peripheral nerve injuries remain permanent.<sup>4</sup>

In the closed claims database study, ulnar neuropathy is the most common lesion representing 28% of all peripheral nerve injury claims, followed by the brachial plexus (20%), lumbosacral nerve root (16%), and spinal cord (13%).<sup>2,3</sup> Interestingly, the distribution of nerve injury claims has changed over time. From 1980 through 1984, ulnar neuropathy claims decreased from 37% to 17% in the 1990s, and spinal cord injury claims increased from 8% in 1980 through 1984 to 27% in the 1990s. The incidence of spinal cord injury and lumbosacral nerve root neuropathy increased over this study period and were predominantly associated with regional anesthesia. Epidural hematoma and chemical injuries represented 29% of the known mechanisms of injury among the claims filed.<sup>2,83,84</sup>

In a different retrospective study of 380,680 patients at a single university tertiary care institution, 112 peripheral nerve injuries were observed in the perioperative period, an incidence of 0.3%.<sup>85</sup> Most injuries were sensory (60%) or combined sensory and motor (24%), with only 14% pure motor injuries. This study provides a significantly different numerator and denominator than the ASA Closed Claims Project, and its data contrast with the most recent claims data in which more claims were filed after the administration of regional anesthesia.

Peripheral nerves are made up of bundles of endoneurium wrapped axons bundled into fascicles, which are wrapped in perineurium. Schwann cells provide a myelin sheath to enhance conduction for myelinated nerves. Peripheral nerves are vascular metabolically active structures. The vasa nervorum provides blood flow via a capillary network.<sup>86</sup> Injuries are classified in neurology by the Seddon or Sunderland Classifications. These classifications are based upon neuronal anatomy and can be clinically correlated.<sup>87</sup> There are three main mechanisms for peripheral nerve injury: stretch, compression, and transection. Transection can be partial or complete and can be due to sharp or blunt transection. Compression injuries can be due to compression of vascular structures causing ischemic injury or due to direct nerve or myelin compression.<sup>87</sup> All of these mechanisms can affect sensory and motor nerves.<sup>88</sup>

Perioperative peripheral nerve injury is complex and multifactorial in etiology. Because sensation is blocked by unconsciousness or regional anesthesia, early warning symptoms of pain with normal spontaneous repositioning are absent.<sup>81,89</sup> Patient comorbidities that contribute to peripheral nerve injuries include: hypertension, diabetes, peripheral vascular disease, older age, and heavy alcohol and tobacco use.<sup>4</sup> Extremes of weight, both low body mass index and obesity, are also risk factors. General and epidural anesthesia appeared to be risk factors, compared with monitored anesthesia care, spinal anesthesia, and peripheral nerve blocks. Prolonged surgical times are an additional risk factor.<sup>1,85</sup>

## BOX 34.1 Summary of the 2018 American Society of Anesthesiologists Practice Advisory for the Prevention of Perioperative Peripheral Neuropathies

### Preoperative Assessment

- Review a patient's preoperative history and perform a physical examination to identify: body habitus, preexisting neurologic symptoms, diabetes mellitus, peripheral vascular disease, alcohol dependency, arthritis, and sex.
- When judged appropriate, ascertain whether patients can comfortably tolerate the anticipated position.

### Upper Extremity Positioning

- Positioning Strategies to Reduce Perioperative Brachial Plexus Neuropathy
  - When possible, limit arm abduction in a supine patient to 90 degrees. The prone position may allow patients to comfortably tolerate abduction of their arms to greater than 90 degrees.
- Positioning Strategies to Reduce Perioperative Ulnar Neuropathy
  - Supine Patient with Arm on an Armboard: Position the upper extremity to decrease pressure on the postcondylar groove of the humerus (ulnar groove). Either supination or the neutral forearm positions may be used to facilitate this action.
  - Supine Patient with Arm tucked at Side: Place the forearm in a neutral position.
  - Flexion of the Elbow: When possible, avoid flexion of the elbow to decrease the risk of ulnar neuropathy.
- Positioning Strategies to Reduce Perioperative Radial Neuropathy
  - Avoid prolonged pressure on the radial nerve in the spiral groove of the humerus.
- Positioning Strategies to Reduce Perioperative Median Neuropathy
  - Avoid extension of the elbow beyond the range that is comfortable during the preoperative assessment to prevent stretching of the median nerve.
  - Periodic assessment of upper extremity position during procedures
  - Periodic perioperative assessments may be performed to ensure maintenance of the desired position.

### Lower Extremity Positioning

- Positioning Strategies to Reduce Perioperative Sciatic Neuropathy
  - Stretching of the Hamstring Muscle Group: Positions that stretch the hamstring muscle group beyond the range that

is comfortable during the preoperative assessment may be avoided to prevent stretching of the sciatic nerve.

- Limiting Hip Flexion: Since the sciatic nerve or its branches cross both the hip and the knee joints, assess extension and flexion of these joints when determining the degree of hip flexion.
- Positioning Strategies to Reduce Perioperative Femoral Neuropathy
  - When possible, avoid extension or flexion of the hip to decrease the risk of femoral neuropathy.
- Positioning Strategies to Reduce Perioperative Peroneal Neuropathy
  - Avoid prolonged pressure on the peroneal nerve at the fibular head.

### Protective Padding

- Padded armboards may be used to decrease the risk of upper extremity neuropathy.
- Chest rolls in the laterally positioned patient may be used to decrease the risk of upper extremity neuropathy.
- Specific padding to prevent pressure of a hard surface against the peroneal nerve at the fibular head may be used to decrease the risk of peroneal neuropathy.
- Avoid the inappropriate use of padding (padding too tight) to decrease the risk of perioperative neuropathy.

### Equipment

- When possible, avoid the improper use of automated blood pressure cuffs on the arm to reduce the risk of upper extremity neuropathy.
- When possible, avoid the use of shoulder braces in a steep head-down position to decrease the risk of perioperative neuropathies.

### Postoperative Assessment

- Perform a simple postoperative assessment of extremity nerve function for early recognition of peripheral neuropathies.

### Documentation

- Document specific perioperative positioning actions that may be useful for continuous improvement processes.

From the Practice Advisory for the prevention of perioperative peripheral neuropathies: an updated report by the American Society of Anesthesiologists Task Force on prevention of perioperative peripheral neuropathies. *Anesthesiology*. 2018;128:11–26.

Ascertaining the presence of preoperative neuropathies and paresthesias is particularly important as injured nerves are more susceptible to injury in a phenomenon described as the double crush syndrome. The theory is that two separate subclinical nerve insults can act synergistically to produce a clinically significant neuropathy.

Usually, the exact mechanism of injury for a particular patient cannot be determined.<sup>2</sup> With the exception of spinal cord injuries, the mechanism of nerve injury remains incompletely explained by scientific studies. Most nerve injuries, particularly those to nerves of the upper extremity such as the ulnar nerve and brachial plexus, occurred in the presence of adequate positioning and padding. Nevertheless, we must prevent nerve injuries to the best of our abilities. The ASA released an updated practice advisory in 2018 to help guide prevention of perioperative nerve injury (Box 34.1).<sup>4</sup> Positions that permit stretching of the nerves

and pressure to anatomic locations known to carry nerves prone to injury must be avoided, such as the ulnar cubital tunnel and the peroneal nerve coursing over the fibular head (Table 34.1). Padding and support should distribute weight over as wide an area as possible; however, no padding material has been shown to be superior. Whenever possible, the patient's position should appear natural.

## ULNAR NERVE INJURY

The ulnar nerve lies in a superficial position at the elbow. Morbidity associated with ulnar neuropathy can be severe. In a prospective study among 1502 patients undergoing noncardiac surgery, 7 patients developed perioperative ulnar neuropathy, of which 3 patients had residual symptoms after 2 years.<sup>90</sup> In a study on the effect of arm position on the ulnar nerve somatosensory-evoked potentials

**TABLE 34.1** Most Common Nerve Injuries in the American Society of Anesthesiologists Closed Claims Database 1990–2010

Nerve Injury	Recommendations for Prevention
Ulnar nerve (14%)	<ul style="list-style-type: none"> <li>■ Avoid excessive pressure on the postcondylar groove of the humerus.</li> <li>■ Keep the hand and forearm either supinated or in a neutral position.</li> </ul>
Brachial plexus (19%)	<ul style="list-style-type: none"> <li>■ When utilizing a steep head-down (Trendelenburg) position:           <ul style="list-style-type: none"> <li>■ Avoid the use of shoulder braces and beanbags when possible (use nonsliding mattresses).</li> <li>■ Avoid abduction of the arm(s) when possible.</li> <li>■ Avoid excessive lateral rotation of the head, either in the supine or prone position.</li> <li>■ Limit abduction of the arm to &lt;90 degrees in the supine position.</li> <li>■ Avoid the placement of high “axillary” roll in the decubitus position—keep the chest roll out of the axilla to avoid neurovascular compression.</li> <li>■ Use ultrasound to locate the internal jugular vein for central line placement.</li> </ul> </li> </ul>
Spinal cord (25%) and lumbosacral nerve root or cord (18%)	<ul style="list-style-type: none"> <li>■ Be aware that the fraction of spinal cord injuries is increasing, probably in relation to use of regional anesthesia.</li> <li>■ Avoid severe cervical spine flexion or extension when possible.</li> <li>■ Follow current guidelines for regional anesthesia in patients on anticoagulant therapy.</li> </ul>
Sciatic and peroneal nerves (7%)	<ul style="list-style-type: none"> <li>■ Minimize the time in the lithotomy position.</li> <li>■ Use two assistants to coordinate simultaneous movement of both legs to and from the lithotomy position.</li> <li>■ Avoid excessive flexion of the hips, extension of the knees, or torsion of the lumbar spine.</li> <li>■ Avoid excessive pressure on peroneal nerve at the fibular head.</li> </ul>

ASA, American Society of Anesthesiologists.

Data from ASA Closed Claims Project 1990 to 2010.

Practice advisory for the prevention of perioperative peripheral neuropathies 2018: An updated report by the American Society of Anesthesiologists Task Force on Prevention of Perioperative Peripheral Neuropathies. *Anesthesiology*. 2018;128:11–26.

(SSEPs) in 15 healthy awake male volunteers, the supinated position was associated with the least pressure on the ulnar nerve, and the neutral position was the next most favorable. When in the neutral position on a surgical armrest, pressure decreased as the arm was abducted between 30 and 90 degrees. Interestingly, not all patients had symptoms of nerve compression when the SSEP was abnormal.<sup>17</sup> Current consensus is that the cause of ulnar nerve palsy is multifactorial and not always preventable.<sup>91,92</sup> In a large retrospective review of perioperative ulnar neuropathy lasting longer than 3 months, the onset of symptoms occurred more than 24 hours postoperatively in 57% of patients; 70% were men and 9% experienced bilateral symptoms. Very thin or obese patients were at increased risk, as were those with prolonged postoperative bed rest. No association with intraoperative patient position or anesthetic technique was confirmed.<sup>93</sup> The ASA Closed Claims Project also demonstrated that perioperative ulnar neuropathy occurred predominately in men, in an older population, and with

a delayed onset (median of 3 days).<sup>2</sup> The large predominance of ulnar injury in men may possibly be explained by anatomic differences. Men have a more developed and thickened flexor retinaculum with less protective adipose tissue and a larger tubercle of the coronoid process that can predispose them to nerve compression in the cubital tunnel.<sup>94,95</sup> In the published ASA Closed Claims Project data, only 9% of ulnar injury claims had an explicit mechanism of injury, and in 27% of claims, the padding of the elbows was explicitly documented.<sup>2</sup> Postoperative ulnar nerve palsy can occur without any apparent cause, even when padding and positioning of the patient’s arm was carefully managed and documented in the anesthetic record.<sup>18</sup>

## BRACHIAL PLEXUS INJURY

The brachial plexus is susceptible to stretching because of its long superficial course from the neck to the arm via the axilla with two points of fixation—the cervical vertebrae and the axillary fascia. The nerves are vulnerable to compression as they pass between the clavicle and the first rib because of the proximity and mobility of both the clavicle and the humerus (see Fig. 34.6). Among patients undergoing noncardiac surgeries, the incidence of brachial plexus injury is reported to be 0.02%.<sup>96</sup> After brachial plexus injury, the patient often complains of sensory deficit in the distribution of the ulnar nerve. This symptom is most commonly associated with intraoperative arm abduction greater than 90 degrees, lateral rotation of the head away from the side of the injury, asymmetric retraction of the sternum for internal mammary artery dissection during cardiac surgery, or direct trauma or compression. To avoid injury, patients should ideally be positioned with the head midline, arms kept at the sides, the elbows mildly flexed, and the forearms supinated, without pressure on the shoulders or the axilla.

Brachial plexus injury is particularly associated with the use of shoulder braces in patients undergoing surgery in the Trendelenburg position. Medial placement of the braces can compress the proximal roots, and lateral placement of the braces can stretch the plexus by displacing the shoulders against the thorax (see Fig. 34.6). The patient with injury often complains of painless motor deficit in the distribution of the radial and median nerves; however, pain may also be present. A report of three cases of upper- and middle-trunk brachial plexopathy after robotic prostatectomy highlights the potential risk of a combination of compression of the shoulder girdle against the thorax in the steep Trendelenburg position with abduction of an arm.<sup>26</sup> Signs of vascular compromise to the upper extremities, such as difficulty obtaining consistent blood pressure or a poor pulse oximetry signal, may be indications of compromise to the neurovascular bundle as reported in a case of bilateral injury related to shoulder braces with abduction of the arms in the Trendelenburg position.<sup>24</sup> Studies of the brachial plexus tension test in human volunteers and nerve strain in cadavers have demonstrated deleterious positional elements including arm abduction, rotation, or flexion of the head away from the affected arm, elbow and wrist extension, and depression of the shoulder girdle.<sup>25</sup> For transaxillary robotic thyroidectomy, a recently developed approach has the arm abducted to 180 degrees. An incidence of brachial plexus injury

has been reported to be 0.3%.<sup>97</sup> When an extreme position is used, neurophysiologic monitoring, such as motor-evoked potentials and SSEPs, has been shown to detect an evolving injury and allow for repositioning to prevent permanent damage.<sup>98,99</sup> Nerve function monitoring may therefore become increasingly common with newer surgical techniques that carry increased risk related to patient positioning.

In patients undergoing cardiac surgery requiring median sternotomy, brachial plexus injury has been specifically associated with the C8 to T1 nerve roots. In a prospective study in which the incidence of injury was 4.9%, 73% of the injuries occurred on the same side as the internal jugular vein cannulation; however, this study antedated the widespread use of ultrasound to guide cannulation.<sup>100</sup> Unilateral sternal retraction to harvest the mammary artery is associated with brachial plexus dysfunction, presumably caused by stretching the nerves. SSEP monitoring of the brachial plexus during sternal retraction has been shown to predict injury.<sup>101</sup>

In the 1999 ASA Closed Claims Project report, 10% of brachial plexus injuries were directly attributed to patient positioning. Of those, one half involved the use of shoulder braces in patients in the Trendelenburg position.<sup>2</sup> Consequently, nonsliding mattresses should be used, along with a concerted effort to avoid compression of the shoulders as much as possible.<sup>21,22</sup> Of the 311 brachial plexus injuries in the ASA Closed Claims Project, 59 (19%) occurred after a regional block without general anesthesia, including axillary and interscalene blocks.<sup>2</sup> In those cases, the role of patient positioning cannot be determined.

## OTHER UPPER EXTREMITY NERVE INJURY

In a retrospective study of 1000 consecutive spine surgeries that used SSEP monitoring, five arm positions were compared regarding SSEP changes in the upper extremities. A modification of the arm position reversed 92% of upper extremity SSEP changes. The incidence of position-related upper extremity SSEP changes was significantly higher in the prone “superman” (7%) and lateral decubitus (7.5%) positions, compared with the supine arms out, supine arms tucked, and prone arms tucked positions (1.8%-3.2%). Reversible SSEP changes were not associated with postoperative deficits (Chapter 39).<sup>24</sup>

Although quite rare, the radial nerve can be injured from direct pressure as it traverses the spiral groove of the humerus in the lower one third of the arm. The injury often exhibits a wrist drop with an inability to abduct the thumb or extend the metacarpophalangeal joints. An isolated median nerve injury most often occurs during the insertion of an intravenous needle into the antecubital fossa in a patient who has been anesthetized where the nerve is adjacent to the medial cubital and basilic veins. Patients with this injury are unable to oppose the first and fifth digits and have decreased sensation over the palmar surface of the lateral three and a half fingers. Surprisingly, in an evaluation of the ASA Closed Claims Project database from 1970 to 2007, peripheral intravenous and arterial line insertion accounted for 2.1% of all claims filed, particularly among patients who underwent cardiac surgery where the arms were tucked and

the lines were not visible for inspection.<sup>102</sup> Nerve injury accounted for 17% of intravenous line complications, second only to skin slough or necrosis (28%) and swelling, inflammation, and infection (17%).

## LOWER EXTREMITY NERVE INJURY

Injuries to the sciatic and common peroneal nerves occur most often in the lithotomy position. Because of its fixation between the sciatic notch and the neck of the fibula, the sciatic nerve can be stretched with external rotation of the leg. The sciatic nerve and its branches cross the hip and knee joints and are stretched by hyperflexion of the hips or extension of the knees. The common peroneal nerve, a branch of the sciatic, is most often damaged from the compression between the head of the fibula and an external structure, such as the frame of a leg support. Most often, patients who suffer a peroneal nerve injury will complain of a foot drop and the inability to extend the toes in a dorsal direction or evert the foot. In a prospective study of 991 patients undergoing surgery under general anesthesia in the lithotomy position, the incidence of lower extremity neuropathies was 1.5%, with injuries to the sciatic and peroneal nerves representing 40% of the cases. Interestingly, symptoms were predominantly paresthesia, with onset within 4 hours of surgery and resolution generally within 6 months. No motor deficits were noted, but in a previous retrospective study, the same authors found the incidence of severe motor disability in patients who underwent surgery in the lithotomy position to be 1 in 3608.<sup>103,104</sup>

Injury to the femoral or obturator nerves generally occurs from lower abdominal surgical procedures with excessive retraction. The obturator nerve can also be injured during a difficult forceps delivery or by excessive flexion of the thigh to the groin. A femoral neuropathy will exhibit decreased flexion of the hip, decreased extension of the knee, or a loss of sensation over the superior aspect of the thigh and medial or anteromedial side of the leg. An obturator neuropathy will exhibit an inability to adduct the leg with decreased sensation over the medial side of the thigh.

In a retrospective review of 198,461 patients undergoing surgery in the lithotomy position from 1957 to 1991, injury to the common peroneal nerve was the most common lower extremity motor neuropathy, representing 78% of nerve injuries. A potential cause of the injury was the compression of the nerve between the lateral head of the fibula and the bar holding the legs. When the “candy cane” stirrups are used, special attention must be paid to avoid compression (see Fig. 34.9). The injury was more common with patients who had low body mass index, recent cigarette smoking, or prolonged duration of surgery.<sup>103</sup> Perhaps as a result of an increased awareness of potential injuries, no lower extremity motor neuropathies were reported in a prospective review of 991 patients undergoing surgery in the lithotomy position from 1997 to 1998. Paresthesias in the distribution of the obturator, lateral femoral cutaneous, sciatic, and peroneal nerves were reported in 1.5% of patients, and nearly all recovered. Surgical times longer than 2 hours were significantly associated with this complication.<sup>104</sup>

## EVALUATION AND TREATMENT OF PERIOPERATIVE NEUROPATHIES

When a nerve injury becomes apparent postoperatively, it is essential to perform and document a directed physical examination to correlate the extent of sensory or motor deficits with the preoperative examination as well as any intraoperative events. It is prudent to seek neurologic consultation to help define the neurogenic basis, localize the site of the lesion, and determine the severity of injury for guiding prognostication. With proper diagnosis and management, most injuries resolve, but months to years may be required.<sup>88,105,106</sup> In addition, perioperative neuropathies associated with pain must be differentiated from surgically induced neuropathic pain, which is receiving increasing attention by surgeons because it affects an estimated 10% to 40% of surgical patients postoperatively.<sup>107</sup>

If a new sensory or motor deficit is found postoperatively, then electrophysiologic evaluation by a neurologist within the first week may provide useful information concerning the characteristic and temporal pattern of the injury. Another examination after 4 weeks, when enough time has elapsed for the electrophysiologic changes to evolve, will provide more definitive information about the site and severity of the nerve injury. Regardless, electrophysiologic testing must be interpreted within the clinical context. No single test can define the cause of injury. Nerve conduction studies may be useful to evaluate potential peripheral nerve injuries, as they permit the assessment of both motor and sensory nerves. To evaluate motor integrity, the nerve is supramaximally stimulated at two points along its course, and a recording is made of the electrical response of one of the muscles that it innervates. The size of the muscle action potential provides an estimate of the number of motor axons and muscle fibers that are activated by the stimulus. For sensory conduction studies, the nerve fiber is supramaximally stimulated at one point and the sensory nerve action potential is recorded from another point. The latency of the response can be interpreted as a reflection of the number of functioning sensory axons. Nerve conduction studies are useful for several reasons; they may reveal the presence of a subclinical polyneuropathy that made the individual nerves more susceptible to injury and help distinguish between axon loss and demyelination, which has significant implications regarding course and overall prognosis.

For motor neuropathy, an electromyogram can be performed to characterize the injury. An electromyographic examination involves recording the electrical activity of a muscle from a needle electrode inserted within it. If present, abnormalities may point to the affected component in the motor unit, which consists of the anterior horn cell, its axon and neuromuscular junctions, and the muscle fibers that it innervates. Certain findings are suggestive of denervation, including the presence of abnormal spontaneous activity in the resting muscle (fibrillation potentials and positive sharp waves, which results from muscle irritability) and increased insertion activity. Insertion activity increases within a few days of muscle denervation, whereas abnormal spontaneous activity takes 1 to 4 weeks to develop, depending on the distance from the nerve lesion to the muscle. Depending on the pattern of abnormalities, an electromyographic study may distinguish between radiculopathies, plexopathies, and neuropathies.

Most sensory neuropathies are generally transient and require only reassurance to the patient with follow-up visits, whereas most motor neuropathies include demyelination of peripheral fibers of a nerve trunk (neurapraxia) and generally take 4 to 6 weeks for recovery. Injury to the axon within an intact nerve sheath (axonotmesis) or complete nerve disruption (neurotmesis) can cause severe pain and disability. When reversible, recovery often takes 3 to 12 months. Interim physical therapy is recommended to prevent contractures and muscle atrophy.<sup>105,106</sup>

## Pressure Injuries

Pressure injuries are a significant source of patient morbidity and healthcare expenditures in the United States and internationally. Approximately 23% of all pressure ulcers occur while patients are in operating rooms.<sup>108</sup> General anesthesia and length of surgical procedure are both risk factors for pressure injury development. The National Pressure Ulcer Advisory Panel recently revised their definitions and classification scales for pressure injuries, formerly referred to as pressure ulcers.<sup>109</sup> Pressure injury is injury to the skin, and/or underlying tissue, due to pressure or shearing forces. Currently, there are no universal guidelines for pressure injury prevention. The Association of Perioperative Registered Nurses and the Joint Commission have statements issued stating that the prevention of pressure injuries is a joint responsibility shared by all members of the healthcare team. Understanding the risks of pressure injury is essential to preventing their occurrence.

Often early signs of pressure injury start with nonblanching skin erythema. The skin is more resistant to pressure injury than muscle and can actually mask a more extensive injury underneath.<sup>110</sup> This is likely due to increased O<sub>2</sub> requirements of muscle. Pressure injuries associated with operations are often not seen at the time of operation but could be diagnosed days after.<sup>111,112</sup> In the supine position, areas most at risk include the sacrum, heels, and occiput. In the prone position, the chest and knees are at highest risk for pressure injury, and in the sitting position, the ischial tuberosities are at greatest risk.<sup>74</sup>

Factors contributing to the development of pressure injuries include pressure over bony prominences, shear force, skin breakdown, compromised blood flow, immobility, and decreased sensation. Infection, inflammation, edema, and steroids are all also contributing factors.<sup>113</sup> Patient comorbidities such as diabetes, peripheral vascular disease, obesity, low body mass index, and poor nutrition are also known risks.<sup>108</sup>

There are case reports, and very few larger studies, assessing specific medical device-related pressure injuries. One retrospective study found that approximately 0.65% of all pressure injuries were due to medical devices. Nasal cannulas, endotracheal tubes, nasogastric tubes, and cervical collars were all associated with pressure injuries.<sup>114</sup>

Hypothermia and hypotension during surgery, such as during cardiopulmonary bypass (CPB) surgery, may increase the incidence of these complications. Pressure alopecia, caused by ischemic hair follicles, is related to prolonged immobilization of the head with its full weight falling on a limited area, usually the occiput. Hard objects should

not be placed under the head as they may create focal areas of pressure. Consequently, ample cushioning of the head and, if possible during prolonged surgery, periodic rotation of the head, are prudent to redistribute the weight.

## Bite Injuries

Transcranial motor-evoked potentials (Tc-MEPs) are increasingly used for both spine surgical procedures and also neurosurgical procedures. Tc-MEPs involve contraction of the temporalis and masseter muscle, which has been implicated in tongue, lip, and even tooth injuries due to biting motion. Two large retrospective reviews, each with more than 170,000 cases employing Tc-MEPs, found an overall incidence of 0.14% to 0.63%, and the tongue was most frequently injured (~80% of all associated injuries).<sup>38,115</sup> Injury severity ranged from minor bruising to necessity of laceration repair by suture in 15% to 23% of patients.

Macroglossia following surgery in the sitting position has been reported, presumably due to pressure, ischemia, and decreased venous outflow. A recent review of case reports for macroglossia after neurosurgical procedures found macroglossia was associated with prolonged operative times (50% of cases were over 8 hours) and suboccipital and posterior fossa surgeries (40%).<sup>116</sup> Excessive neck flexion can also obstruct the endotracheal tube and place significant pressure on the tongue, leading to edema. Classically, two finger breadth distance between the chin and chest is recommended. Extra caution is advised in cases with neck flexion if TEE is used for air embolism monitoring, because the esophageal probe lies between the flexed spine and the airway and endotracheal tube, adding to the potential for compression of laryngeal structures and the tongue.

At this time there are no specific recommendations for prevention of bite injuries or macroglossia. Double-sided bite blocks may help in surgical procedures using Tc-MEP, although studies of macroglossia document bite blocks in 50% of patients. The most important prevention measures are ensuring proper placement of bite blocks and rechecking placement throughout the case.

## Anesthesia Outside the Operating Room

Anesthesia providers are increasingly involved with gastrointestinal endoscopy, cardiac catheterization, interventional radiology, neuroradiology, magnetic resonance imaging, and computed tomography in hospital locations outside the operating room, as well as for office-based procedures (Chapter 73).<sup>117</sup> Anesthesia care may be specifically requested if an individual is not expected to tolerate the position required for the procedure because of comorbidities such as congestive heart failure, pulmonary disease, or morbid obesity. In addition, although positions customarily used for procedures without anesthesia may be generally safe for patients who are awake, they may pose serious risks to those under anesthesia.

Because of the less familiar environment, relative lack of positioning equipment, and a variability in staff and

nursing training with regard to patient positioning, planning, and continued vigilance are particularly important in settings outside the operating room. Diagnostic tables may not lend themselves to established intraoperative solutions to patient positioning challenges. The ability to initiate the Trendelenburg position to augment venous return and cardiac output rapidly is often lacking. In such an environment, where practice patterns often evolve in the context of nonanesthetized patients, the anesthesiologist must verify the safety of each patient's position.

## Perioperative Visual Loss

POVL is a rare but serious complication. Ischemic optic neuropathy (ION), and retinal arterial occlusion (RAO) are the main causes.<sup>118,119</sup> Other causes include cortical blindness,<sup>120</sup> acute glaucoma,<sup>121</sup> choroidal and vitreous hemorrhage,<sup>122</sup> and gas bubble expansion after retinal surgery.<sup>123</sup> The discussion here is confined to visual loss that follows nonocular surgery because eye damage after ocular surgery is well described in the ophthalmology literature. Most of our attention is focused on retinal artery occlusion and ION.

Retrospective studies, surveys, and case reports provide much of the current knowledge on POVL. Two large studies showed that perioperative ION is rare, occurring in approximately 1 in 60,000 to 125,000 anesthetic procedures in the overall surgical population.<sup>124,125</sup> Spine fusion and cardiac surgery are associated with higher incidence of POVL than other operative procedures. Shen examined the POVL prevalence in the US Nationwide Inpatient Sample, for the eight most commonly performed surgical procedures, excluding obstetric and gynecologic surgery. ION occurred most frequently in spine (3.09/10,000, 0.03%) and cardiac surgery (8.64/10,000, 0.086%).<sup>126</sup> The yearly rates of POVL have been decreasing in the 10-year period from 1996 to 2005, and for spine surgery have continued to decline as well.<sup>126,127</sup> Patil found an overall rate of 0.094% in spine surgery.<sup>128</sup> In previous, smaller case series, Stevens found ION in 4 of 3450 spine surgeries (0.1%).<sup>129</sup> Chang and Miller reviewed 14,102 spine surgery procedures in one hospital, identifying 4 with ION (0.028%).<sup>130</sup> After cardiac surgery, the incidence may be as high as 1.3%,<sup>131</sup> but is between 0.06% to 0.113% in more recent, larger retrospective studies.<sup>132-134</sup>

Myers conducted a retrospective case-control study of 28 patients with visual loss after spine surgery.<sup>135</sup> The ASA Postoperative Visual Loss Registry reported 93 cases of visual loss after spine surgery.<sup>136</sup> Nuttall performed a retrospective case-control study of cardiac surgery patients at the Mayo Clinic.<sup>132</sup> A retrospective, case-controlled study of risk factors in perioperative ION in spine surgery, a collaborative effort of 17 American and Canadian medical centers, has been reported.<sup>137</sup> These studies are described in detail in subsequent sections of this chapter.

### RETINAL ISCHEMIA: BRANCH AND CENTRAL RETINAL ARTERY OCCLUSION

Central retinal artery occlusion (CRAO) decreases blood supply to the entire retina, whereas branch retinal artery occlusion

**TABLE 34.2** Differential Diagnosis: Eye Examination in Retinal, Optic Nerve, or Visual Cortex Injury\*

	<b>AION</b>	<b>PION</b>	<b>Cortical Blindness</b>	<b>CRAO</b>	<b>BRAO</b>
Optic disk	Pale swelling, peripapillary flame-shaped hemorrhages, edema of optic nerve head Late: Optic atrophy	Initially normal Late: Optic atrophy	Normal	Normal Late: Optic atrophy	Normal Late: Optic atrophy
Retina	Normal; may have attenuated arterioles	Normal; may have attenuated arterioles	Normal	Cherry-red macula <sup>†</sup> ; pallor and edema, narrowed retinal arteries	Emboli may be present <sup>‡</sup> ; partial retinal whitening and edema
Light reflex	Absent or RAPD	Absent or RAPD	Normal	Absent or RAPD	Normal or RAPD
Fixation and accommodation	Normal	Normal	Impaired	May be impaired with external compression	May be impaired with external compression
Optokinetic nystagmus	Normal	Normal	Absent	Normal	Normal
Response to visual threat	Yes, if some vision remains	Yes, if some vision remains	No	Yes	Yes
Object tracking	Normal, if some vision remains	Normal, if some vision remains	Absent	Normal	Normal
Ocular muscle function	Normal	Normal	Normal	May be impaired if results from external compression	May be impaired if results from external compression
Perimetry	Altitudinal defect; scotoma	Altitudinal defect; blind; scotoma; Often no light perception	Hemianopia (depending on lesion location); periphery affected usually	Usually blind	Scotoma; usually normal periphery

\*Typical symptoms and signs are listed. Some patients may have varying findings as a result, among other factors, of timing of examination relative to symptom onset.

<sup>†</sup>Because of a lack of overlying inner retinal cells in the fovea, the intact choroidal circulation is visible as a cherry-red spot.

<sup>‡</sup>Cholesterol, platelet-fibrin emboli, calcified atheromatous material.

AION, Anterior ischemic optic neuropathy; BRAO, occlusion of a retinal arterial branch; CRAO, central retinal arterial occlusion; PION, posterior ischemic optic neuropathy; RAPD, relative afferent pupillary defect.

(BRAO) is a localized injury; these are generally unilateral. There are four mechanisms: (1) external compression of the eye, (2) decreased arterial supply (embolism to retinal arterial circulation or decreased systemic blood flow), (3) impaired venous drainage, and (4) thrombosis from a coagulation disorder.<sup>138</sup> The most common in the perioperative period is improper positioning with external compression producing sufficiently high IOP to stop blood flow in the central retinal artery. It most often occurs during spine surgery performed with the patient in the prone position. Pressure within the orbit also can be increased after retrobulbar hemorrhage, associated usually with vascular injury from sinus or nasal surgery.<sup>139</sup>

Although rare in most surgical procedures, emboli can directly impair blood flow in the central retinal artery or produce BRAO. Paradoxical embolism from the operative site reaching the arterial circulation through a patent foramen ovale has been reported in perioperative retinal vascular occlusion.<sup>140</sup> Venous drainage can be impaired after radical neck surgery by jugular vein ligation.<sup>141</sup> Retinal microemboli, however, are common during open heart surgery.<sup>142</sup>

### Clinical Findings

There is painless visual loss, abnormal pupil reactivity, opacification or whitening of the ischemic retina, and narrowing of retinal arterioles.<sup>143</sup> BRAO is characterized by cholesterol, and calcific or pale platelet fibrin emboli. A

cherry-red macula with a white ground-glass appearance of the retina and attenuated arterioles is a “classic” sign.<sup>144</sup> Pallor in the ischemic, overlying retina makes visible the red color of the intact, underlying choroidal circulation, but its absence does not rule out RAO. Differential diagnosis from other causes of visual loss is presented in Table 34.2.

### Mechanisms of Retinal Ischemia

The retinal blood supply is derived from the retinal and choroidal vessels.<sup>145</sup> After RAO, some O<sub>2</sub> may still be supplied by diffusion from outer retinal layers via the choroid. In monkeys, eyes with CRAO showed little damage in the macular retina after 97 minutes of ischemia. After 240 minutes, damage was profound and irreversible.<sup>146</sup> But proximal occlusion of the central retinal artery may not necessarily extrapolate to external compression of the eye.<sup>147</sup> Increased IOP from external compression is a more severe insult because of the profound simultaneous decreases in both retinal and choroidal blood flows,<sup>148,149</sup> and the greater susceptibility of the inner retinal cells to damage from pressure.<sup>150</sup> Ischemic tolerance time is probably shorter with external compression.<sup>151,152</sup>

### Central Retinal Artery Occlusion

The cause of perioperative CRAO is usually external compression of the eye, although it may also occur in cardiac surgery,

suspected from emboli.<sup>153,154</sup> Altered facial anatomy may predispose to damage by pressure from anesthesia masks or headrests. In osteogenesis imperfecta, for example, fibrous coats of the eye are thin and immature because of deficiency of collagen fibers, persistent reticulin fibers, and increased mucopolysaccharide ground substance.<sup>155</sup> Sclerae and corneas are thin and exophthalmos common, rendering the eye more vulnerable to damage from external pressure.<sup>156</sup> The horsehoe headrest leaves limited space for eyes, and the eye may inadvertently contact the headrest. Rectangular and horsehoe headrests were implicated in most reports of external compression.<sup>157,158</sup> Kumar reviewed CRAO cases after spine surgery, noting that signs and symptoms included unilateral vision loss, no light perception, afferent pupil defect, periorbital or eyelid edema, chemosis, proptosis, ptosis, supraorbital paresthesia, hazy or cloudy cornea, corneal abrasion, loss of eye movements, ecchymosis, or other trauma near the eye.<sup>159</sup> Macular or retinal edema, a cherry-red spot, or attenuated retinal vessels were often present. Four patients with external compression had retinal pigmentary alterations, suggesting simultaneous choroidal circulatory ischemia.<sup>160,161</sup> Early orbital computed tomography or magnetic resonance imaging showed proptosis and extraocular muscle swelling.<sup>159</sup> Findings were similar to "Saturday night retinopathy" in intoxicated individuals with ocular compression.<sup>162</sup>

Hollenhorst described unilateral blindness in patients positioned prone for neurosurgery and replicated the findings in monkeys with 60 minutes of elevated IOP together with hypotension (six of the eight human subjects did not have hypotension). In the monkey, histologic findings were retinal edema and dilated vascular channels, followed by retinal structural damage, and axonal loss in the optic nerve 4 months later, due to retrograde axonal degeneration after the death of retinal ganglion cells.<sup>163</sup>

Bui documented that during acute IOP increases in rats, changes in visual function assessed by electroretinography progressed from inner to outer retina, that is, retinal ganglion cells were the most sensitive, abnormal at IOPs 30 to 50 mm Hg; photoreceptors were not affected until IOP was higher.<sup>164</sup> The duration of increased IOP that injures the retina varies, with ischemic times as short as 20 or more than 30 or 45 minutes (Table 34.3).<sup>165,166</sup>

Modern head-positioning devices such as square or circular foam headrests with cutouts for the eyes and a mirror to view the eyes should prevent ocular compression.<sup>167</sup> However, unilateral RAO in a prone-positioned patient whose head was in a square foam headrest with goggles covering the eyes has been reported. There is limited space between the headrest and goggles. The patient exhibited signs of direct compression of the eye by the goggles, which, ironically, were designed as eye protectors.<sup>168</sup>

Orbital compartment syndrome, an acute ophthalmologic injury, requiring prompt decompression to relieve the increased IOP, can occur from perioperative intraorbital hemorrhage, orbital emphysema, or intraorbital bacitracin ointment and has been described during endoscopic sinus surgery.<sup>169</sup> There have also been several case reports<sup>170-172</sup> where its occurrence may have been related to positioning, such as in a patient undergoing spine surgery and positioned prone.

### Cardiac Surgery and Retinal Arterial Occlusion

The largest case series of perioperative RAO is in cardiac surgery.<sup>153</sup> This recent study retrospectively examined RAO (CRAO and BRAO) in cardiac surgery using the Nationwide Inpatient Sample. More than 5.8 million cardiac operative procedures were estimated from 1998 to 2013, with 4564 RAO cases, an incidence of 7.8/10,000. Associated with increased RAO were giant cell arteritis, transient cerebral ischemia, carotid artery stenosis, embolic stroke, hypercoagulability, myxoma, diabetes mellitus with ophthalmic complications, and aortic insufficiency. Perioperative factors were bleeding, aortic and mitral valve surgery, and septal surgery. These results indicate that conditions that predispose to embolic phenomena, such as carotid disease, opening of the heart during surgery, and preexisting abnormal retinal vasculature (diabetic retinopathy) are potential predictors for RAO in cardiac surgery. Embolization during CPB remains a cause of retinal vascular occlusion. Better means for detecting and preventing this complication are needed.

### Branch Retinal Artery Occlusion

BRAO usually leads to permanent ischemic retinal damage with partial visual field loss. Symptoms may not be immediately apparent if the visual field loss is peripheral or when only a small scotoma is present. BRAO is primarily from emboli and, less often, vasospasm. Most case reports describe embolization from intravascular injections, the surgical field, or CPB in cardiac surgery. Microemboli during CPB have been shown by retinal fluorescein angiography.<sup>173</sup> With a bubble oxygenator, all patients had perfusion defects versus 50% with a membrane oxygenator.<sup>174</sup> In coronary artery bypass graft surgery, multiple calcific emboli in branches of the central retinal artery are not unusual, resulting in visual field deficits of varying size and location.<sup>175</sup> In pigs, mechanisms of air embolism during CPB included nonperfusion, vascular leakage and spasm, red blood cell sludging, and hemorrhage. Priming with perfluorocarbons blocked many of these mechanisms.<sup>176</sup>

BRAO was described in a patient in the prone position for spine surgery. After surgery a patent foramen ovale was

**TABLE 34.3** Animal Studies of Retinal Ischemia and Time Required to Produce Injury

Author	Animal	Ischemia Method	Ischemia Time
Hayreh et al. (1980, 2004) <sup>146,147</sup>	Monkey	Central retinal artery ligation	>100-240 min
Ettache et al. (2001) <sup>151</sup>	Rat (brown Norway)	Increased intraocular pressure	20 and 40 min
Roth et al., Zhang et al. (1998, 2002) <sup>152,165</sup>	Rat (S-D)	Central retinal artery ligation, increased intraocular pressure	45 and 60 min
Zhu et al. (2002) <sup>166</sup>	Mouse (ND4)	Increased intraocular pressure	30, 45, 60 min

discovered. The patient likely sustained a paradoxical air, fat, or bone marrow embolization from the operative site in the lumbar spine.<sup>140</sup> A large retrospective series on RAO in spine surgery has also recently been published.<sup>154</sup>

### Considerations in Head and Neck Surgery

The incidence of orbital complications after endoscopic sinus surgery is estimated at 0.12%.<sup>177</sup> Vascular injury during the procedure can cause orbital compartment syndrome with compression of the arterial and venous circulations and in CRAO and optic nerve injury.<sup>178</sup> Indirect damage to the central retinal artery from intraarterial injections of 1% lidocaine with epinephrine has also been described; the mechanism is thought to be arterial spasm or embolism.<sup>179</sup> Orbital surgery is associated with an estimated 0.84% incidence of vision loss.<sup>180</sup> Risk is higher in patients undergoing facial polytrauma repair, optic canal decompression, or orbital apex surgery from an intracranial approach.<sup>181</sup>

Case reports have described sudden irreversible blindness due to BRAO following injection of various drugs into the head and neck region.<sup>182</sup> Super-selective carmustine injection into the internal carotid artery to treat gliomas, or fat injected into the orbit for cosmetic surgery, also have been complicated by visual loss from RAO. This complication can also occur from a neuroradiologic or angiographic or embolism procedure in the head and neck.<sup>183,184</sup>

### Prognosis, Treatment, and Prevention

Perioperative RAO results in permanent loss of vision in most cases. Currently available treatment is unsatisfactory. Ocular massage to more peripheral arterial branches could be instituted to decrease IOP and dislodge emboli, if present.<sup>143</sup> Intravenous acetazolamide may increase retinal blood flow. Five percent carbon dioxide in 95% O<sub>2</sub> can enhance dilation and increase O<sub>2</sub> delivery from retinal and choroidal vessels.<sup>185</sup> Further treatment may include thrombolysis, contraindicated after certain surgical procedures. Fibrinolysis through a catheter in the ophthalmic artery within 6 to 8 hours after spontaneous CRAO was associated with improved visual outcome; pooled analysis of trials showed promising results particularly in incomplete CRAO.<sup>186-189</sup> Localized hypothermia to the eye is a simple technique that has decreased injury in animal studies after ischemia, and probably should be instituted because of its minimal risk.<sup>190-192</sup>

In patients positioned prone for surgery, a foam headrest should be used with the eyes properly placed in the opening; the position of the head and the eyes should be checked intermittently about every 20 minutes by palpation or visualization. A headrest that combines a foam headrest with a mirror immediately below, which enables the eyes to be seen easily during surgery, is useful. The use of goggles to cover the eyes is not advised when the head is positioned prone in a conventional square foam headrest. The horseshoe headrest must be used with great caution, and safer choices are available. For the patient positioned prone for cervical spine surgery, this headrest should not be used because of the likelihood of head movement and compression of the eye. Rather, the most effective method for preventing head movement is to place the head in pins. For most procedures in which the patient is prone, any of the commercially available square foam headrests are recommended, where the head is positioned straight down in the neutral position.

In nasal and sinus surgery and in neuroradiologic procedures, the most important principles are avoidance of inadvertent injections into, or compromise of, the ocular circulation. After endoscopic sinus surgery, patients should be checked for signs of acutely elevated IOP (such as blurred vision, eye pain, and nausea) suggestive of orbital hemorrhage. If present, immediate ophthalmologic consultation should be obtained.

### ISCHEMIC OPTIC NEUROPATHY

ION, primarily manifesting spontaneously without warning signs, is the leading cause of sudden visual loss in patients older than 50 years of age, with an estimated annual incidence of nonarteritic ION in the United States of 2.3/100,000.<sup>193</sup> Two types of ION—*anterior* (AION) and *posterior* (PION)—have been described and can be arteritic or nonarteritic by mechanism. Arteritic AION, caused by temporal arteritis, is a systemic disease, which generally occurs in patients older than 60 years of age, and has a female preponderance. Spontaneously occurring ION, unrelated to surgical procedures, is usually caused by AION.<sup>194</sup>

Nonarteritic ION is overwhelmingly the type found perioperatively. It has been reported after a wide variety of surgical procedures, most after cardiac surgery,<sup>195</sup> spinal fusion,<sup>137</sup> head and neck surgery,<sup>196,197</sup> orthopedic joint procedures,<sup>198</sup> and surgery on the nose or sinuses.<sup>199</sup> Cases also have been described after vascular surgery, general surgical and urologic procedures (radical prostatectomy), cesarean section and gynecologic surgery, and liposuction.<sup>200</sup> The lack of controlled studies, and poorly defined pathologic and risk factors, still limit understanding of perioperative ION, although a number of recent retrospective case-control studies in spine and in cardiac surgery are yielding increasing knowledge of risk factors.<sup>127,134</sup> An animal model of perioperative ION has recently been described as well.<sup>201</sup>

### Mechanisms

Disruption of the blood-brain barrier occurs early in AION. There are sparse studies of PION; thus most of this discussion concerns AION. Fluorescein angiography showed dye leakage in the optic nerve head,<sup>202</sup> correlating with early onset of optic disk edema, even before symptoms.<sup>203</sup> The relationship between disruption of the blood-brain barrier and ischemic injury is not known. Earlier studies showed classic blood-brain barrier properties in the optic nerve head<sup>204</sup>; however, more recent immunohistochemical studies of microvessels in the monkey and human optic nerve head suggest a lack of classic blood-brain barrier characteristics in the prelaminar region,<sup>204</sup> which could explain the early edema.

Guy showed that carotid artery occlusion in rats produced a swollen optic nerve within 24 hours.<sup>205</sup> Positive nitrotyrosine immunostaining in the ischemic optic nerve suggests a possible role for nitric oxide (NO) and O<sub>2</sub> free radicals, expected to increase disruption of the blood-brain barrier. Bernstein produced rodent AION by photothrombotic vessel occlusion, and circulation to the optic nerve was lost within 30 minutes; edema peaked 1 to 2 days later and resolved by 5 days.<sup>206</sup> A pale, shrunken optic nerve resembled the limited

pathologic studies of human AION.<sup>207</sup> After 6 days, the optic nerve showed axonal swelling and collapse. By 37 days, the retinal ganglion cells were reduced by approximately 40%. Permanent changes included septal thickening and axonal loss, most evident in the center, also similar to that in the human optic nerve. Presently, the number of cases of ION with documented histopathological study is limited.<sup>208</sup>

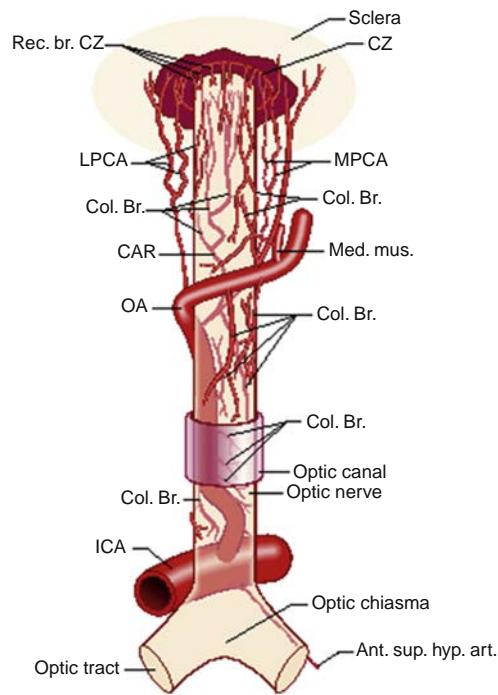
Clinical studies of AION with fluorescein angiography showed delayed filling of the prelaminar optic disk in 76% of subjects and was not found in normal eyes. This suggests that delayed filling is the primary process, not disk edema,<sup>194</sup> while Hayreh attributed AION to individual variations in blood supply to the optic nerve.<sup>209</sup> This theory is supported by anatomic studies and the variability of visual loss in AION. But the watershed concept—that impaired perfusion and distribution within a posterior ciliary artery predisposes the optic disk to infarction—is disputed. Arnold and Hepler demonstrated that delayed filling of watershed zones was more common in normal eyes than in patients with AION.<sup>202</sup> Thus reduced perfusion pressure in the region of the paraoptic branches of the short posterior ciliary arteries results in optic disk hypoperfusion, rather than a watershed event.<sup>210</sup> Histopathologic examination in AION showed that the infarction was mainly in the retrolaminar region.<sup>211</sup> This implicates as the source of decreased blood flow the short posterior ciliary arteries as directly supplying the optic disk.

A small optic disk (small cup-to-disk ratio) may increase susceptibility to AION because axons of the optic nerve pass through a narrower opening as they exit the eye. Mechanisms of injury resulting from a crowded disk include mechanical axoplasmic flow obstruction, stiff cribriform plate, and decreased availability of neurotrophic factors to retinal ganglion cells.<sup>212-214</sup>

### Blood Supply to the Optic Nerve

ION affects the anterior portion of the optic nerve in AION or beyond the retrolaminar region, and behind the eye in PION. Anatomy of and blood supply to the anterior and posterior optic nerves differ.<sup>209</sup> The anterior portion is proximal to the lamina cribrosa, an elastic, collagenous tissue through which the optic nerve, central retinal artery, and central retinal vein pass as they enter the optic disk. The anterior portion includes the superficial nerve fiber layer and the prelaminar region, a thick tissue that constitutes most of the optic disk volume.<sup>215</sup> The superficial nerve fiber layer, composed of axons extending from the retinal ganglion cells, is anterior to the plane extending across the optic nerve from the peripapillary Bruch membrane. Immediately posterior is the prelaminar region, adjacent to the peripapillary choroid. The laminar region is a transition zone between columns of glial cells and dense connective tissue plates. Astrocytes are predominant in the anterior optic nerve, and oligodendrocytes and microglial cells are more common in the posterior or retrobulbar optic nerve. Neural fibers transit the laminar region through fenestrations. The retrolaminar region is the posterior portion of the optic nerve and consists of meningeal sheaths and myelinated axons. The diameter of the optic nerve is enlarged in this area to approximately 3 mm.

The superficial nerve fiber layer derives its blood supply mainly from arterioles in the retina, although in the temporal regions it may receive blood from the posterior ciliary



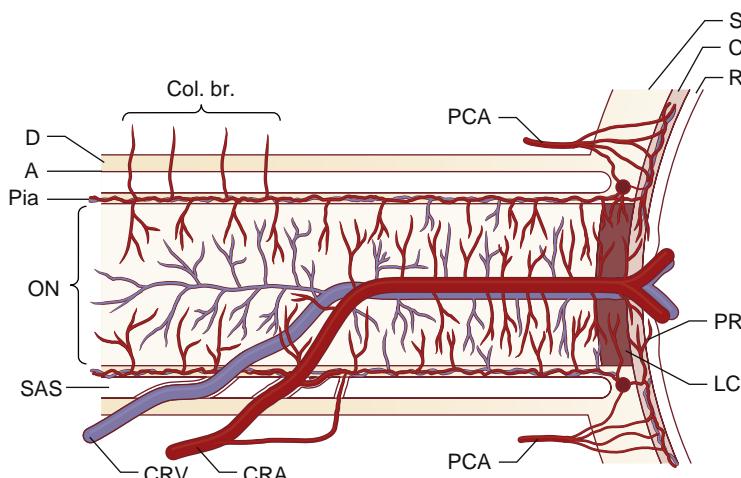
**Fig. 34.22** The origin, course, and branches of the ophthalmic artery, including the posterior ciliary arteries, as seen from above. *Ant. sup. hyp. art.*, Anterior superior hypophyseal artery; *CAR*, central retinal artery; *Col. Br.*, collateral branches; *CZ*, circle of Zinn and Haller; *ICA*, internal carotid artery; *LPCA*, lateral posterior ciliary artery; *Med. mus.*, medial muscular artery; *MPCA*, medial posterior ciliary artery; *OA*, ophthalmic artery; *Rec. br.*, recurring branches. (From Pillanur LE, Harris A, Anderson DR, et al, eds. *Current Concepts on Ocular Blood Flow in Glaucoma*. The Hague, Netherlands: Kugler; 1999.)

arteries. The prelaminar region is perfused by centripetal branches of the peripapillary choroid and vessels from the circle of Zinn-Haller (Fig. 34.22), which are not found in every eye.<sup>209</sup> Whether the region has a choroid-derived source of blood is controversial. The laminar region is supplied by centripetal branches from the short posterior ciliary arteries or by the circle of Zinn-Haller, but the short posterior ciliary arteries are the primary inputs. Longitudinal anastomoses of capillaries can be seen in the prelaminar and laminar regions and may provide some circulation, although their functional importance is not clearly known.

The retrolaminar, posterior portion of the optic nerve, which is affected in PION (Fig. 34.23), is perfused by two main vascular supplies. The peripheral centripetal vascular system is the major supply and is found in all optic nerves; it is formed by recurrent branches of the peripapillary choroid and the circle of Zinn-Haller. Pial branches of the central retinal artery and other orbital arteries, the ophthalmic artery, and the posterior ciliary arteries also contribute. Branches of the pial vasculature run in the septa of the nerve. The axial centrifugal vascular system is formed by small branches from the intraneuronal part of the central retinal artery and is not present in every eye; thus differences in blood supply in the posterior optic nerve may render some individuals more susceptible to PION.<sup>216</sup>

### Control of Blood Flow

Studies of autoregulation of blood flow in the optic nerve head have yielded conflicting results because of limited



**Fig. 34.23 The blood supply to the optic nerve.** The anterior portion of the optic nerve is located to the left, whereas the posterior portion (closer to the brain) is on the right. The anterior portion of the nerve derives its blood supply from the posterior ciliary arteries (PCA) and the choroid (C), whereas the posterior optic nerve derives its blood supply from penetrating pial arteries (collateral branches [Col. br.]) and branches of the central retinal artery (CRA). A, Arachnoid; CRV, central retinal vein; D, dura; LC, long ciliary artery; ON, optic nerve; PR, short posterior ciliary artery; R, retina; S, sclera; SAS, subarachnoid space. (From Hayreh SS. Ischemic optic neuropathy. Department of Ophthalmology, University of Iowa. <http://www.medicine.uiowa.edu/eye/AION-part2>. Accessed August 8, 2014)

measurement techniques. Blood flow in the optic nerve head is autoregulated within a range of perfusion pressures similar to those in the brain of monkeys and sheep. In a small sample of atherosclerotic monkeys, however, autoregulation was defective.<sup>217</sup> This study did not directly measure blood flow; rather, it measured glucose consumption, and the sample size was small. Other evidence of autoregulation is seen in the posterior portion of the optic nerve. In cats, blood flow in the optic nerve measured directly by autoradiography remained constant in the prelaminar, laminar, and postlaminar nerve across a range of systemic mean arterial blood pressure values from 40 to more than 200 mm Hg.<sup>218</sup>

In 13 healthy volunteers, blood flow in the optic nerve head measured by laser Doppler flowmetry was constant between ocular perfusion pressures of 56 to 80 mm Hg.<sup>219</sup>; in another study, flow was preserved at extremely high IOP that resulted in a minimal perfusion pressure of 22 mm Hg.<sup>220</sup> Other investigators found that flow was preserved in the optic nerve head until ocular pressure reached levels of 40 mm Hg. However, 2 of 10 young healthy volunteers in the study failed to demonstrate autoregulation.<sup>221</sup> Using color Doppler imaging in humans, another group showed that flow velocity in the posterior ciliary arteries decreased at extremely high IOP. These findings seem to support the theory that “watershed” areas in the distribution of the posterior ciliary arteries predispose some patients, including otherwise healthy ones with no known vascular disease, to damage to the anterior portion of the optic nerve when perfusion pressure is decreased, either after systemic blood pressure decreases or IOP is elevated. At present, however, no clinical technique can reliably detect such patients.

### Histopathologic Findings

There are few reports on the histopathologic examination of the optic nerve in ION. Of three PION cases evaluated after surgical procedures, all showed infarcts in the intraorbital portion of the optic nerve, but results were not consistent. Two patients had lesions in the central axial portion with

peripheral axonal sparing; the other had the opposite pattern in one eye and complete axonal loss in the other.<sup>200</sup> Despite a larger autopsy series in AION, the location of the infarct has also not been documented. Tesser and colleagues<sup>207</sup> showed that in a patient with spontaneous AION, axonal loss was in the superior optic nerve, encircling the central retinal artery. The infarct was in the intraocular portion of the nerve, extending 1.5 mm posteriorly.

### Patient Characteristics in Perioperative Ischemic Optic Neuropathy

Most of the cases occurring after spine surgery have been PION.<sup>200</sup> AION occurs more frequently after cardiac surgery. ION's onset is typically within the first 24 to 48 hours after surgery and is frequently noted on awakening, although later onset has been described, particularly in sedated patients.<sup>137</sup> Patients present typically with painless visual loss, afferent pupil defect or nonreactive pupils, complete visual loss, no light perception, or visual field deficits. Color vision is decreased or absent. In AION, altitudinal visual field deficits may be present. Optic disk edema and hemorrhages are seen on symptom onset in AION; in PION, the optic disk appears normal even though the patient reports visual loss. Over a span of weeks to months, optic atrophy develops. The lesion may be unilateral or bilateral, but most post-spine surgery ION cases are bilateral. Orbital magnetic resonance imaging is frequently nondiagnostic, although some have described changes including enlargement of the nerve from edema or perineurial enhancement.<sup>222,223</sup> Visual evoked potential and pattern evoked electroretinogram are abnormal.<sup>224</sup>

### Retrospective Case Series

Buono and Foroozan reviewed 83 reported cases of PION, some of which were perioperative.<sup>200</sup> Approximately 54% followed spine surgery, 13% radical neck dissection, and 33% other surgery. Mean age was 52 years; patients who had spine surgery were younger (mean age, 44 years) than those in the other groups. Approximately two thirds were

men. In 75%, visual loss was apparent within 24 hours. For 54% of affected eyes, initial visual acuity was light perception, with greater than 60% bilateral. In 38%, vision improved, but of 14 patients with no light perception initially, 12 (85%) had no improvement. Mean lowest hemoglobin was 9.5 g/dL (range: 5.8-14.2 g/dL), mean lowest systolic blood pressure was 77 (48-120 mm Hg), mean intraoperative blood loss was 3.7 L (0.8-16 L), and mean operative duration was 8.7 hours (3.5-23 hours). The drawback of this study is the limited amount of information on perioperative ION and its reliance on previously reported cases.

### Spine Surgery

Ho reviewed cases of AION and PION after spine surgery. In the 5 AION and 17 PION cases, median ages were 53 and 43 years, respectively.<sup>225</sup> Most followed lumbar spine fusion. Mean operative time for AION was 522 minutes and for PION was 456 minutes. For AION, the range of the lowest mean arterial pressure was 62 to 78 mm Hg; for PION, it was 52 to 85 mm Hg. Mean lowest intraoperative hematocrit was 27% in PION. Mean blood loss was 1.7 and 5 L for AION and PION, respectively. Crystalloid/colloid volumes averaged 6.0/0.8 and 8.0/2.2 L for AION and PION, respectively. Sixty percent with AION and 27% with PION had diabetes mellitus; coronary artery disease was noted in 20% of patients with AION and in none with PION. Prevalence of hypertension was similar (40% or 53%). Symptoms were reported within 24 hours of surgery in 40% of patients with AION; 59% of patients with PION reported symptoms immediately on awakening and 88% within 24 hours. Visual acuity improved somewhat in 60% of AION and 65% of PION cases. This study is limited by its reliance upon literature reports.

In a retrospective case-control study of 28 patients with visual loss after spine surgery, Myers and colleagues found no difference in lowest systolic blood pressure or hematocrit in the affected versus unaffected patients.<sup>135</sup> Approximately 40% of these patients had no risk factors for vascular disease preoperatively; a similar percentage in the two groups had hypertension or were smokers. This study's limitations were that controls were not randomly chosen and matching of controls to cases was not adequately explained.

Spine surgery patients with ION in the ASA Postoperative Visual Loss Registry had an average blood loss of 2.0 L, and the lowest hematocrit was 26%.<sup>136</sup> Decreases in blood pressure varied widely from preoperative baseline: in 33%, the lowest systolic blood pressures were greater than 90 mm Hg; in 20%, the lowest was 80 mm Hg or less. Approximately 57% of patients had systolic or mean arterial blood pressure 20% to 39% below preoperative baseline, and 25% of patients were at 40% to 49% below preoperative baseline. Deliberate hypotension was used in approximately 25% of patients. Nearly all cases involved surgery exceeding 6 hours. In the majority of patients, estimated blood loss was greater than 1 L, the median estimated blood loss was 2 L, and the median lowest hematocrit was 26%. Large-volume fluid resuscitation was typical, with median crystalloid administration of approximately 10 L. Most of the patients underwent thoracic, lumbar, or lumbar-sacral fusion procedures that were often repeat operations that involved multilevel surgery. Surgical positioning devices included the

**TABLE 34.4** Factors Increasing the Odds Ratio of Developing Perioperative ION in Lumbar Spine Fusion Surgery

	Odds Ratio	P Value
Male	2.53 (1.35-4.91)	.005
Obesity	2.83 (1.52-5.39)	.001
Wilson frame	4.30 (2.13-8.75)	<.001
Anesthesia duration, per hour	1.39 (1.22-1.58)	<.001
Estimated blood loss, per 1 L	1.34 (1.13-1.61)	.001
Colloid as percent of nonblood replacement, per 5%	0.67 (0.52-0.82)	<.001

Wilson frame (30%), Jackson spinal table (27%), and soft chest rolls (20%). A foam pad was used for head positioning for 57%; 19% had the head in a Mayfield head holder. PION accounted for the majority of cases, compared with AION. Patients in ASA physical status 1 or 2 accounted for 64% of cases. The mean age was 50 years. Approximately, 41% had hypertension, 16% diabetes mellitus, and 10% coronary artery disease. Limitations of this study are related to data collection and lack of control nonaffected cases for comparison.

This limitation was addressed by a follow-up comparison of the ION spine dataset with randomly selected, matched controls from 17 academic medical centers in North America. Results are summarized in Table 34.4. After multivariable analysis, six factors conferred higher risk for ION in lumbar spine fusion: male gender, obesity, Wilson frame positioning, anesthesia duration, large blood loss, and a relatively low ratio of colloid to crystalloid fluid resuscitation.<sup>137</sup> This study was the first large and well-matched case control study of perioperative ION. The limitations are the relatively limited amount of preoperative data, no distinction between AION and PION, and the possibility that controls did not represent a population-matched sample.

The Nationwide Inpatient Sample is a random sample of discharge data from 20% of US hospitals. Rubin and colleagues analyzed trends in ION incidence in spine fusion from 1998 to 2012 (more than 2.5 million discharges). ION prevalence was 1.02/10,000, with an encouraging, still unexplained, significant decrease over time.<sup>127</sup> Significantly associated with ION were age, blood transfusion, and obesity; female sex was inversely associated. These results are important because they were obtained from a very large, randomly collected sample, and suggested the importance of specific preoperative factors. But there are limitations. The Nationwide Inpatient Sample relies on the accuracy of diagnosis and coding. Verification of medical diagnoses are not possible. Both over- and under-coding are possible. The coding depends on entry of the data by professional coders; however, the accuracy depends upon the diagnoses recorded by physicians and the procedure description provided by the surgeon.<sup>226</sup>

### Cardiac Surgery

Shapira and colleagues studied 602 patients undergoing CPB at a single institution under moderate systemic hypothermia (25°C) with pulsatile flow and a membrane

oxygenator.<sup>131</sup> Phenylephrine maintained perfusion pressure above 50 mm Hg. Eight patients (1.2%) had AION. There were no differences in preoperative vascular risk factors in those with or without visual loss. CPB time was longer in patients with AION (252 vs. 164 minutes), and minimum hematocrit was lower (18% vs. 21%) compared with unaffected patients. There were no differences in flow indices, perfusion pressures, and carbon dioxide tension. Patients with AION had a greater 24-hour postoperative weight gain (18% vs. 11%) and required more vasoactive drugs to maintain hemodynamics than did patients with unaffected vision. Visual symptoms were usually reported between days 1 and 3 postoperatively, soon after removal of mechanical ventilatory support. This study is limited due to the small sample size and single institution design.

Nuttall and colleagues performed a larger retrospective case-control study of approximately 28,000 patients who had cardiac surgery at the Mayo Clinic from 1976 to 1994, with 17 patients with ION (0.06%).<sup>132</sup> By univariate analysis, significant risk factors included lower minimum postoperative hemoglobin, clinically severe vascular disease, preoperative angiogram within 48 hours of CPB, longer CPB duration, red blood cell transfusions, and the use of non-red blood cell blood components. Patients with ION underwent longer CPB runs; no differences were found in pre-CPB or post-CPB systemic blood pressures. Nine cases of bilateral ION were reported; disk edema was not found in 5 patients (29%), who may have had PION. Small cup-to-disk ratio (<0.3) was identified in 5 patients (29%) with ION. This study was limited by a large number of comparisons, small sample, single institution design, and no distinction between AION and PION. A more recent series by Holy and colleagues showed similar results, but it included other surgical procedures, complicating interpretation of the results with cardiac surgery.<sup>227</sup> Kalyani and colleagues reviewed cases of ION after 9701 cardiac surgeries over 9-year period at a single institution. Specific risk factors could not be determined from the 11 patients (0.11%) with ION.<sup>133</sup>

Rubin examined ION in the largest series of cardiac surgery cases to date, using the Nationwide Inpatient Sample (1998-2012), as described earlier.<sup>134</sup> There were more than 5 million discharges meeting inclusion criteria with 794 (0.014%) ION cases. Average yearly incidence was 1.43 of 10,000 cardiac procedures. Increasing risk were carotid artery stenosis, stroke, diabetic or hypertensive retinopathy, macular degeneration, glaucoma, and cataract. Female sex and uncomplicated diabetes mellitus type 2 decreased risk. This study was large but has the same limitations as other studies using the National Inpatient Sample. Intriguingly, it does suggest that preoperative degenerative eye diseases may predict patients that will develop ION.

### Controversies and Anesthesia Management Recommendations

This discussion will primarily concern spinal fusion procedures, where the largest number of cases have been described. For more detail, the reader is referred to the practice advisories of the ASA.<sup>228-230</sup>

**Length of Surgery.** Both Myers<sup>135</sup> and the Postoperative Visual Loss (POVL) Study Group<sup>137</sup> reported increased risk with long duration of spine fusion surgery. Therefore,

staging of spinal fusion procedures, particularly those for anterior and posterior surgery, may be advisable (but see later). A discussion between the surgeon and anesthesia provider should occur in selected cases. Revision spinal fusion procedures are common, and these operations may be longer in duration and involve larger blood loss.<sup>231</sup>

**Hypotension.** Intraoperative hypotension has been cited as a risk factor by a number of authors of case reports,<sup>232,233</sup> but this risk has not been confirmed by case control studies, with one exception.<sup>135,137,227</sup> Patil and colleagues reported a higher odds ratio for ION in patients who sustained hypotension.<sup>128</sup> However, the diagnostic coding of hypotension in this study from the Nationwide Inpatient Sample is not defined, cannot be confirmed, and the timing (during the perioperative period or not) and the degree of hypotension are not specified.<sup>234</sup>

Hypotension can potentially lead to a decrease in perfusion pressure in the optic nerve and to ischemic injury because of either anatomic variation in the circulation or abnormal autoregulation and an inability to adequately compensate for decreased perfusion pressure. The degree of hypotension that is potentially dangerous is difficult to determine because of the lack of data.<sup>230</sup> Judgment and discussion are thus advisable when surgeons request a decrease in blood pressure to decrease blood loss in spine surgery. In cardiac surgery, special considerations exist regarding the optimal systemic perfusion pressures to be maintained during CPB.<sup>235</sup>

**Hemodilution and Blood Loss.** Clinical blood transfusion practice in surgical patients, based on ASA practice guidelines,<sup>236</sup> suggests that transfusion is not generally required for hemoglobin values higher than 8.0 g/dL, and thus isovolumic hemodilution is common in patients undergoing spine fusion. The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists reviewed the available evidence with respect to cardiac surgery, and has issued a similar clinical practice guideline.<sup>237</sup> Some authors suggested that allowing hemoglobin to decrease, as is common in anesthesia practice, may increase the risk for ION<sup>238</sup>; however, whether this practice should be changed in surgical procedures such as spine or heart surgery—or in any operative procedure—remains controversial.

In uncontrolled hemorrhage in which blood volume is not maintained, decreased O<sub>2</sub> delivery to the optic nerve could result in either AION or PION.<sup>239</sup> But how low or for how long the hemoglobin concentration must decrease to lead to this complication is not known. However, the presence of recurrent and profound hemorrhage has been described in many reports. The argument that blood loss in the presence of maintained intravascular volume (hemodilution) is harmful seems less scientifically grounded. It has been shown experimentally in miniature pigs that blood flow in the optic nerve head, as measured by laser Doppler imaging, was maintained during isovolumic hemodilution with a 30% decrease in hematocrit. Moreover, O<sub>2</sub> tension at the vitreal surface increased 15%.<sup>240</sup> Also, Lee and colleagues demonstrated that extreme decreases in hematocrit (15%) and mean arterial pressure (50 mm Hg) in adult pigs resulted in significant reductions in blood flow to the optic nerve. But no histologic or optic nerve function was studied,

and the pig brain and eye circulation significantly differ from that of humans.<sup>241</sup> Roth and associates showed that hemodilution and extreme head-down tilt in rats resulted in significant changes in visual evoked potentials, electrical activity originating in retinal ganglion cells, and increased glial reactivity in the optic nerve; thus, if extrapolated to humans, caution is in order during extreme hemodilution with the head-down tilt.<sup>201</sup>

**Head Positioning.** Many reports of ION include patients who were in the prone position, raising the possibility that positioning itself contributes to altered venous hemodynamics within the optic nerve. The patient's head should be level with or above the heart, when possible, and in a neutral position during spine surgery performed with the patient in the prone position. When the patient is positioned for spine surgery in the Wilson frame, the head may be below the level of the back; the head can be elevated using pillows or the bed placed in reverse Trendelenberg.<sup>242</sup> With the Jackson table, the head is maintained at the level with the back.<sup>229</sup>

Several studies found that IOP increased in the prone position and was influenced by the position of the operating room table. However, there has been no correlation between IOP changes and visual outcome or visual function.<sup>242</sup> Cheng and colleagues found that in anesthetized patients, mean ( $\pm$  standard deviations) IOP increased significantly on initial prone positioning relative to supine ( $27 \pm 2$  vs.  $13 \pm 1$  mm Hg). After 5 hours in the prone position, IOP remained increased at  $40 \pm 2$  mm Hg. None of the 20 patients in the study experienced visual loss. The largest increases in IOP were evident near the time patients were awakening.<sup>243</sup> Although these data suggest that ocular perfusion pressure may decline even during maintenance of normotension, some experimental design issues must be considered in interpreting these results. The main issue is that the largest increases in IOP were evident near the time of awakening from anesthesia. Accordingly, IOP could have increased because of light anesthesia. Moreover, the study did not include a supine group to control for the effects of fluid administration on IOP. Such control is important because prone positioning itself may not explain the large increases in IOP. These results are valuable as well as of concern, but further studies are needed to fully evaluate their significance.

External pressure on the eye is a potential concern when a patient is positioned prone for surgery. Many cases of ION have occurred when pressure could not have been placed on the eye. Such cases include patients in pin head holders<sup>244</sup> and those in whom the head was turned with the affected eye placed upward.<sup>245</sup> But ION would not occur without retinal damage in a situation in which external compression was applied (see earlier discussion). Although we demonstrated that high IOP decreased retinal and choroidal blood flows in cats,<sup>148</sup> Geijer and Bill specifically measured the impact of graded increases in IOP on blood flow in the retina and optic nerve in monkeys.<sup>246</sup> When IOP was elevated such that perfusion pressure was decreased to levels above 40 cm H<sub>2</sub>O, small effects on retinal blood flow and in the prelaminar portion of the optic nerve were noted. When perfusion pressure was less than 40 cm H<sub>2</sub>O, retinal and prelaminar flows were proportional to the perfusion

pressure. At very high IOP, blood flow stopped in the retina and the prelaminar area, but flow in the retrolaminar region increased. High IOP results in a redistribution of blood flow that favors the retrolaminar portion of the optic nerve. Therefore, an increase in IOP would not produce an isolated ION without also causing retinal damage. Further support is that sustained increases in IOP significantly decreased both retinal and choroidal blood flow, and even small increases in IOP damaged the retinal ganglion cells, which are sensitive to pressure alterations.<sup>247,248</sup>

**Fluid Administration.** The theory that massive intravascular fluid resuscitation could be a pathogenic factor in perioperative ION remains speculative, but it does have some merit. Conceivably, fluid administration could result in increased IOP, accumulation of fluid in the optic nerve, or both. Because the central retinal vein exits out of the optic nerve, an internal compartment syndrome may occur in the optic nerve. Alternatively, fluid accumulation in the vicinity of the lamina cribrosa may compress axons as they transit this region. In the report by Cullinane and colleagues,<sup>249</sup> trauma patients who were acidotic received massive blood replacement and most had abdominal compartment syndrome. Analysis of these patients is complicated because of the presence of numerous systemic alterations. Sullivan and colleagues described a retrospective series of 13 burn patients with 25% or greater body surface area burns and massive fluid resuscitation. IOP was elevated more than 30 mm Hg in four patients at 48 hours after admission, all of whom received more than 27 L of intravenous fluid. Eye findings and vision diagnoses were not described.<sup>250</sup> Large-volume fluid replacement is generally seen in spinal fusion surgery.<sup>251</sup> Patients in the ASA Postoperative Visual Loss Registry received on average 9.7 L of crystalloid intraoperatively,<sup>137</sup> and increased postoperative weight gain was identified in a case-control study of visual loss after heart surgery,<sup>131</sup> suggesting, although not proving, that fluid replacement may play a role. The finding of the POVL Study Group was that the odds ratio for developing ION was increased as the percent colloid of non-blood replacement decreased.<sup>137</sup> It is possible that the use of colloids may decrease edema in the optic nerve during surgery, particularly when the patient is placed prone for surgery. However, at present, such edema has not yet been demonstrated. In healthy volunteer subjects, placement in the prone position led to an increase in diameter of the optic nerve.<sup>242</sup> This could be due to venous hypertension. New magnetic resonance imaging methods may enable the study of edema and venous hemodynamics in the optic nerve in the near future. Animal models also may provide a means to study these perioperative factors. No study has shown any relationship among periorbital edema, IOP, and ION. Fluid administration could be a pathogenic factor in ION, especially in patients positioned prone or undergoing cardiac surgery, but the mechanisms involved, in addition to the amounts and nature of fluid required, remain undefined.

**Anatomic Variation.** Anatomic variation in the circulation of the optic nerve may potentially predispose patients to the development of ION. The location of potential watershed zones in the anterior and posterior circulation and

the presence of disturbed autoregulation, even in normal patients,<sup>108</sup> are of concern but at present cannot be predicted clinically. Few human studies have been conducted on the relationship between perfusion pressure and changes in blood flow in the optic nerve. Human studies generally show preserved blood flow at clinically used or even lower ranges of perfusion pressure, but these studies have focused primarily on the anterior portion of the optic nerve.<sup>219</sup> In the studies that used laser Doppler flowmetry, depth of penetration of the measuring device is critical. Measurements might have been closer to the retinal blood vessels than the optic nerve head, and these do not measure optic nerve circulation. It is not currently feasible to measure blood flow in the human retrolaminar optic nerve. In animal studies, blood flow is preserved in various layers of the optic nerve, including the retrolaminar area, at a mean arterial blood pressure as low as 40 mm Hg.<sup>218</sup>

**Vasoconstrictors.** Hayreh and colleagues theorized that AION is related to excessive secretion of vasoconstrictors, which in turn could lower optic nerve perfusion to dangerously low levels.<sup>252</sup> However, the theory was based on the development of AION in patients who sustained massive hemorrhage. Vasopressors are used to maintain blood pressure in circumstances, such as after cardiac surgery and in cases in which vasomotor tone is decreased. Shapira and colleagues showed an association between prolonged use of epinephrine or long bypass time and ION in patients undergoing open heart surgery.<sup>131</sup> Lee and Lam reported a case of ION in a patient after lumbar spine fusion during which phenylephrine infusion was used to maintain blood pressure.<sup>253</sup> They later presented a series of four case reports of ION in critically ill patients with significant systemic illness who required prolonged use of vasopressors and inotropic agents to maintain blood pressure and cardiac output. However,  $\alpha$ -adrenergic receptors are not located in the optic nerve and the blood-brain barrier prevents entry of systemically administered agents, except possibly in the prelaminar zone of the nerve. Therefore, the role of vasopressor use in ION remains unclear, and no clear guidance with respect to risk for ION can be provided at this time.

**Informed Consent.** A single institution survey reported that patients prefer to be informed of the risk of visual loss in spine surgery.<sup>254</sup> It seems advisable to have the discussion with patients that are at higher risk of developing ION. Often it is difficult to do when, as is common, the patient is first seen soon before surgery. It may be preferable for anesthesiologists and surgeons to develop a means to inform patients earlier of the risk of ION.

**Staging and Minimally Invasive Spine Fusion.** Increasingly, neurosurgeons have been using minimally invasive surgical techniques for lumbar spine surgery and fusion.<sup>255</sup> These methods reduce the amount of blood loss and fluid requirements, but cases of ION have arisen under these circumstances as well.<sup>256</sup> Another strategy not under the direct control of the anesthesia provider is to consider staging of complex spine procedures. However, in some instances the anesthesiologist may be able to persuade a surgeon to follow a less ambitious surgical plan. This decision requires an assessment of the associated increased

risks for multiple surgeries (infection, spinal instability) but may significantly shorten the duration of each procedure. However, perioperative complications such as infection and deep vein thrombosis may be increased.<sup>257-261</sup> Another strategy is to advocate for patients by regular preoperative conferencing with surgeons. Anticipating high blood loss and other risks may enhance perioperative planning and care in spine surgery patients.

### Prognosis, Treatment, and Prevention

No effective treatment exists for ION. A few cases of treating perioperative ION have been reported. Acetazolamide decreases IOP and may improve flow to the optic nerve head and retina. Diuretics such as mannitol or furosemide reduce edema.<sup>262</sup> In the acute phase, corticosteroids may reduce axonal swelling, but in the postoperative period they may increase wound infection. Because steroids are of unproven benefit, their use must be carefully weighed.<sup>263</sup> Increasing ocular perfusion pressure or hemoglobin concentration may be appropriate when ION is found in conjunction with significant decreases in blood pressure and hemoglobin concentration. Maintaining the patient in a head-up position if increased ocular venous pressure is suspected may be advantageous, but its use must be balanced against decreased arterial supply with the head-up position. Clearly, if a patient has visual loss from ocular compartment syndrome, immediate decompression (lateral canthotomy) is indicated.

In their review of perioperative PION reports in the literature, Buono and Foroozan summarized the lack of proof that treatment altered the course of PION. In a few anecdotal case reports, increasing blood pressure or hemoglobin, or applying hyperbaric O<sub>2</sub>, improved visual outcome.<sup>200</sup> The use of neuroprotective agents or drugs that lower IOP, valuable in theory, has never been shown to result in improvement.<sup>248</sup> Stevens and colleagues, who compiled a report of ION in patients after spine surgery, had apparent improvement of vision in two patients when anemia and hypotension were corrected.<sup>129</sup> One patient demonstrated partial improvement that subsequently regressed, and one patient showed more clear signs of improvement. However, as Buono and Foroozan mentioned, it is difficult to ascertain if improvement came from treatment, because some patients recover vision spontaneously after PION.<sup>200</sup>

### American Society of Anesthesiologists Advisories (Updated With 2019 Advisory)

The 2006 ASA Task Force on Perioperative Blindness concluded that high-risk patients who have surgery that is prolonged in duration and/or have large blood loss have an increased risk of POVL.<sup>228</sup> Yet POVL was not related to blood loss per se, hemoglobin levels, or the use of crystalloids. In 2012, another ASA Task Force published an update regarding POVL primarily associated with spine surgery.<sup>229</sup> While major changes were not made, analysis of the literature was updated and the recommendations were more detailed. For example, the 2006 Summary had 7 bullet points. In contrast, the 2012 Summary of Advisory Statements has 22 bullet points subdivided into Preoperative, Intraoperative, Staging of Surgical Procedures, and Postoperative Management (Box 34.2). The 2012 ASA Task Force on POVL reviewed the additional literature and concluded that newer findings and the literature do not justify major

## BOX 34.2 American Society of Anesthesiologists 2012 Task Force Summary of Advisory Statements

### I. Preoperative Considerations

- At this time, there were no identifiable preoperative patient characteristics that predispose patients to perioperative posterior ischemic optic neuropathy (ION).
- There is no evidence that an ophthalmic or neuro-ophthalmic evaluation would be useful in identifying patients at risk for perioperative visual loss.
- The risk of perioperative ION may be increased in patients who undergo prolonged procedures, have substantial blood loss, or both.
- Prolonged procedures, substantial blood loss, or both are associated with a small, unpredictable risk of perioperative visual loss.
- Because the frequency of visual loss after spine surgery of short duration is infrequent, the decision to inform patients who are *not* anticipated to be "high risk" for visual loss should be determined on a case-by-case basis.

### Intraoperative Management

#### Blood Pressure Management

- Arterial blood pressure should be monitored continually in high-risk patients.
- The use of deliberate hypotensive techniques during spine surgery can be associated with the development of perioperative visual loss. Therefore the use of deliberate hypotension for these patients should be determined on a case-by-case basis.
- Central venous pressure monitoring should be considered in high-risk patients. Colloids should be used along with crystalloids to maintain intravascular volume in patients who have substantial blood loss.

#### Management of Anemia

- Hemoglobin or hematocrit values should be monitored periodically during surgery in high-risk patients who experience sub-

stantial blood loss. A transfusion threshold that would eliminate the risk of perioperative visual loss related to anemia cannot be established at this time.

#### Use of Vasopressors

- There is insufficient evidence to provide guidance for the use of  $\alpha$ -adrenergic agonists in high-risk patients during spine surgery.

#### Patient Positioning

- The Task Force believes that there is no pathophysiologic mechanism by which facial edema can cause perioperative ION. There is no evidence that ocular compression causes isolated perioperative anterior ION or posterior ION. However, direct pressure on the eye should be avoided to prevent central retinal artery occlusion (CRAO).
- The high-risk patient should be positioned so that the head is level with or higher than the heart when possible.

#### Staging of Surgical Procedures

- Although the use of staged spine surgery procedures in high-risk patients may entail additional costs and patient risks (e.g., infection, thromboembolism, or neurologic injury), it also may decrease these risks and the risk of perioperative visual loss in some patients.

#### Postoperative Management

- The consensus of the Task Force is that a high-risk patient's vision should be assessed when the patient becomes alert.
- If there is concern regarding potential visual loss, an urgent ophthalmologic consultation should be obtained to determine its cause.
- There is no role for antiplatelet drugs, steroids, or intraocular pressure-decreasing drugs in the treatment of perioperative ION.

From Practice advisory for perioperative visual loss associated with spine surgery: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Visual Loss. *Anesthesiology*. 2012; 116: 274–285.

changes in the 2006 recommendations. A further update was published in 2019.<sup>230</sup>

## VISUAL LOSS AFTER VITRECTOMY AND VITREAL GAS BUBBLE TAMPONADE

Patients who have undergone vitrectomy with perfluorocarbon gas tamponade ( $C_3F_8$ ) are at risk for gas bubble expansion and loss of vision from acutely increased IOP. Patients anesthetized for a subsequent surgical procedure with gas mixtures containing nitrous oxide ( $N_2O$ ) after vitrectomy sustained retinal vascular occlusion from acute gas bubble expansion.  $N_2O$  anesthesia affects the size of the intraocular gas bubble. Wolf and colleagues demonstrated that  $N_2O$  and  $O_2$  resulted in a more than threefold increase in  $SF_6$  gas bubble volume, in contrast to a 50% increase with air ventilation and 35% increase with  $O_2$  ventilation alone.<sup>264</sup> Perfluorocarbon gas remains in the eye for at least 28 days. Visual loss has been reported with  $N_2O$  anesthesia administered as long as 41 days after vitrectomy and gas bubble tamponade. Therefore, patients should wear a warning tag to alert the anesthesiologist to the presence of the gas bubble in the vitreous, and  $N_2O$  should not be used in patients who have had recent vitrectomy and gas bubble tamponade.<sup>265,266</sup>

## Conclusion

The positioning of patients under anesthesia care is a major responsibility requiring great attention to detail and constant vigilance. Positioning for optimal surgical exposure but the potential for lasting harm to patients from improper positioning must guide our actions. Each position has significant physiologic effects on ventilation and circulation. In addition, despite increased awareness, position-related complications, including peripheral nerve injuries, continue to remain a significant source of patient morbidity. As surgical techniques evolve, extreme positions sometimes permit advantages, such as smaller incisions and more effective displacement of internal organs to facilitate surgical exposure. Unfortunately, associated risks may increase with positions that would not be tolerated when patients are awake. Anesthesiologists and surgeons must work together with all operating room staff when each patient is positioned to promote comfort and safety in addition to securing the desired surgical exposure. Ideally, the final position should appear natural; that is, a position that the patient would comfortably tolerate if awake and unsedated for the anticipated duration of the procedure.