

### BOX 31.3 Recommendations for Preoperative Noninvasive Evaluation of Left Ventricular Function

#### Class IIa (Reasonable to Perform)

- It is reasonable for patients with dyspnea of unknown origin to undergo preoperative evaluation of LV function.
- It is reasonable for patients with heart failure with worsening dyspnea or other change in clinical status to undergo preoperative evaluation of LV function.

#### Class IIb (May Be Considered)

- Reassessment of LV function in clinically stable patients with previously documented LV dysfunction may be considered if there has been no assessment within a year.

#### Class III (Should Not Be Performed Since It Is Not Helpful)

- Routine preoperative evaluation of LV function is not recommended.

LV, Left ventricle.

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. *Circulation*. 2014;130:e278–e333.

in their usual stable state (i.e., compensated heart failure) or have recently significantly worsened (i.e., decompensated heart failure). Decompensated heart failure is a very high-risk condition that warrants postponement of surgery for all except lifesaving emergency procedures.<sup>7</sup> No consensus exists on how long nonemergent surgery should be deferred after resolution of acute decompensated heart failure, although a reasonable approach is to delay elective procedures (including most time-sensitive procedures) for 1 month, and urgent procedures for 24 hours.

On physical examination, the findings of heart failure may be subtle. Furthermore, they can vary between HFrEF versus HFpEF, and between compensated versus decompensated states. More useful signs for determining heart failure include a third heart sound, jugular venous distension, pulmonary rales, and lower extremity edema.<sup>26</sup> A chest radiograph may provide further diagnostic guidance, especially in dyspneic patients, with pulmonary vascular redistribution and interstitial edema useful findings for supporting the presence of heart failure.<sup>26</sup> Natriuretic peptide measurement can further clarify whether a patient has heart failure. Both BNP and NT pro-BNP have excellent diagnostic performance, especially for ruling out heart failure, in the ambulatory setting (pooled negative likelihood ratio values 0.29-0.38 at manufacturers' recommended thresholds)<sup>164</sup> and emergency department setting (pooled negative likelihood ratio values 0.08-0.13 at manufacturers' recommended thresholds).<sup>165</sup> Preoperative natriuretic peptide concentrations also provide other potentially important information. Both BNP and NT pro-BNP concentrations are markers of perioperative cardiac risk (see section on "Ischemic Heart Disease"). In addition, for heart failure patients who have undergone prior natriuretic peptide measurement, preoperative BNP or NT pro-BNP testing provides insights into whether patients remained in their usual stable clinical state. Consistent with these data, the ESC/ESA

guidelines recommend preoperative natriuretic peptide measurement in patients who have established or suspected heart failure, and are undergoing noncardiac intermediate or high-risk noncardiac surgery.<sup>9</sup> While routine preoperative echocardiography (or other noninvasive ventricular function measurement) is not useful, such specialized testing is helpful for assessment of dyspnea of unknown origin or recent altered clinical status in an individual with known heart failure. Furthermore, both American and European guidelines are supportive of selective preoperative echocardiography in clinically stable patients with known ventricular dysfunction,<sup>9</sup> especially in the absence of testing in the previous year (see Box 31.3).<sup>7</sup> Other tests for patients with heart failure include ECGs and blood sampling to measure electrolyte and creatinine concentration. Digoxin levels are not routinely determined unless toxicity, undertreatment, or noncompliance is suspected.

Consideration should be given for collaborative perioperative management with a cardiologist or heart failure specialist of severely affected heart failure patients (i.e., NYHA III or IV; decompensated heart failure) who will undergo intermediate-risk or high-risk procedures. Most medical therapy, including  $\beta$ -adrenergic blockers, hydralazine, nitrates, and digoxin, should be continued preoperatively. Loop diuretics (e.g., furosemide) can be continued on the day of surgery for most procedures since this strategy does not increase risks of intraoperative hypotension or adverse cardiac events.<sup>166</sup> The exception is lengthy high-risk procedures with projected significant blood loss or fluid requirements, in which potent diuretics should be held on the morning of surgery. Since ACEI and ARB administration within 24 hours before surgery is associated with increased risks of intraoperative hypotension,<sup>85</sup> and postoperative myocardial injury,<sup>86</sup> it is reasonable to withhold these medications for 24 hours before surgery, provided that they are restarted postoperatively once patients are hemodynamically stable (see section on "Hypertension").<sup>87,88</sup> Patients on anticoagulant therapy will likely need these medications temporarily discontinued before surgery (see later section on "Atrial Fibrillation"). In addition, patients with pacemakers, ICDs, and CRT devices have their own special perioperative considerations (see later section on "Cardiovascular Implantable Electronic Devices").

### Murmurs and Valvular Abnormalities

When a cardiac murmur is identified during preoperative assessment, the subsequent goals are to identify any associated cardiovascular symptoms (e.g., dyspnea, chest discomfort, orthopnea, fatigue, syncope), determine the underlying cause of the murmur, and distinguish clinically significant murmurs from unimportant ones. For example, benign functional murmurs occur with turbulent flow across the aortic or pulmonic outflow tracts during high-flow states such as hyperthyroidism, pregnancy, or anemia. Murmurs can be graded according to loudness (Table 31.7), however, the loudness of a murmur does not necessarily indicate the severity of a lesion. In contrast, the location of the murmur, and changes in intensity associated with maneuvers can be informative (Table 31.8). A Valsalva maneuver decreases right- and left-heart filling, thereby reducing the intensity of most murmurs except those of mitral valve prolapse and hypertrophic cardiomyopathy. Standing also decreases preload, and

thereby increases the intensity of murmurs of mitral valve prolapse and hypertrophic cardiomyopathy. Conversely, squatting increases venous return and afterload, thereby increasing most murmurs except those of mitral valve prolapse and hypertrophic cardiomyopathy. Having the patient repeatedly perform a hand grip increases heart rate and arterial blood pressure, thereby augmenting murmurs of mitral regurgitation and aortic insufficiency; conversely, this maneuver decreases murmurs of aortic stenosis and hypertrophic cardiomyopathy. The likelihood of a murmur being pathologic increases in the presence of increased age, cardiovascular risk factors, other abnormal heart sounds, cardiomegaly, abnormal ECG, evidence of excessive intravascular volume, and a history of rheumatic fever, pulmonary disease, or anorectic drug use. Diastolic or continuous murmurs are almost always pathologic and require further evaluation. Nonetheless, it is typically not easy to distinguish benign from pathologic murmurs based on history and physical examination alone. Thus, cardiovascular medicine guidelines now recommend transthoracic echocardiography for the initial evaluation of any patient with suspected valvular heart disease.<sup>167</sup> Additionally, perioperative guidelines recommend preoperative echocardiography for any patient who has clinically suspected moderate or severe valvular stenosis or regurgitation, and no echocardiogram within the previous year.<sup>7,9</sup> For patients with known valvular heart disease, repeat echocardiography is recommended if there has been a significant change in clinical status or physical examination since the last test.

**TABLE 31.7** Grading the Intensity of Cardiac Murmurs

Grade	Description
I	Faintest that can be heard with difficulty
II	Faint but easily heard
III	Moderately loud without a thrill
IV	Loud with a palpable thrill
V	Very loud but still need stethoscope (thrill present)
VI	Heard without a stethoscope

**Aortic Stenosis.** Aortic valve stenosis is the leading cause of left ventricular outflow obstruction in adults. In high-income countries, aortic stenosis principally occurs because of the progressive calcific disease of a native trileaflet valve or a congenitally bicuspid valve. Stenosis of bicuspid valves typically occurs when individuals are in their fourth and fifth decades of life, whereas stenosis of native trileaflet valves occurs once individuals are age 60 years old or older. Aortic stenosis severity is classified based on the valve area and mean transvalvular pressure gradient (Table 31.9). A limitation of using the pressure gradient alone to assess severity is that the gradient may decrease if the left ventricle systolic function begins to decrease. In patients with known aortic stenosis, serial echocardiography is recommended every 6 to 12 months for patients with severe disease, every 1 to 2 years for moderate disease, and every 3 to 5 years for mild disease. After a prolonged asymptomatic phase, symptoms may develop in affected patients once stenosis becomes severe. The cardinal symptoms of severe aortic stenosis are angina, heart failure, and syncope, but patients are much more likely to complain of exertional dyspnea and decreased exercise tolerance.

Aortic stenosis causes a systolic ejection murmur (see Table 31.8), best heard in the right upper sternal border and often radiating to the neck. A similar murmur occurs with aortic *sclerosis*, which is defined as thickening of the aortic valve without associated stenosis. Aortic sclerosis is present in 25% of individuals age 65 years or older, and 50% of individuals age 80 years or older. Aortic sclerosis is associated with an increased risk of cardiovascular events, and a 2% annual risk of progression to aortic stenosis.<sup>168</sup> The radiating pattern of the systolic ejection murmur can help rule out aortic stenosis, with the absence of radiation to the right clavicle being associated with a negative likelihood ratio of 0.1 for aortic stenosis.<sup>169</sup> In addition to a systolic ejection murmur, aortic stenosis is associated with a delayed carotid upstroke and paradoxically split second heart sound. Any patient with a previously undiagnosed suspicious systolic murmur should have an echocardiogram, especially since noncardiologists have difficulty in distinguishing murmurs of aortic stenosis from those of aortic sclerosis. Typical ECG abnormalities associated with aortic stenosis include LVH (often with a strain pattern), left axis deviation, and LBBB.

**TABLE 31.8** Descriptions of Murmurs Associated With Cardiac Abnormalities

Lesion	Location	Timing	Description
<b>Aortic Stenosis</b>	Second parasternal interspace	Midsystolic	Crescendo-decrescendo, radiates to the carotids; with or without $S_3$ , $S_4$ ; Valsalva maneuver and sustained hand grip exercise decrease intensity
<b>Aortic Insufficiency</b>	Third and fourth parasternal interspaces	Holodiastolic	Decrescendo, blowing, high pitched, radiates to the carotids; Austin-Flint rumble at the apex; squatting, hand grip exercise, and leaning forward increase intensity
<b>Mitral Stenosis</b>	Apex	Middiastolic	Opening snap; low-pitched rumble radiates to the axilla; squatting and hand grip exercise increase intensity
<b>Mitral Regurgitation</b>	Apex	Holosystolic	High pitched, blowing, radiates to the axilla; loud $S_3$ ; standing decreases intensity; squatting and hand grip exercise increase intensity
<b>Mitral Valve Prolapse</b>	Apex	Late systolic	Crescendo, midsystolic click; Valsalva maneuver and standing increase intensity; squatting decreases intensity
<b>Hypertrophic Cardiomyopathy</b>	Apex, lower left sternal border	Midsystolic	$S_4$ , Single $S_2$ ; Valsalva maneuver and standing increase intensity; squatting, passive leg raising, and hand grip exercise decrease intensity

Moderate to severe aortic stenosis is associated with increased risk of perioperative cardiovascular complications.<sup>170,171</sup> Nonetheless, contemporary studies suggest that noncardiac surgery can be performed with acceptable mortality risks in individuals with asymptomatic severe aortic stenosis.<sup>171</sup> Thus, guidelines support proceeding with major elective noncardiac surgery in patients with asymptomatic severe aortic stenosis, provided that appropriate intraoperative and postoperative hemodynamic monitoring is available.<sup>7,9</sup> Conversely, for patients with symptomatic severe aortic stenosis, aortic valve replacement should be considered before their planned noncardiac surgery.<sup>7,9</sup> If a symptomatic patient is deemed high-risk or ineligible for surgical aortic valve replacement, alternative intervention options include transcatheter aortic valve replacement (TAVR) or percutaneous aortic balloon dilation.<sup>7,9</sup> Multidisciplinary collaboration with a cardiologist is invaluable for the perioperative management of these high-risk patients.

Patients with moderate to severe aortic stenosis also have an increased risk of bleeding from an *acquired* von Willebrand syndrome, which occurs in 67% to 92% of patients with severe stenosis.<sup>172</sup> The underlying pathophysiology is mechanical disruption of von Willebrand multimers during turbulent blood flow through the narrowed valve. Of note, prophylaxis for infective endocarditis is not recommended.<sup>173</sup>

**Aortic Insufficiency.** Aortic valve insufficiency occurs with valvular leaflet disease, aortic root dilation, or both. Causes of valvular disease include rheumatic heart disease, bicuspid valves, collagen vascular disease, and endocarditis. With respect to aortic root dilation, causes include ankylosing spondylitis, osteogenesis imperfecta, syphilis, hypertension, age-related degeneration, Marfan syndrome, and collagen vascular diseases. These causes generally lead to progressive chronic aortic insufficiency that remains asymptomatic for decades. In contrast, acute aortic insufficiency can result from trauma, infections, or aortic dissection; this is an emergent condition that results in cardiogenic shock.

On auscultation, aortic insufficiency is associated with a diastolic murmur (see Table 31.8), the intensity of which does not correlate well with the severity of regurgitation.<sup>174</sup> Patients typically have a widened pulse pressure, which manifests as Corrigan or water-hammer pulses (bounding carotid pulse with a rapid downstroke), de Musset sign (head bob with each heart beat), Duroziez sign (systolic and diastolic bruit heard over the femoral artery when it is partially compressed), and Quincke pulses (capillary pulsations in the fingertips or lips). Although auscultation by a cardiologist can help rule in or rule out aortic regurgitation

(based on the presence or absence of an early diastolic murmur),<sup>175</sup> the accuracy of auscultation by noncardiologists is uncertain.<sup>26</sup> Thus, an echocardiogram is helpful for any patient suspected of having a diastolic murmur.

Limited prior research suggests that patients with moderate-to-severe aortic insufficiency experience increased risks of perioperative mortality and morbidity, especially in the presence of impaired left ventricular function (ejection fraction < 55%) or renal insufficiency.<sup>176</sup> Nonetheless, expert consensus from current guidelines is supportive of patients with asymptomatic severe aortic insufficiency to proceed with major noncardiac surgery accompanied by careful perioperative management, including hemodynamic monitoring, afterload control, and fluid balance.<sup>7,9,167</sup> Prophylaxis for infective endocarditis is not recommended.<sup>173</sup>

**Mitral Stenosis.** Mitral stenosis is much rarer than aortic stenosis, and almost always related to rheumatic heart disease. Other less common causes include mitral annular calcification and radiation-associated valve disease. The normal mitral valve has a cross-sectional area of 4 to 6 cm<sup>2</sup>. Mitral stenosis involves progressive reduction of this area, with shortness of breath with exertion occurring when the area falls below 2.5 cm<sup>2</sup>, and symptoms at rest occurring once the area falls below 1.5 cm<sup>2</sup>. Severe mitral stenosis is defined by a valve area less than 1 cm<sup>2</sup> and is typically associated with a pulmonary artery systolic pressure > 50 mm Hg, and a resting mean transvalvular gradient  $\geq$  10 mm Hg.

When mitral stenosis becomes symptomatic, patients experience dyspnea, fatigue, orthopnea, pulmonary edema, and hemoptysis because of increased left atrial pressures and decreased cardiac output. Atrial fibrillation can also develop, in turn causing heart failure in the short term and thrombosis in the long term. Patients with atrial fibrillation require long-term anticoagulation, with recent guidelines recommending vitamin K antagonist therapy (e.g., warfarin) as opposed to DOACs.<sup>173</sup> Pulmonary hypertension (see later section on “Pulmonary Hypertension”) and right-sided heart failure can also occur in patients with significant stenosis. The physical examination should evaluate for rales and signs of right-sided heart failure such as jugular venous distention, peripheral edema, hepatomegaly, right ventricular heave, and ascites. On auscultation, mitral stenosis is associated with a diastolic murmur that should be evaluated with echocardiography.

Medical management includes  $\beta$ -adrenergic blockers for controlling heart rate, antiarrhythmic agents for preventing or controlling atrial fibrillation, and anticoagulants in patients with atrial fibrillation. Both  $\beta$ -adrenergic blockers and antiarrhythmic agents should be continued preoperatively, while anticoagulation should be managed in conjunction with the treating cardiologist and surgeon. Prophylaxis for infective endocarditis is not recommended.<sup>173</sup> If a patient with mitral stenosis meets guideline-based indications for valvular intervention (e.g., percutaneous mitral balloon commissurotomy),<sup>167</sup> consideration should be given to performing this intervention before major elective noncardiac surgery.<sup>7,9</sup> If an asymptomatic patient with severe mitral stenosis has valve morphology that is not favorable for a percutaneous intervention, it is still reasonable to proceed with major elective noncardiac

**TABLE 31.9** Grading Severity of Aortic Stenosis

Grade	Transvalvular Jet Velocity (m/s)	Mean Pressure Gradient (mm Hg)	Valve Area (cm <sup>2</sup> )
Mild	2.0–2.9	<20	$\geq$ 1.5
Moderate	3–3.9	20–39	1.0–1.5
Severe	$\geq$ 4	$\geq$ 40	<1.0

surgery provided that appropriate intraoperative and postoperative hemodynamic monitoring is used.<sup>7</sup>

**Mitral Regurgitation.** Acute mitral regurgitation can occur in the setting of myocardial infarction, trauma, or infective endocarditis. Chronic mitral regurgitation is typically associated with degenerative mitral valve disease (including mitral valve prolapse), rheumatic heart disease, ischemic heart disease, and cardiomyopathies. Chronic mitral regurgitation progresses very gradually. Symptoms develop relatively late, and typically only after onset of left ventricular dysfunction. Associated symptoms are initially vague, but progress to fatigue, dyspnea, and atrial fibrillation with disease progression.

On auscultation, patients with mitral regurgitation usually have a holosystolic murmur heard best at the cardiac apex (see Table 31.8). The murmur grade is somewhat correlated with the severity of mitral regurgitation in primary mitral valve disease (e.g., degenerative mitral valve disease), but not in secondary functional regurgitation (e.g., ischemic heart disease, cardiomyopathies). Although auscultation by a cardiologist can help determine mitral regurgitation (based on the presence or absence of a late systolic or holosystolic murmur in the mid-left thorax), the accuracy of auscultation by noncardiologists is uncertain.<sup>26</sup> Thus, an echocardiogram is helpful for any patient with a suspicious systolic murmur. Chronic mitral regurgitation is generally well tolerated perioperatively, unless other valvular lesions (e.g., mitral stenosis) or left ventricular dysfunction coexist. Consistent with these observations, limited prior research suggests that patients with mitral regurgitation have increased risks of cardiovascular complications, but not mortality.<sup>177</sup> Current guidelines suggest that patients with asymptomatic severe mitral regurgitation can proceed to major elective noncardiac surgery provided that appropriate intraoperative and postoperative hemodynamic monitoring is available.<sup>7</sup> Prophylaxis for infective endocarditis is no longer recommended.<sup>173</sup>

**Mitral Valve Prolapse.** Mitral valve prolapse is characterized by the systolic billowing of an abnormally thickened mitral valve leaflet into the left atrium, with or without coexistent mitral regurgitation. Diagnostic criteria for mitral valve prolapse have evolved to the current definition based on echocardiography alone, namely  $\geq 2$  mm billowing of any portion of the mitral leaflets above the annular plane in the long axis view.<sup>178</sup> It is the common cause of isolated mitral regurgitation requiring surgical repair in high-income countries. Nonetheless, only 4% of patients with mitral valve prolapse have severe valvular regurgitation, with most affected individuals having mild, trace, or no mitral regurgitation.<sup>179</sup> The condition may be primary (i.e., myxomatous degeneration) or secondary (e.g., associated with Marfan syndrome, Ehlers-Danlos syndrome, and osteogenesis imperfecta). Nonspecific symptoms (e.g., atypical chest pain, palpitations, dyspnea, exercise intolerance, dizziness) have been attributed, albeit unreliably, to mitral valve prolapse—in what has been termed as the “mitral valve prolapse syndrome.”

On auscultation, these patients may have a systolic click and a mid-systolic murmur at the cardiac apex (that intensifies with a Valsalva maneuver). Auscultation by a cardiologist can help diagnose mitral valve prolapse (based on

the presence or absence of a systolic click and murmur); however, the accuracy of auscultation by noncardiologists is uncertain.<sup>26</sup> From the perioperative perspective, the key issue is to differentiate patients with clinically significant mitral valve regurgitation from those with an incidental finding of prolapse that does not warrant further evaluation. Thus, echocardiography may be helpful to further investigate murmurs suspected of representing significant mitral regurgitation. Prophylaxis for infective endocarditis is no longer recommended.<sup>173</sup>

**Tricuspid Regurgitation.** Tricuspid regurgitation is a common valvular abnormality, with 70% of normal adults exhibiting a small degree of tricuspid regurgitation on echocardiography. Since it is usually asymptomatic and not easily audible on physical examination, tricuspid regurgitation is most commonly noted as an incidental echocardiographic finding. Significant tricuspid regurgitation is most commonly caused by dilatation of the right ventricle and tricuspid annulus (i.e., secondary disease). Causes of secondary tricuspid regurgitation include left-sided heart failure, mitral valve disease (stenosis or regurgitation), primary pulmonary disease (e.g., pulmonary hypertension), left-to-right intracardiac shunts (e.g., atrial septal defect, ventricular septal defect), pulmonary artery stenosis, and right ventricle disease (e.g., arrhythmogenic right ventricular dysplasia). Tricuspid regurgitation is less commonly caused by processes directly affecting the tricuspid valve (i.e., primary disease), such as Ebstein anomaly, infective endocarditis (typically in intravenous drug users), rheumatic heart disease, carcinoid syndrome, connective tissue disorders (e.g., Marfan syndrome), myxomatous degeneration, or direct injury (e.g., permanent pacemaker or ICD lead). Certain drugs—namely anorectics (fenfluramine, phentermine) and pergolide (dopamine agonist)—have also been associated with primary tricuspid regurgitation.

Patients with mild or moderate tricuspid regurgitation are generally asymptomatic. Individuals with severe regurgitation may report pulsations in the neck (related to distended jugular veins), as well as symptoms of right-sided heart failure (e.g., ascites, peripheral edema) and underlying conditions (e.g., pulmonary hypertension). Relevant findings on physical examination include distended jugular veins, hepatomegaly, ascites, dependent edema, and a right ventricular heave on chest palpation. On auscultation, tricuspid regurgitation causes a holosystolic murmur that is heard best at the midsternal border or subxiphoid area. Nonetheless, the murmur is often absent or very soft, even with severe regurgitation. The intensity of the murmur can be increased using maneuvers that increase venous return (e.g., inspiration, abdominal pressure). Although auscultation by a cardiologist can help determine moderate-to-severe tricuspid regurgitation (based on the presence or absence of increased murmur intensity with inspiration or abdominal pressure), the accuracy of auscultation by noncardiologists is uncertain.<sup>26</sup> Thus, echocardiography may be helpful in a patient with a suspicious murmur, especially within the context of signs or symptoms of right-sided heart failure. The preoperative management of patients with severe tricuspid regurgitation should be guided by the presence of any underlying conditions, right-sided heart failure, and known or suspected pulmonary hypertension. Where

indicated, perioperative management should be conducted collaboratively with a heart failure cardiologist or pulmonary hypertension specialist. Prophylaxis for infective endocarditis is no longer recommended.<sup>173</sup>

**Hypertrophic Cardiomyopathy.** Hypertrophic cardiomyopathy is a genetic disorder of the myocardium, which can result in dynamic left ventricular outflow tract obstruction, myocardial ischemia, diastolic dysfunction, and mitral regurgitation (related to systolic anterior motion of the mitral valve leaflets). Most affected individuals have a relatively normal lifespan; however others are at risk for progressive heart failure, sudden cardiac death, and atrial fibrillation. Most patients with hypertrophic cardiomyopathy are asymptomatic. When symptoms are present, they are quite variable, and not well correlated with the extent of LVH or outflow tract obstruction. Typical associated symptoms include fatigue, exertional dyspnea, atypical or angina chest pain, exertional presyncope or syncope, and palpitations. Symptomatic patients may be prescribed long-term medical therapy with negative inotropic agents (i.e.,  $\beta$ -blockers, verapamil, disopyramide). Other symptomatic individuals with severe left ventricular outflow tract obstruction may require intervention with either surgical myectomy or alcohol septal ablation. Some patients may also undergo ICD insertion if they are deemed high-risk for sudden cardiac death.

Although the physical examination in a patient with hypertrophic cardiomyopathy may be normal, the classic finding on auscultation (see Table 31.8) is a mid-systolic murmur that increases with maneuvers to decrease ventricular size (e.g., Valsalva maneuver) and decreases with maneuvers to increase ventricular size (e.g., passive leg raise). Auscultation by a cardiologist can help rule in or rule out hypertrophic cardiomyopathy (based on decreased murmur intensity with passive leg elevation or increased murmur intensity with shifts from a squatting to standing position), however, the accuracy of auscultation by noncardiologists is uncertain.<sup>26</sup> Accordingly, an echocardiogram should be obtained if a patient has a personal (or family) history of exertional syncope or cardiac arrest; a suspicious murmur is found on auscultation; or concerning ECG findings (i.e., LVH, ST-segment abnormalities, T-wave abnormalities) are observed in an otherwise healthy nonhypertensive patient. In general, patients with hypertrophic cardiomyopathy can safely undergo most low-risk and intermediate-risk noncardiac surgical procedures, especially with close hemodynamic monitoring and management. Medical therapy (e.g.,  $\beta$ -adrenergic blockers, verapamil) should be continued perioperatively, but prophylaxis for infective endocarditis is no longer recommended.<sup>173</sup> Appropriate perioperative management should be instituted for any patient who has an associated ICD.

**Prosthetic Heart Valves.** In patients with prosthetic heart valves, the preoperative evaluation should determine the underlying indication that led to valve replacement; type, age, and current status of the valve prosthesis; need for long-term anticoagulation entailed by the valve prosthesis; and planned perioperative anticoagulation management plan. The anesthesiologist should review the most recent echocardiogram, and order a repeat echocardiogram

if there are any signs or symptoms suggestive of valve dysfunction (e.g., new onset heart failure).<sup>167</sup> In addition, a recent complete blood count may be helpful since these patients may have a valve-related hemolytic anemia.

Anticoagulation with a vitamin K antagonist (e.g., warfarin) is required for 3 to 6 months after open surgical bioprosthetic valve implantation, after which patients can be transitioned to aspirin therapy alone (75–100 mg daily).<sup>167</sup> Life-long aspirin therapy is recommended for patients who have undergone TAVR, as well as clopidogrel (75 mg daily) for the first 6 months in all patients and vitamin K antagonists for the first 3 months in select individuals.<sup>173</sup> Conversely, patients with mechanical prosthetic valves require life-long therapy with both aspirin and vitamin K antagonists.<sup>167</sup> Importantly, DOACs—such as dabigatran, rivaroxaban, edoxaban, or apixaban—should not be used for anticoagulation therapy in patients with mechanical heart valves.<sup>167</sup> In general, decisions about temporary preoperative discontinuation of anticoagulants, duration of anticoagulant discontinuation, need for “bridging” therapy with a shorter-acting drug, and type of bridging agent (intravenous heparin or LMWH) should be made in conjunction with the treating cardiologist and surgeon. Current guidelines make recommendations for bridging therapy largely based on the location of the mechanical heart valve and nature of planned surgery (Box 31.4).<sup>173</sup> Prophylaxis for infective endocarditis is recommended for

#### BOX 31.4 Recommendations for Preoperative Bridging Anticoagulation Therapy in Patients With Mechanical Heart Valves

##### Class I (Recommended)

- Continuation of vitamin K antagonist anticoagulation with a therapeutic INR is recommended in patients with mechanical heart valves undergoing minor procedures (e.g., dental extractions, cataract removal) where bleeding is easily controlled.
- Temporary interruption of vitamin K antagonist anticoagulation, without bridging agents while the INR is subtherapeutic, is recommended in patients with a bileaflet mechanical AVR and no other risk factors\* for thrombosis who are undergoing invasive or surgical procedures.

##### Class IIa (Is Reasonable)

- Bridging anticoagulation therapy during the time interval when the INR is subtherapeutic preoperatively is reasonable on an individualized basis—with the risks of bleeding weighed against the benefits of thromboembolism prevention—for patients who are undergoing invasive or surgical procedures with a (i) mechanical AVR and any thromboembolic risk factor, (ii) older-generation mechanical AVR, or (iii) mechanical MVR.

\*Risk factors include atrial fibrillation, previous thromboembolism, hypercoagulable condition, older-generation ball-cage or tilting disc mechanical valve, left ventricular systolic dysfunction, and  $\geq 2$  mechanical valves.

AVR, Aortic valve replacement; INR, international normalized ratio;

MVR, mitral valve replacement.

From Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135:e1159–e1195.

specific procedures (see section on “Infective Endocarditis Prophylaxis”).<sup>173</sup>

### Infective Endocarditis Prophylaxis

Patients at risk for infective endocarditis (e.g., valve replacement, complex congenital heart disease, previous endocarditis) and scheduled for procedures with the potential for transient bacteremia must be identified preoperatively. Current guidelines have dramatically scaled back the indications for prophylaxis. For example, current ACC/AHA guidelines recommended prophylaxis only for patients who are both at increased risk of developing infective endocarditis and also experiencing adverse outcomes from endocarditis (Box 31.5).<sup>173</sup> These target patient subgroups are also with those identified in the most recent ESC guidelines.<sup>180</sup> Prophylaxis is required when eligible patients undergo dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa. Prophylaxis is not required when these same individuals undergo nondental procedures (e.g., transesophageal echocardiography, gastroscopy, colonoscopy, cystoscopy, dermatological procedures), unless there is active infection at the procedure site.<sup>173</sup>

### Rhythm Disturbances on the Preoperative Electrocardiogram

Arrhythmias and conduction disturbances are common during the perioperative period. Supraventricular and ventricular arrhythmias are associated with increased perioperative risk, both because of the arrhythmias themselves and because they are markers for cardiopulmonary disease. Uncontrolled atrial fibrillation (i.e., causing symptoms or hemodynamic compromise) and high-risk ventricular tachyarrhythmias (see section on “Ventricular Arrhythmias”) are high-risk conditions that warrant postponement of elective surgery until evaluation and stabilization are complete. Rapid atrial fibrillation (rates > 100 beats/min), symptomatic bradycardia, or high-grade heart block (e.g.,

third-degree heart block) also warrants postponement of elective procedures to facilitate evaluation, stabilization, and possible cardiology evaluation.

First-degree atrioventricular (AV) block is defined as a PR interval exceeding 0.20 ms with an associated heart rate of 50 to 100 beats/min; it is considered generally benign. Second-degree heart block is defined by a PR interval exceeding 0.20 ms and the presence of some blocked atrial beats (resulting in a dropped or missing QRS complex after a P wave). There are two types of second-degree block. Mobitz type I block (also called Wenckebach block) is characterized by progressive lengthening of the PR interval until the dropped beat occurs. It is a more benign block that is related to AV nodal delay, easily responsive to atropine, and unlikely to progress to complete heart block. Mobitz type II block is characterized by a fixed and prolonged PR interval that does not change before the dropped QRS complex. It is related to an infranodal block, capable of progressing to complete heart block, and generally treated with a pacemaker (unless it is due to a reversible cause such as ischemia or drugs). Third-degree AV block or complete heart block, which is characterized by complete dissociation between the atrial and ventricular beats, requires pacemaker placement unless a reversible source is identified. A prolonged QT interval should prompt an evaluation of electrolytes (including magnesium and calcium), and search for any potentiating drugs. Syncope, presyncope, or a family history of sudden death in a patient with a prolonged QT interval mandates a cardiology consultation (see section on “Long QT Syndrome”).

Three factors determine the need for permanent pacemaker treatment for an arrhythmia, namely whether the arrhythmia is associated with symptoms, where the conduction abnormality is located, and whether a reversible cause can be identified. Indications for perioperative pacemaker placement are the same as those in nonsurgical patients (common indications listed in Box 31.6).<sup>181</sup> In general, pacemaker placement is required for symptomatic bradycardia or conduction delays that lead to syncope or presyncope. Conduction disease below the AV node (i.e., in the His-Purkinje system) is also generally less stable and likely benefits from permanent pacemaker placement. The presence of such conduction disease is suggested by a normal or minimally prolonged PR interval, Mobitz type II block, and QRS complex abnormalities (BBB, fascicular block, or both).

BBBs can be classified as complete versus incomplete, and right bundle branch block (RBBB) versus LBBB. BBBs may be normal variants in some individuals, or the result of age-related fibrosis in the conduction system. Nonetheless, they can be associated with important underlying conditions. For example, LBBB may be related to structural heart disease (i.e., hypertensive heart disease, IHD, cardiomyopathies, valvular heart disease), while RBBB may be the result of elevated right ventricular pressures (i.e., pulmonary hypertension, cor pulmonale, pulmonary embolism), prior radiation exposure, myocarditis, and structural heart disease (i.e., IHD, cardiomyopathies, valvular heart disease, congenital heart disease). The presence of a BBB is not itself an indicator of increased perioperative cardiovascular risk,<sup>182</sup> especially after accounting for known clinical risk factors.<sup>100</sup> Nonetheless, data from the nonoperative

#### BOX 31.5 Cardiac Conditions for Which Endocarditis Prophylaxis Is Recommended

- Previous infective endocarditis
- Prosthetic cardiac valves, including transcatheter-implanted prostheses, and homografts
- Prosthetic material used for cardiac valve repair, such as annuloplasty rings and chords
- Unrepaired cyanotic congenital heart disease, including palliative shunts and conduits
- Repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device
- Cardiac transplant with valve regurgitation due to a structurally abnormal valve

Prophylaxis is reasonable before dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa.

From Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135: e1159–e1195.

setting suggest that a recent onset or new diagnosis of a bundle branch should prompt a more extensive evaluation for undiagnosed cardiovascular disease. For example, LBBB is associated with increased risks of incident cardiovascular disease,<sup>183</sup> cardiovascular mortality,<sup>183</sup> and mortality in the nonoperative setting.<sup>184</sup> Additionally, RBBB is associated with increased risks of mortality in patients with suspected IHD, known IHD, and heart failure.<sup>185,186</sup> Based on this approach, if preoperative evaluation does not suggest significant pulmonary disease, IHD, structural heart disease, or Brugada syndrome (see section on “Brugada Syndrome”), no further preoperative evaluation of an isolated asymptomatic RBBB is warranted. Conversely, RBBB in a patient with known or suspected pulmonary disease (e.g., pulmonary hypertension) may suggest severe respiratory or vascular compromise; thus, consideration should be given to pulmonary evaluation and echocardiography if intermediate- or high-risk surgery is planned.

**Atrial Fibrillation.** Atrial fibrillation is a common arrhythmia characterized by a variable irregular ventricular response, and an absence of regular or organized atrial

### BOX 31.6 Common Indications for a Permanent Pacemaker

#### Class I Indications

- Sinus bradycardia with symptoms due to the bradycardia (typically seen with heart rates less than 40 bpm or with frequent sinus pauses)
- Symptomatic chronotropic incompetence (i.e., impaired heart rate response to exercise)
- Third-degree AV block
- Advanced second-degree AV block (block of  $\geq 2$  consecutive P waves)
- Symptomatic Mobitz I or II second-degree AV block
- Mobitz II second-degree AV block with a widened QRS or chronic bifascicular block, regardless of symptoms
- Exercise-induced second- or third-degree AV block

#### Class II Indications

- Sinus bradycardia (heart rate  $< 40$  bpm) with symptoms suggestive (but not definitively so) of bradycardia
- Sinus node dysfunction with a history of unexplained syncope
- Chronic heart rates  $< 40$  bpm in an awake but minimally symptomatic patient
- Asymptomatic Mobitz II second-degree AV block with a narrow QRS interval
- Bifascicular or trifascicular block associated with syncope possibly related to intermittent third-degree heart block
- First-degree AV block with a very long PR interval (which effectively leads to AV dissociation and hemodynamic compromise)

AV, Atrioventricular; bpm, beats per minute.

Class I Indications: Permanent pacing is definitely beneficial, useful, and effective.

Class II Indications: Permanent pacing may be indicated but there is conflicting evidence and/or divergence of opinion.

From Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2013;127:e283–e352.

activity. The arrhythmia is classified as paroxysmal (i.e., terminates spontaneously or with intervention within 7 days of onset), persistent (i.e., fails to self-terminate within 7 days), long-standing persistent (i.e., lasts more than 12 months), or permanent (i.e., persistent atrial fibrillation where a joint decision has been made by the patient and clinician to no longer pursue a rhythm control strategy).<sup>187</sup> Atrial fibrillation can occur in the absence of any structural heart disease (previously termed “lone atrial fibrillation”), or in combination with underlying disorders. In high-income countries, hypertension and ischemic heart disease are the most common underlying disorders, while in low and middle-income countries, rheumatic heart disease is a very common associated condition. Other associated conditions include valvular heart disease, heart failure, hypertrophic cardiomyopathy, congenital heart disease, obesity, diabetes mellitus, CKD, and increased age. Potentially reversible acute triggers for atrial fibrillation are hyperthyroidism and recent surgery (especially cardiac or thoracic surgery).

Affected individuals are at elevated risk for death, heart failure, thromboembolic events (i.e., stroke), and hospitalization. In the nonoperative setting, treatment involves ventricular rate control, consideration of rhythm control to restore sinus rhythm, and prevention of systemic embolization. In large randomized trials, strategies that focused on heart rate control versus rhythm control have shown similar effects on the risks of stroke or death.<sup>188,189</sup> The CHA<sub>2</sub>DS<sub>2</sub>-VASc score (Table 31.10) can be used to estimate the long-term systematic embolization risk in patients with atrial fibrillation.<sup>190</sup> Based on this score, patients can be classified as low-risk (0 points: 0.2% annualized stroke rate), intermediate-risk (1 point: 0.6% annualized stroke rate), or high-risk ( $\geq 2$  points:  $> 2.2\%$  annualized stroke rate).<sup>191</sup> Based on strong randomized controlled trial data,<sup>192</sup> current ACC/AHA guidelines recommend long-term oral anticoagulation for patients with nonvalvular atrial fibrillation (i.e.,

**TABLE 31.10** Scoring Scheme for the CHA<sub>2</sub>DS<sub>2</sub>-VASc Score

Risk Factor	Points
Heart Failure	1
Associated signs and symptoms, or left ventricular systolic dysfunction	
Hypertension	1
Age $\geq 75$ years	2
Diabetes mellitus	1
Previous stroke, transient ischemic attack, or thromboembolism	2
Vascular Disease	1
Myocardial infarction, peripheral artery disease, or aortic plaque	
Age 65–74 years	1
Female sex	1

CHADS<sub>2</sub>, Congestive heart failure, hypertension, age  $> 75$ , diabetes, prior stroke/transient ischemic attack schema; CHA<sub>2</sub>DS<sub>2</sub>-VASc, Birmingham 2009 schema.

From Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro heart survey on atrial fibrillation. *Chest.* 2010;137:263–272.

unrelated to mitral stenosis or prosthetic heart valves) and CHA<sub>2</sub>DS<sub>2</sub>-VASC scores of 2 or more, and support omitting anticoagulation in individuals with CHA<sub>2</sub>DS<sub>2</sub>-VASC scores of zero.<sup>187</sup> There is more uncertainty about the best treatment for individuals with CHA<sub>2</sub>DS<sub>2</sub>-VASC scores of 1. Consistent with this uncertainty, ACC/AHA guidelines indicate that (1) oral anticoagulant therapy, (2) aspirin therapy, or (3) omitting anticoagulation are all reasonable approaches in these intermediate-risk patients.<sup>187</sup> With respect to specific anticoagulant therapy, patients can be prescribed either a vitamin K antagonist (e.g., warfarin) or DOAC (e.g., dabigatran, rivaroxaban, edoxaban, apixaban) as reasonable options for patients with nonvalvular atrial fibrillation.

Although atrial fibrillation has typically been ignored during preoperative cardiac risk assessment, accumulating evidence challenges this approach in two main respects. Specifically, preexisting atrial fibrillation appears to be an indicator of increased perioperative risk. For example, in a large international multicenter prospective cohort study, preexisting atrial fibrillation was associated with an elevated risk of postoperative cardiovascular events (i.e., stroke, cardiovascular death, myocardial injury, heart failure, or cardiac arrest),<sup>193</sup> but not death.<sup>77</sup> In an American population-based retrospective cohort study, chronic atrial fibrillation was associated with a significantly higher risk of perioperative stroke.<sup>194</sup>

The preoperative evaluation of patients with atrial fibrillation focuses on underlying conditions (e.g., ischemic heart disease), complications (e.g., heart failure, stroke), rate or rhythm control strategies, and anticoagulation strategies. Patients with rapid ventricular rates (>100 beats/min) typically require rate control before any elective surgery. Patients with both atrial fibrillation and slow ventricular rate without rate-controlling medications may have sick sinus syndrome. They should be questioned regarding any previous episodes of syncope or presyncope. Any long-term  $\beta$ -adrenergic blockers, digoxin, calcium channel blockers, or antiarrhythmic medications should be continued.

The critical component for preoperative planning for most patients with atrial fibrillation is appropriate perioperative management of long-term anticoagulants. This management should ideally be conducted collaboratively with the treating physician and responsible surgeon. There are three overarching issues, namely (1) whether temporary preoperative discontinuation is needed, (2) when oral anticoagulants should be discontinued, and (3) whether bridging therapy with LMWH is required.<sup>195</sup> It is reasonable to continue vitamin K antagonist therapy if an individual does not have patient-related risk factors for bleeding (e.g., liver disease, abnormal renal function, prior bleeding complications), and is scheduled for a procedure without important bleeding risk (e.g., dental extraction, simple cutaneous procedures, pacemaker insertion). Otherwise, patients should have their anticoagulant medications temporarily discontinued before surgery, including all patients who are receiving DOACs or might need neuraxial anesthesia. If a decision to temporarily discontinue oral anticoagulants is made, vitamin K antagonists should be stopped 5 days before surgery. A longer discontinuation period may be needed for initial international normalized ratio (INR) values greater than 3.0. Ideally, the INR should be rechecked within 24 hours before surgery,<sup>195</sup> and a low dose of oral vitamin K

administered for any INR result above 1.5. The timing of preoperative discontinuation of DOACs (Table 31.11) should be guided by the specific drug prescribed, expected procedural bleeding risk, renal function (based on estimated glomerular filtration rate [GFR]), and planned use of neuraxial anesthesia.<sup>195,196</sup> The ongoing multicenter Perioperative Anticoagulant Use for Surgery Evaluation prospective cohort study is expected to provide more high-quality data on the safety of a further simplified strategy for preoperative discontinuation of DOACs (Table 31.12).<sup>197</sup>

Accumulating evidence indicates that most patients with nonvalvular atrial fibrillation do not require bridging therapy if their anticoagulant therapy is temporarily discontinued before surgery. For example, in the multicenter Bridging Anticoagulation in Patients Who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure and Surgery (BRIDGE) randomized trial, placebo was non-inferior to LMWH bridging therapy with respect to risks of arterial thromboembolism following perioperative interruption of vitamin K antagonist therapy.<sup>198</sup> In addition, bridging therapy led to increased risks of major bleeding. When interpreting the trial data, the challenge pertains to their generalizability to patients in clinical practice. For example, about 62% of the 1884

**TABLE 31.11** Expert Consensus Recommendations on Preoperative Direct Oral Anticoagulant Discontinuation (Recommended Time Interval from Last Preoperative Dose)

Direct Factor Xa Inhibitor (i.e., Rivaroxaban, Edoxaban, Apixaban)	Direct Thrombin Inhibitor (i.e., Dabigatran)
<b>LOW BLEEDING RISK PROCEDURES (ACC RECOMMENDATIONS)*</b>	
eGFR $\geq$ 80 mL/min: $\geq$ 24 h	eGFR $\geq$ 30 mL/min: $\geq$ 24 h
eGFR 50–79 mL/min: $\geq$ 36 h	eGFR 15–29 mL/min: $\geq$ 36 h
eGFR 30–49 mL/min: $\geq$ 48 h	eGFR < 15 mL/min: No data (consider $\geq$ 48 h)
eGFR 15–29 mL/min: $\geq$ 72 h	
eGFR < 15 mL/min: No data	
<b>UNCERTAIN, INTERMEDIATE, OR HIGH BLEEDING RISK PROCEDURES (ACC RECOMMENDATIONS)*</b>	
eGFR $\geq$ 80 mL/min: $\geq$ 48 h	eGFR $\geq$ 30 mL/min: $\geq$ 48 h
eGFR 50–79 mL/min: $\geq$ 72 h	eGFR < 30 mL/min: No data (consider $\geq$ 72 h)
eGFR 30–49 mL/min: $\geq$ 96 h	
eGFR 15–29 mL/min: $\geq$ 120 h	
eGFR < 15 mL/min: No data	
<b>PLANNED NEURAXIAL ANESTHESIA (ASRA RECOMMENDATIONS)†</b>	
Uniform approach: 120 h	72 h
Approach based on eGFR	
■ eGFR $\geq$ 80 mL/min: $\geq$ 72 h	
■ eGFR 50–79 mL/min: $\geq$ 96 h	
■ eGFR 30–49 mL/min: $\geq$ 120 h	
■ eGFR < 30 mL/min: Not recommended	

ACC, American College of Cardiology; ASRA, American Society of Regional Anesthesiologists; eGFR, estimated glomerular filtration rate (Cockcroft-Gault equation).

\*From Doherty JU, Gluckman TJ, Hucker WJ, et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force. *J Am Coll Cardiol*. 2017;69:871–898.

†From Horlocker TT, Vandermeulen E, Kopp SL, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). *Reg Anesth Pain Med*. 2018;43:263–309.

**TABLE 31.12** Simplified Protocol for Preoperative Direct Oral Anticoagulant Discontinuation—as Assessed in the Perioperative Anticoagulant Use for Surgery Evaluation Study

Direct Thrombin Inhibitor (i.e., Dabigatran)	Direct Factor Xa Inhibitor (i.e., Rivaroxaban, Apixaban)
<b>LOW BLEEDING RISK PROCEDURES (NO PLANNED NEURAXIAL ANESTHESIA)</b>	
eGFR ≥ 50 mL/min: last dose 2 days before surgery	eGFR ≥ 30 mL/min: last dose 2 days before surgery
eGFR 30–49 mL/min: last dose 4 days before surgery	
<b>HIGH BLEEDING RISK PROCEDURES (NO PLANNED NEURAXIAL ANESTHESIA)</b>	
eGFR ≥ 50 mL/min: last dose 3 days before surgery	eGFR ≥ 30 mL/min: last dose 3 days before surgery
eGFR 30–49 mL/min: last dose 5 days before surgery	

eGFR, Estimated glomerular filtration rate.\*

\*Should be calculated using the Cockcroft-Gault equation.

From Douketis JD, Spyropoulos AC, Anderson JM, et al. The Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) Study for patients on a direct oral anticoagulant who need an elective surgery or procedure: design and rationale. *Thromb Haemost*. 2017;117: 2415–2424.

participants in the BRIDGE trial had an expected 1-year stroke rate less than 5% (i.e., equivalent to CHA<sub>2</sub>DS<sub>2</sub>-VASC score ≤ 4), while about 14% had an expected 1-year stroke rate over 10% (equivalent to CHA<sub>2</sub>DS<sub>2</sub>-VASC score ≥ 7). To help clinicians better navigate clinical decision making, the ACC published a 2017 expert consensus report on perioperative anticoagulation management in nonvalvular atrial fibrillation.<sup>195</sup> In the case of vitamin K antagonist therapy, the recommended approach is to omit bridging therapy in low-risk patients who have CHA<sub>2</sub>DS<sub>2</sub>-VASC scores of 4 or less and no prior stroke, TIA, or systemic embolization. Conversely, bridging therapy should be considered for high-risk patients with CHA<sub>2</sub>DS<sub>2</sub>-VASC scores of 7 or more, recent (i.e., prior 3 months) stroke, TIA, or systemic embolization. For intermediate-risk patients (i.e., those not meeting either the low-risk or high-risk criteria), bridging therapy should be considered if there is no significant bleeding risk and a more remote time (more than 3 months) of stroke, TIA, or systemic embolization. Bridging therapy is generally not needed after preoperative interruption of DOACs because of their relatively short half-lives.

**Supraventricular Arrhythmias.** Supraventricular tachycardia can result from rapidly firing ectopic atrial foci with rapid conduction through the AV node, or from a reentry mechanism. Pathways for a reentry mechanism typically involve the AV node-Purkinje system and an accessory reentry pathway. In a reentry mechanism, the cycle self-perpetuates because conduction occurs down one pathway and up the other. Pharmacologic AV blockade (i.e., adenosine, verapamil, β-adrenergic blockers) can help slow the ventricular rate in most supraventricular tachycardias, with the exception of Wolff-Parkinson-White (WPW) syndrome. WPW syndrome is characterized by the presence of an accessory pathway (bundle of Kent) that permits both retrograde and antegrade conduction. Antegrade conduction over the

accessory pathway results in a short PR interval (<0.12 ms) and a slurring of the upstroke of the QRS complex (termed a delta wave). Individuals with WPW syndrome are predisposed to supraventricular tachycardia. Additionally, treatment of supraventricular tachycardia in affected individuals with AV nodal blocking drugs can paradoxically increase conduction over the accessory pathway, thus potentially causing ventricular fibrillation. Thus, *acute* supraventricular tachycardia in these patients should be treated with electrical cardioversion (especially if hemodynamically unstable), ibutilide,<sup>199</sup> or procainamide. Long-term management of WPW syndrome typically involves catheter ablation of the recurrent accessory pathway. Long-term antiarrhythmic medications should be continued perioperatively in patients with known supraventricular tachycardia.<sup>9</sup>

**Ventricular Arrhythmias.** Ventricular ectopic beats can be differentiated from atrial ectopic beats by a wide QRS complex (>0.12 ms) and absence of an associated P-wave. To help predict the risk of sudden death, ventricular arrhythmias may be classified based on the type of rhythm disturbance and presence of underlying heart disease.

- **Benign** ventricular arrhythmias include isolated ventricular premature beats (VPBs) without associated heart disease. Affected individuals have no increased risk of sudden cardiac death, and do not need further cardiology evaluation.
- **Potentially lethal** arrhythmias include more than 30 VPBs per hour, or nonsustained ventricular tachycardia in association with underlying heart disease. Affected individuals are at moderately high risk of sudden cardiac arrest and may benefit from an ICD. They also require cardiology evaluation and echocardiography, along with the possible need for cardiac stress testing, coronary angiography, and electrophysiology testing.
- **Lethal** arrhythmias include sustained ventricular tachycardia, ventricular fibrillation, and VPBs associated with underlying heart disease, depressed cardiac function, and hemodynamic compromise. Affected individuals are at high risk for sudden cardiac arrest, and likely benefit from an ICD. They also require cardiology evaluation and echocardiography, along with possible cardiac stress testing, coronary angiography, and electrophysiology testing. In general, reversible causes of ventricular arrhythmias (e.g., hypokalemia, ischemia, acidosis, hypomagnesemia, drug toxicity, endocrine dysfunction) should be sought out and treated. Any long-term antiarrhythmic medications should be continued perioperatively.<sup>9</sup>

**Long QT Syndrome.** The long QT syndrome (LQTS) is a myocardial repolarization disorder associated with a prolonged QT interval. The QT interval is measured using a 12-lead ECG (preferably leads II and V5) from the onset of the QRS complex to the end of the T wave. Since the interval varies inversely with heart rate, a corrected QT interval (QT<sub>c</sub>) can be calculated, with the most common formula being:

$$QT_c = \frac{QT \text{ interval}}{\sqrt{RR \text{ interval}}}$$

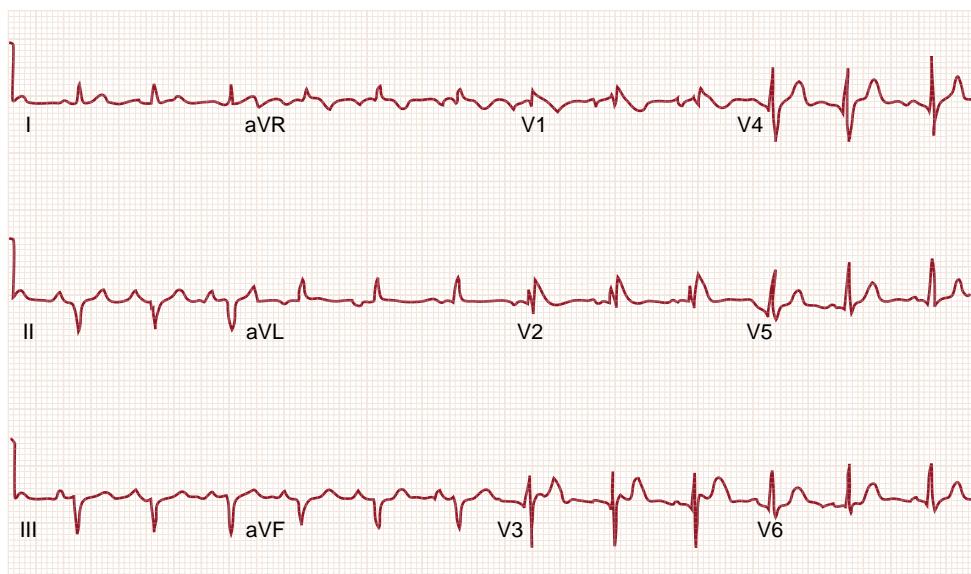


Fig. 31.7 Typical 12-lead electrocardiogram in a patient with Brugada syndrome.

In adults, an abnormally prolonged QTc is defined as a value exceeding the 99th percentile. The QTc is prolonged if exceeding 0.48 seconds in women and 0.47 seconds in men.<sup>200</sup> Individuals with LQTS are predisposed to developing *torsades de pointes*, a polymorphic ventricular tachycardia with frequent variations of the QRS axis or morphology. Affected patients are generally asymptomatic in the absence of arrhythmias. Conversely, after the onset of an arrhythmia, they may develop palpitations, syncope, seizures, and sudden cardiac death.

LQTS may be either congenital (i.e., genetic) or acquired. Causes of acquired LQTS include antiarrhythmic drugs (e.g., quinidine, sotalol, dofetilide, ibutilide), psychotropic medications (e.g., haloperidol, methadone), erythromycin, cisapride, and metabolic abnormalities (i.e., hypokalemia, hypomagnesemia, hypocalcemia). Notably, while amiodarone does markedly prolong the QT interval, it is rarely associated with *torsades de pointes* except in association with hypokalemia. The 2010 ACC/AHA scientific statement on the prevention of *torsades de pointes* suggests that QTc be documented before initiation or after an increased dose of QT-prolonging drugs, and thereafter at least every 8 to 12 hours.<sup>200</sup> Other components of treatment for LQTS include  $\beta$ -adrenergic blockers (congenital LQTS), ICD implantation, and correction of underlying metabolic disorders.

**Brugada Syndrome.** Brugada syndrome is a rare cause of sudden cardiac arrest that occurs in the absence of structural heart disease. It is an autosomal dominant disorder that is more common in men, rarely diagnosed in children, and often affects individuals of Asian ethnicity. Patients usually have normal findings on echocardiography, stress testing, and cardiac magnetic resonance imaging (MRI). The most significant clinical manifestations are ventricular arrhythmias, syncope, and sudden death. Patients may also be at increased risk of atrial arrhythmias, especially atrial fibrillation. Brugada syndrome is characterized by an ECG with pseudo-RBBB and persistent ST-segment elevation in leads V<sub>1</sub> to V<sub>3</sub> (Fig. 31.7). Unlike usual RBBB, a widened S

wave in the left lateral leads is usually absent in Brugada syndrome. In some patients, these ECG changes are transient and provoked by medications. Asymptomatic patients who have these typical ECG features but no other associated clinical criteria have been described as having “Brugada pattern.” The website [www.brugadadrugs.org](http://www.brugadadrugs.org) lists drugs that are associated with adverse events in Brugada syndrome. These medications include some commonly used anesthetic drugs, such as propofol and bupivacaine. The syndrome has no proven pharmacologic treatment; indeed, class I antiarrhythmic medications (e.g., flecainide, procainamide) and  $\beta$ -adrenergic blockers can worsen the risk of lethal arrhythmias. ICD implantation is the standard of care for Brugada syndrome.

### Cardiovascular Implantable Electronic Devices

Cardiovascular implantable electronic devices (CIEDs), which include both permanent pacemakers and ICDs, are very common. For example, in the United States alone, about 190,000 permanent pacemakers and 145,000 ICDs are implanted every year (see Chapter 38).<sup>201,202</sup> The preoperative evaluation should characterize the device with respect to type, age, manufacturer, model number, current settings, and timing of recent interrogation. Patients frequently carry a manufacturers’ identification card with some of this relevant information. Permanent pacemaker capabilities are usually classified using a five-letter code (Table 31.13).<sup>203</sup> The anesthesiologist should also evaluate any coexisting cardiac disease because patients with CIEDs invariably have conditions such as heart failure, IHD, valvular heart disease, or potentially lethal arrhythmias—all of which have perioperative implications. It is especially important to note device features (e.g., rate modulation) that can malfunction with perioperative electromagnetic and other interferences. Sources of electromagnetic interference during the perioperative period include electrocautery (especially monopolar), radiofrequency ablation, lithotripsy devices, and radiation therapy, while direct mechanical interference can occur with guidewire movement during

**TABLE 31.13** Pacemaker Nomenclature

Position I	Position II	Position III	Position IV	Position V
Chamber(s) Paced	Chamber(s) Sensed	Response to Sensing	Rate Modulation	Multisite Pacing
<b>O</b> = None	<b>O</b> = None	<b>O</b> = None	<b>O</b> = None	<b>O</b> = None
<b>A</b> = Atrium	<b>A</b> = Atrium	<b>I</b> = Inhibited	<b>R</b> = Rate modulation	<b>A</b> = Atrium
<b>V</b> = Ventricle	<b>V</b> = Ventricle	<b>T</b> = Triggered		<b>V</b> = Ventricle
<b>D</b> = Dual (A + V)	<b>D</b> = Dual (A + V)	<b>D</b> = Dual (T + I)		<b>D</b> = Dual (A + V)

From Bernstein AD, Daubert JC, Fletcher RD, et al. The revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing. North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group. *Pacing Clin Electrophysiol*. 2002;25:260–264.

central venous catheter insertion.<sup>204</sup> These sources of interference can result in CIED malfunction, such as inappropriate ICD discharge or inappropriate changes in pacing rates. Especially during delicate surgical procedures (e.g., intracranial, spinal, ocular), an unexpected ICD discharge with movement of the patient can have catastrophic results.

In general, the anesthesiologist conducting a preoperative evaluation of a patient with a CIED should collaboratively plan perioperative management with the relevant CIED care team (Box 31.7).<sup>7,204</sup> The CIED care team has been defined as the physicians and physician extenders who monitor the patient's CIED function. Ideally, patients with CIEDs should have these devices interrogated preoperatively, with recommendations that this be performed within the prior 6 months for an ICD, prior 12 months for a permanent pacemaker, and prior 3 to 6 months for any CRT device. Key issues for consideration when planning the perioperative care of a patient with a CIED include whether the patient has an ICD, whether the patient is pacemaker-dependent, and what happens with magnet placement over the CIED. In general, a magnet suspends antitachyarrhythmia therapy in most ICDs, and switch pacemakers (but not ICDs) to an asynchronous pacing mode. There is some disagreement among guidelines whether to place a magnet over the CIED during the intraoperative period,<sup>204,205</sup> versus arrange for temporary device reprogramming (i.e., switch pacemaker to asynchronous mode, and disable anti-tachyarrhythmia ICD).<sup>206</sup> Especially given the complexity of newer generation CIEDs, routine magnet use should not be viewed as an alternative for appropriate preoperative preparation. Collaboration with the CIED care team is the preferred approach for managing these patients in an individualized manner. Preoperative recommendations for CIEDs are presented in Box 31.8. In addition, these patients require a preoperative ECG. A chest radiograph is not mandatory before surgery but can reveal the device location and manufacturer's code.

### Peripheral Artery Disease

PAD, which is defined as atherosclerosis of the large-sized and medium-sized noncardiac arterial vasculature, affects about 200 million people worldwide.<sup>207</sup> PAD is diagnosed based on an ankle-brachial index (ABI or ratio of ankle-to-arm systolic blood pressure) of less than 0.90.<sup>208</sup> The disease generally affects lower extremity vessels more than upper extremity vessels. PAD progresses variably across individuals, from an initially asymptomatic phase to intermittent claudication (i.e.,

### BOX 31.7 Proposed Principles for Cardiovascular Implantable Electronic Device Management

The perioperative management of CIEDs must be individualized to the patient, type of CIED, and procedure being performed. A single recommendation for all CIED patients is not appropriate. The CIED care team is defined as the physicians and physician extenders who monitor the CIED function of the patient. The surgical or procedural team should communicate with the CIED care team to identify the type of procedure and likely risk of EMI. The CIED care team should communicate with the procedure team to deliver a prescription for the perioperative management of patients with CIEDs. For most patients, the prescription can be made from a review of the records of the CIED clinic. A small percentage of patients may require consultation from CIED specialists if the information is not available. It is inappropriate to have industry-employed allied health professionals independently develop this prescription.

CIED, Cardiovascular implantable electronic devices; EMI, electromagnetic interference.

From Crossley GH, Poole JE, Rozner MA, et al. The Heart Rhythm Society (HRS)/American Society of Anesthesiologists (ASA) Expert Consensus Statement on the perioperative management of patients with implantable defibrillators, pacemakers and arrhythmia monitors: facilities and patient management: executive summary. *Heart Rhythm*. 2011;8:e1–e18.

extremity pain with activity) to critical limb ischemia. Risk factors for PAD include increased age, smoking, hypertension, diabetes mellitus, CKD, and known atherosclerosis in other sites (e.g., IHD). Conversely, patients with PAD likely have atherosclerosis in other sites (e.g., heart, brain). For example, a systematic review in the nonoperative setting found a prevalence of IHD in individuals with PAD ranged from 60% based on cardiac stress testing to 90% based on coronary angiography.<sup>209</sup> Individuals meeting diagnostic criteria for PAD (i.e., ABI < 0.90) have elevated risks for subsequent myocardial infarction, acute stroke, or cardiovascular death in the nonoperative setting.<sup>210</sup> PAD is also a marker of increased risk in surgical patients. An ABI less than 0.90 is independently associated with an increased risk of cardiovascular complications after noncardiac surgery.<sup>211</sup> Known PAD is also associated with elevated risks of mortality after major noncardiac surgery.<sup>77,78</sup> In addition, claudication related to PAD generally

### BOX 31.8 Preoperative Recommendations for Cardiovascular Implantable Electronic Devices

- Inactivation of ICDs is not absolutely necessary for all procedures
- Not all pacemakers need to be altered to pace asynchronously in all patients or for all procedures
- Pacemakers can be reprogrammed or magnets can be used to force pacemakers to pace asynchronously to prevent inhibition
- ICDs can be reprogrammed or magnets can be used to inhibit ICD arrhythmia detection and tachyarrhythmia functions
- Magnets can/will not force pacemakers in ICDs to pace asynchronously
- Inactivation of ICDs is recommended for all procedures above the umbilicus involving electrocautery or radiofrequency ablation
- It is preferable to change to asynchronous pacing in pacemaker-dependent patients for procedures involving electrocautery or radiofrequency ablation above the umbilicus

The procedure team provides the following information to the CIED team:

- Type of procedure
- Anatomic site of procedure
- Patient position during procedure
- Will electrocautery (and type of cautery) be used?
- Are there other sources of EMI?
- Other issues such as likelihood of damage to leads (e.g., chest procedures), anticipated large blood loss, and surgery in close proximity to CIED

The CIED care team provides the following information to the procedure team:

- Type of device (e.g., pacemaker, ICD)
- Indication for device (e.g., sick sinus syndrome, primary or secondary prevention of lethal arrhythmias)
- Programming (e.g., pacing mode, rate, rate responsive, heart rates for shock delivery)
- Is the patient pacemaker-dependent, and what is the underlying heart rate/rhythm?
- Magnet response
  - Pacing rate
  - Is the device responsive to a magnet?
  - Will ICD functions resume automatically with magnet removal?
  - Does magnet need to be placed off-center?

*CIED*, Cardiovascular implantable electronic device; *EMI*, electromagnetic interference; *ICD*, implantable cardioverter-defibrillator.

Modified from Crossley GH, Poole JE, Rozner MA, et al. The Heart Rhythm Society (HRS)/American Society of Anesthesiologists (ASA) Expert Consensus Statement on the perioperative management of patients with implantable defibrillators, pacemakers and implantable monitors: facilities and patient management: executive summary. *Heart Rhythm*. 2011;8:e1–e18.

limits functional capacity and thereby masks the symptoms of underlying IHD or heart failure.

The preoperative evaluation of PAD should encompass related symptoms (e.g., intermittent claudication, rest pain), risk factors (e.g., hypertension, diabetes mellitus, smoking, CKD), and associated comorbidities (e.g., IHD, CVD). Arterial blood pressure should be measured in both upper extremities, along with the presence of peripheral arterial pulses. Auscultation for bruits over the abdomen and femoral arteries, as well as palpation for abdominal masses, should be part of the vascular examination. Typical

preoperative laboratory testing includes an ECG and blood sampling for a complete blood count, creatinine concentration, and glucose concentration. These individuals may often need further specific workup for IHD with testing such as natriuretic peptides and cardiac stress testing (see section on “Ischemic Heart Disease”). Depending on concomitant risk factors and cardiovascular medications, patients may be on long-term therapy with aspirin, P2Y<sub>12</sub> inhibitors (e.g., clopidogrel), and DOACs. DOACs should be temporarily discontinued before surgery (see section on “Atrial Fibrillation”). In most cases, P2Y<sub>12</sub> inhibitor therapy should also be interrupted before surgery, with the possible exception of cases with very recent coronary stent implantation (see section on “Coronary Stents”). As a general strategy for patients undergoing noncardiac surgery, continuing aspirin perioperatively does not prevent cardiovascular complications except in those with drug-eluting coronary stents,<sup>136</sup> but leads to an increased risk of major bleeding (which is a risk factor for perioperative stroke).<sup>132</sup> Nonetheless, selective continuation of aspirin should be considered in patients undergoing vascular surgery (to mitigate risks of bypass graft occlusion), as well as those with high-risk IHD, prior PCI, or recent stroke (i.e., previous 9 months).<sup>212</sup>

## PULMONARY DISORDERS

See Chapters 13 and 53.

### Asthma

The Global Initiative for Asthma (<http://ginasthma.org>), describes asthma as a “*heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.*” These episodes of airflow obstruction within the lung are often reversible, either spontaneously or with treatment. The airway obstruction can be precipitated by irritants (e.g., smoke), allergens, infections, medications, or airway instrumentation. Worldwide, it is estimated that asthma afflicts more than 300 million people, and is responsible for one in every 250 deaths.<sup>213</sup> Asthma is classified as intermittent, persistent mild, persistent moderate, and persistent severe, based on symptoms, nighttime awakenings, short-acting bronchodilator requirement, functional impairment, and pulmonary function test (PFT) abnormalities. Although spirometry is the preferred diagnostic test for asthma, a normal result does not exclude asthma. Typical findings on PFTs are a reduction in the ratio of the forced expiratory volume in 1 second (FEV<sub>1</sub>) to forced vital capacity (FVC)—with a ratio below 0.7 being indicative of airflow obstruction. Importantly, normal initial PFT results do not necessarily exclude asthma. If results are normal but a diagnosis of asthma is still strongly suspected, a methacholine challenge test or a trial of bronchodilator therapy should be performed. Patients with mild well-controlled asthma have no greater perioperative risk than do individuals without asthma.<sup>214</sup> In addition, PFTs, while helping to establish the diagnosis of asthma, generally have no perioperative prognostic value in these patients.

In a patient with known asthma, the anesthesiologist should inquire about dyspnea, chest tightness, cough

(especially nocturnal), recent exacerbations (with associated triggers), therapy (especially corticosteroids), prior hospitalizations, prior emergency department visits, prior critical care unit admissions, prior need for endotracheal intubation, and recent upper respiratory tract infections (see section on “Upper Respiratory Tract Infections”). It is helpful to ask patients to compare their current asthma symptoms to their “normal” or “best” status based on symptoms, exercise tolerance, and medication requirements. The physical examination should assess the quality of breath sounds, quantity of air movement, degree of wheezing, and oxygen saturation by pulse oximetry. The degree of wheezing does not always correlate with the severity of bronchoconstriction. With severe obstruction, airflow is dangerously restricted, and wheezing diminishes. Wheezing is common in asthma but it is not specific for the disease. For example, wheezing may be present in chronic obstructive pulmonary disease (COPD), gastroesophageal reflux disease, vocal cord dysfunction, tracheal stenosis, bronchial stenosis, cystic fibrosis, allergic bronchopulmonary aspergillosis, and heart failure. Observing the degree of accessory muscle use can also help gauge the severity of bronchoconstriction.

Arterial blood gases are not necessary unless the patient is having a severe acute exacerbation. Patients taking oral corticosteroids should have their blood glucose checked. Chest radiography is needed only if an infection or pneumothorax is suspected. Bronchodilators, corticosteroids (inhaled and oral), and any antibiotics must be continued on the day of surgery.  $\beta$ -adrenergic agonists are a useful prophylactic intervention to lower the risk of bronchospasm after induction of anesthesia. This therapy can be supplemented with a short preoperative course of oral corticosteroids (prednisone 20 mg-60 mg daily for 3-5 days) in any newly diagnosed or poorly controlled asthmatic patient.<sup>215</sup> Importantly, some asthmatics on chronic corticosteroid treatment may need perioperative “stress dose steroids” (see section on “Hypothalamic-Pituitary-Adrenal Disorders”).

### Chronic Obstructive Pulmonary Disease

COPD is a chronic respiratory disease that affects 175 million people worldwide, and causes 3 million deaths every year.<sup>216</sup> It is characterized by persistent airflow obstruction that occasionally is partially reversible (see Chapters 13 and 53). It may be the result of smoking, environmental pollutants (e.g., air pollution),  $\alpha_1$ -antitrypsin deficiency, chronic infections, and long-standing asthma. The Global Initiative for Chronic Obstructive Lung Disease describes COPD as a “*common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases*” (<http://www.goldcopd.org>). COPD includes subtypes such as “chronic bronchitis” and “emphysema.” Chronic bronchitis is defined as a chronic productive cough for 3 months in each of 2 successive years in a patient in whom other causes of chronic cough (e.g., bronchiectasis) have been excluded. Emphysema refers to pathologic structural changes in the lung that can occur with COPD, including enlargement of airspaces distal to the terminal bronchioles, as well as destruction of these airspace walls. The severity of COPD is classified based on both spirometry findings and

symptoms. Once a patient has evidence of airway obstruction on spirometry (FEV<sub>1</sub>/FVC ratio < 0.7), mild FEV<sub>1</sub> airflow limitation is at or greater than 80% of predicted, moderate limitation is FEV<sub>1</sub> between 50% and 79% of predicted, severe limitation is FEV<sub>1</sub> between 30% and 49% of predicted, and very severe limitation is FEV<sub>1</sub> less than 30% of predicted. Symptom severity is classified separately using validated scales.<sup>217</sup> A COPD exacerbation is defined as “*an acute worsening of respiratory symptoms that result in additional therapy*” (<http://www.goldcopd.org>).

The preoperative evaluation of patients with COPD is similar to that of patients with asthma, with an additional emphasis on signs of recent infection (e.g., changes in sputum amount or color). A barrel chest and pursed-lip breathing also suggest advanced disease. COPD is a known risk factor for postoperative pulmonary complications (see section on “Postoperative Pulmonary Complications”).<sup>218</sup> Nonetheless, there is no established threshold of COPD severity indicative of highly prohibitive perioperative risk. In general, PFTs are not useful for estimating perioperative risk in patients with COPD, with the exception of individuals undergoing lung resection surgery (see Chapter 53 and section on “Patients Scheduled for Lung Resection”). In general, preoperative PFTs are indicated when there is uncertainty as to whether the patient’s lung function is optimized, or uncertainty as to the underlying basis for unexplained dyspnea. Patients who are hypoxic, or require supplemental oxygen, may benefit from further testing, including arterial blood gas measurement, in addition to routine measurement of oxygen saturation using pulse oximetry. A chest radiograph is useful only if infection or bullous disease is suspected. A key goal in the preoperative preparation of a patient with COPD is optimizing pulmonary function before any elective surgery. Accordingly, patients with a recent exacerbation may require more intensive bronchodilator treatment, brief courses of antibiotics or oral corticosteroids, and possible deferral of elective surgery. Smoking cessation should be encouraged for any ongoing smokers (see section on “Smokers and Second-Hand Smoke Exposure”). Additionally, consideration can be given to preoperative inspiratory muscle training and physiotherapy in high-risk patients, and discussion about the potential respiratory benefits of neuraxial anesthesia or analgesia (see section on “Postoperative Pulmonary Complications”). Inhalers and other long-term medications for COPD should be continued on the day of surgery, and individuals on chronic corticosteroid treatment may need “stress dose steroids” (see section on “Hypothalamic-Pituitary-Adrenal Disorders”).

### Restrictive Pulmonary Disorders

Restrictive lung disease is characterized by a reduced total lung capacity and may be related to both pulmonary or extrapulmonary conditions. Pulmonary causes include idiopathic interstitial pneumonia, prior lung resection, pulmonary fibrosis, and interstitial lung disease secondary to connective tissue disease. Extrapulmonary causes include chest wall limitations (e.g., kyphoscoliosis, obesity, ankylosing spondylitis), muscle dysfunction (e.g., muscular dystrophies, myasthenia gravis, diaphragm paralysis), and pleural disease (e.g., mesothelioma, effusion, pneumothorax). In a patient with suggestive symptoms or history of

associated diseases, a chest radiograph and PFTs can help establish the diagnosis. Typically, the FEV<sub>1</sub> and the FVC are reduced proportionally such that the FEV<sub>1</sub>/FVC ratio is normal (i.e., > 0.7). Preoperative PFTs can also help assess for acute or progressive worsening of known restrictive lung disease; however, routine testing is not necessary in the absence of clinical suspicion. These patients are also at risk of pulmonary hypertension that may not be recognized because of overlapping symptoms with restrictive lung disease. Thus, echocardiography may also be indicated to investigate causes of worsening symptoms in a patient with known restrictive lung disease.

### **Patients Scheduled for Lung Resection**

Most patients scheduled for lung resection operations have underlying lung disease (this topic is covered in more detail in [Chapter 53](#)). Spirometry is useful in estimating risk and excluding patients who are highly likely to lack adequate pulmonary reserve after the planned resection (see [Chapter 53](#)). Current American College of Chest Physicians (ACCP) guidelines recommend measurement of both FEV<sub>1</sub> and diffusing capacity for carbon monoxide (D<sub>LCO</sub>) in all patients being considered for lung resection surgery.<sup>219</sup> The amount of residual lung function after resection can be estimated by using a combination of spirometry and radionuclide quantitative lung scanning. The predicted postoperative FEV<sub>1</sub> (PPO FEV<sub>1</sub>) is predicted by multiplying the preoperative FEV<sub>1</sub> by the percentage of perfusion to the nonoperative lung or lung region:

$$\text{PPO FEV}_1 = \text{Preoperative FEV}_1 \times \frac{\text{Perfusion to nonresected lung}}{\text{Total perfusion to lungs}}$$

The PPO D<sub>LCO</sub> is calculated using an analogous equation for preoperative D<sub>LCO</sub>. Patients with both PPO FEV<sub>1</sub> and PPO D<sub>LCO</sub> values exceeding 60% of predicted are considered low-risk and can generally proceed directly to surgery. If either value is within the range of 30% to 60% of predicted, simple objective exercise testing with a shuttle walk test or symptom limited stair climbing test is recommended. For individuals with poor performance on these simple tests (i.e., < 400 m on shuttle walk test or < 22 m on stair climbing test), as well as for individuals with either PPO FEV<sub>1</sub> or PPO D<sub>LCO</sub> values less than 30% predicted, the ACCP guidelines recommend CPET to measure peak oxygen consumption (VO<sub>2</sub> peak).<sup>219</sup> A preoperative VO<sub>2</sub> peak greater than 20 mL/kg/min is consistent with low perioperative risk, 10 to 20 mL/kg/min is consistent with moderate risk, and less than 10 mL/kg/min is consistent with high risk. Nonsurgical options should be considered in high-risk scenarios, while shared decision making should be incorporated in any intermediate-risk scenarios.

### **Obstructive Sleep Apnea**

In North America, the prevalence of sleep-disordered breathing is 9% among females aged 30 to 60 years of age, and 24% among males in the same age group (see [Chapter 10](#)).<sup>220</sup> OSA is the most common type of sleep-disordered breathing, with varying prevalence across age groups, ethnicities, and countries. Recent North American estimates suggest that it afflicts about 9% of females aged 50 to 70 years, and 17% of males in this same age group.<sup>221</sup>

OSA is characterized by recurrent upper airway collapse during sleep that leads to reduced or complete cessation of airflow, despite ongoing breathing efforts. Affected individuals develop intermittent hypercapnia, intermittent hypoxemia, and fragmented sleep. Risk factors for OSA include increased age, male sex, obesity, smoking, pregnancy, heart failure, end-stage renal disease, and craniofacial abnormalities. The diagnosis of OSA is based on the presence of symptoms, such as nonrestorative sleep, snoring, hypertension, and the frequency of sleep-related respiratory events during polysomnography or home sleep apnea testing. Once diagnosed, disease severity is typically characterized by the apnea-hypopnea index (AHI), which is the number of apneic and hypopneic episodes per hour of sleep. Mild OSA is defined by 5 to 15 episodes per hour, moderate disease by 16 to 30 episodes per hour, and severe disease by more than 30 episodes per hour. OSA is associated with an increased prevalence of systemic hypertension, pulmonary hypertension, IHD, heart failure, cardiac arrhythmias (i.e., atrial fibrillation, bradycardia, ventricular ectopy), stroke, type 2 diabetes mellitus, obesity hypoventilation syndrome, and nonalcoholic fatty liver disease. The main effective treatments for OSA in the nonoperative setting are continuous positive airway pressure (CPAP) and weight loss.<sup>222-224</sup>

Most cases of OSA in surgical patients remain undiagnosed at the time of surgery.<sup>225</sup> Screening questionnaires can help, in part, address this problem. For example, the eight-item STOP-Bang questionnaire is a straightforward validated tool to screen for OSA in preoperative evaluation clinics ([Fig. 31.8](#)).<sup>226</sup> Surgical patients with scores of 2 or less are at very low risk (negative likelihood ratio 0.24 for AHI  $\geq 5$ ), and those with scores of 5 or more are at increased risk (positive likelihood ratio 1.8 for AHI  $\geq 5$ ).<sup>226</sup> Since individuals with scores of 3 to 4 are in an indeterminate zone, additional screening criteria have been proposed for this subgroup, including serum bicarbonate concentration level at 28 mmol/L or greater,<sup>227</sup> and differentially weighting responses to the questionnaire.<sup>228</sup> There is some uncertainty as to the operational burden of screening all surgical patients for OSA, especially since the positive likelihood ratio for a higher STOP-Bang score is not particularly high. A reasonable option may be to apply screening in higher-risk populations, such as individuals with obesity, associated comorbidities, and known or suspected difficult intubation characteristics.

Patients with OSA are at increased perioperative risk because of the sleep disorder itself and associated comorbidities. Mask ventilation, direct laryngoscopy, endotracheal intubation, and fiberoptic visualization of the airway are more difficult in patients with OSA (see [Chapter 44](#)). In addition, these patients are also more sensitive to the respiratory depressant effects of opioids. In general, patients with OSA have elevated risks of perioperative airway obstruction, hypoxemia, atelectasis, pneumonia, cardiovascular complications, and prolonged hospitalizations.<sup>229</sup> There is uncertainty as to how much of this increased risk is explained by OSA itself, versus associated comorbidities (e.g., IHD, heart failure, diabetes mellitus, obesity). For example, some cohort studies that found that patients with known OSA, or patients screened as being high-risk for OSA, were not at elevated risk of mortality or postoperative hypoxemia, after accounting for coexisting comorbidities.<sup>77,230,231</sup>

**STOP-Bang**  
**Screening for Sleep Apnea**

Have you been diagnosed with sleep apnea by a sleep study? Yes  No

Have you received treatment for sleep apnea, such as CPAP or Bi-PAP? Yes  No

**Please answer the following four questions with a yes or no answer:**

1) Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?

Yes  No

2) Do you often feel tired, fatigued, or sleepy during daytime?

Yes  No

3) Has anyone observed you stop breathing during your sleep?

Yes  No

4) Do you have or are you being treated for high blood pressure?

Yes  No

**FOR STAFF USE ONLY, DO NOT WRITE BELOW THIS LINE**

5) Is the BMI  $\geq 35 \text{ kg/m}^2$ ?

Yes  No

6) Is the patient  $\geq 50$  years of age?

Yes  No

7) Is the neck circumference greater than 15.7 inches (40 cm)?

Yes  No

8) Is the patient male?

Yes  No

Total number of questions answered YES: \_\_\_\_\_ Is the patient at high risk for OSA? Yes  No

**High risk of OSA: Yes to >3 items**

**Fig. 31.8 Stop-Bang questionnaire to screen patients for obstructive sleep apnea.** (From Chung F, Yegneswaran B, Liao P, et al. STOP Questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology*. 2008;108:812–821.)

Preoperative evaluation focuses on characterizing all cases of known OSA, and selectively identifying patients at risk for undiagnosed OSA. In addition, associated comorbidities should be investigated and optimized as deemed clinically appropriate. For example, echocardiography may be indicated if undiagnosed heart failure or pulmonary hypertension is suspected. For patients with known OSA, the anesthesiologist should inquire about known disease severity, document current treatment, and instruct the patient to bring their CPAP equipment or oral appliances on the day of surgery (so that therapy can be restarted promptly after surgery).

### Pulmonary Hypertension

Pulmonary hypertension is defined as a persistent mean pulmonary artery pressure of 25 mm Hg or more at rest. The condition may occur in isolation or with associated medical conditions. Based on the World Health Organization, pulmonary hypertension is classified into 5 groups (Box 31.9).<sup>232</sup> Idiopathic and heritable pulmonary arterial hypertension (formerly called primary pulmonary hypertension) are relatively rare. Other more common forms occur with a variety of diseases including cardiac, pulmonary, liver, thromboembolic, and collagen vascular diseases (e.g., scleroderma, systemic lupus erythematosus

[SLE]). Pulmonary hypertension is also associated with human immunodeficiency virus (HIV) infection, anorectic drug exposure (e.g., fenfluramine), OSA, and chronic liver disease (especially with portal hypertension).

Patients with pulmonary hypertension have a high rate of perioperative morbidity and mortality.<sup>233-235</sup> Hypoxia, hypercarbia, hypothermia, vasoconstrictor use, and increased sympathetic tone (even from anxiety) during the perioperative period increase pulmonary vascular resistance, with the potential for acute decompensation with right-sided heart failure. Occult pulmonary hypertension is more problematic than the fully recognized disease because symptoms may be attributed to other diseases, and perioperative decompensation may occur unexpectedly. Current American and European guidelines recommend that affected patients be managed collaboratively with a pulmonary hypertension specialist team during the perioperative period, and that they undergo surgery at centers with requisite expertise.<sup>7,9</sup>

It may be challenging to detect pulmonary hypertension *de novo* during preoperative evaluation. The initial symptoms of pulmonary hypertension are usually nonspecific and insidious. Diagnosis is also typically delayed, with about 20% of patients having symptoms for more than 2 years prior to a formal diagnosis.<sup>236</sup> Typical initial symptoms

### BOX 31.9 Classification Scheme for Pulmonary Hypertension

#### Pulmonary Arterial Hypertension

1. Idiopathic pulmonary arterial hypertension
2. Heritable pulmonary arterial hypertension
3. Drug-induced or toxin-induced pulmonary arterial hypertension
4. Associated with other conditions
  - (a). Connective tissue disease
  - (b). Congenital heart disease
  - (c). Portal hypertension
  - (d). Human immunodeficiency virus infection
  - (e). Schistosomiasis
5. Pulmonary venoocclusive disease and/or pulmonary capillary hemangiomatosis
6. Persistent pulmonary hypertension of newborn

#### Pulmonary Hypertension Related to Left-heart Disease

1. Left ventricular systolic dysfunction
2. Left ventricular diastolic dysfunction
3. Valvular heart disease
4. Extrinsic compression of central pulmonary veins
5. Congenital or acquired obstruction of the left heart inflow or outflow tract, and congenital cardiomyopathies

#### Pulmonary Hypertension Related to Lung Disease or Hypoxemia

1. Chronic obstructive pulmonary disease
2. Interstitial lung disease
3. Other pulmonary diseases with mixed restrictive and obstructive pattern
4. Sleep disordered breathing
5. Alveolar hypoventilation disorders
6. Developmental lung disease
7. Chronic exposure to high altitude

#### Chronic Thromboembolic Pulmonary Hypertension

##### Pulmonary Hypertension with Unclear Multifactorial Etiology

1. Hematologic disorders (chronic hemolytic anemia, myeloproliferative disorders, splenectomy)
2. Systemic disorders (sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis)
3. Metabolic disorders (glycogen storage disease, Gaucher disease, thyroid disorders)
4. Other conditions (tumor obstruction, fibrosing mediastinitis, chronic kidney disease, segmental pulmonary hypertension)

From: Simonneau G, Gatzoulis M, Adiata I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62: D34–D41.

are exertional dyspnea, lethargy, and fatigue. With disease progression, symptoms related to right ventricular overload develop—these symptoms include exertional chest pain, exertional syncope or presyncope, upper abdominal pain (i.e., liver congestion), and dependent edema. Physical examination may reveal a split  $S_2$  with a loud second component, right ventricular heave, tricuspid regurgitation murmur, ascites, hepatomegaly, jugular venous distention, and peripheral edema. An ECG and echocardiogram are useful in patients with suspected pulmonary hypertension, and those with moderate-to-severe known disease. Typical ECG findings include right axis deviation, RBBB, right ventricular hypertrophy, and tall R waves in leads  $V_1$  and  $V_2$ . Right atrial hypertrophy and “P-pulmonale” may be present in

severe pulmonary hypertension, with peaked P waves, usually in leads II, III, aVF, and  $V_1$ . An echocardiogram is the initial screening test of choice for pulmonary hypertension. It can estimate pulmonary arterial pressures, assess right ventricular function, identify left-sided heart failure, and detect structural heart disease (e.g., valvular heart disease, congenital heart disease). Patients with significant echocardiographic findings may require subsequent right and left cardiac catheterizations, especially given the potential inaccuracy of estimating right-sided pressures by echocardiography alone. Other useful laboratory tests include complete blood count, electrolyte concentrations, creatinine concentrations, and liver function tests (i.e., liver congestion or drug-related side effects).

Patients with pulmonary hypertension may be receiving treatment with diuretics, calcium channel blockers, supplemental oxygen, phosphodiesterase type 5 inhibitors (e.g., sildenafil, tadalafil), endothelin receptor antagonists (e.g., bosentan, ambrisentan), and prostacyclin pathway agonists (e.g., iloprost, epoprostenol). Some drugs are given by continuous intravenous infusions, and even momentary interruption of therapy can be catastrophic. In general, all these medications should be continued perioperatively.<sup>7,9</sup> Some patients may be anticoagulated. The timing of any preoperative anticoagulant discontinuation, and assessment for bridging therapy, should be made collaboratively with a pulmonary hypertension specialist team.

#### Smokers and Second-Hand Smoke Exposure

Tobacco exposure, either directly or through “second-hand” smoke, increases the risk of many perioperative complications, including respiratory, cardiac, and infectious events. Current smokers have elevated risks for a range of postoperative complications, including mortality, cardiac complications, pulmonary complications, acute stroke, and surgical site infections.<sup>237,238</sup> Overall, about two thirds of smokers want to quit.<sup>239</sup> The U.S. Public Health Service recommends that “*all physicians should strongly advise every patient who smokes to quit because evidence shows that physician advice to quit smoking increases abstinence rates.*”<sup>240</sup> Even brief advice by a physician to quit smoking increases quit rates (relative risk 1.66; 95% CI, 1.42–1.94),<sup>241</sup> albeit from a very low baseline rate of 2% to 3%. Among intensive smoking cessation interventions, both behavioral counselling and medications have demonstrated efficacy, with evidence supporting further improvement in efficacy with combination therapy.<sup>242</sup> The main pharmacologic interventions for smoking cessation are nicotine replacement therapy (i.e., nicotine patches, gum, or lozenges), varenicline, and bupropion. Both bupropion and varenicline should be started at least 1 week before an attempt at quitting. Many hospitals, insurance companies, communities, and governmental agencies offer smoking cessation programs. Excellent advice and guidelines are available online (e.g., [https://www.cdc.gov/tobacco/quit\\_smoking/index.htm](https://www.cdc.gov/tobacco/quit_smoking/index.htm) and <https://smokefree.gov>) or via telephone (e.g., 1-800-QUIT-NOW in the United States).

Being scheduled for surgery is a “teachable moment” for promoting smoking cessation, with population-based survey data from the United States showing significant increases in smoking cessation rates after major surgery.<sup>243</sup> Within this context, interventions in the preoperative

evaluation clinic result in higher rates of short-term smoking cessation (i.e., within 3–6 months after surgery).<sup>244</sup> Although there is uncertainty about the robustness of smoking cessation rates over the long term,<sup>245</sup> randomized controlled trials have demonstrated reduced nicotine dependence of up to 1 year postoperatively following perioperative smoking cessation interventions.<sup>246,247</sup>

The perioperative benefits of smoking abstinence are realized within the first year after cessation.<sup>248</sup> Nonetheless, there remains uncertainty regarding the minimum required period to accrue benefits. In previous systematic reviews, clinical benefits of preoperative smoking cessation were demonstrated only when it occurred at least 3 to 4 weeks before surgery.<sup>249,250</sup> These benefits include reduced risks for respiratory and wound healing complications. Despite an early study reporting an increased perioperative risk (this association was not statistically significant) in recent quitters,<sup>251</sup> a systematic review found no increased risk of adverse events with quitting smoking soon before surgical procedures (i.e., within 8 weeks).<sup>252</sup> Thus, motivated patients should be encouraged to quit smoking at any point before surgery. Quitting has many theoretical benefits, even within a few days before operation. Soon after a patient quits smoking, carbon monoxide levels decrease, thereby improving oxygen delivery and use. Cyanide levels decrease, which benefits mitochondrial oxidative metabolism. Other beneficial effects include lower nicotine levels (which improves vasodilatation) and clearance of many toxic substances that impair wound healing.

### Upper Respiratory Tract Infections

Traditionally, elective surgical procedures were cancelled when patients, especially children, presented with current or recent upper respiratory tract infections. The concern pertains to associated airway hyperreactivity that predisposes patients to laryngospasm, bronchospasm, atelectasis, coughing, airway obstruction, hypoxia, stridor, and breath-holding.<sup>253</sup> Prior evidence suggests that this airway hyperreactivity lasts for 2 to 4 weeks after an upper respiratory tract infection.<sup>253,254</sup> Nonetheless, since most of these associated perioperative respiratory events are mild and easily managed with modern anesthesia care, cancellation is no longer routine. For patients with severe symptoms (e.g., high fever), especially in the presence of other health conditions (e.g., significant asthma, heart disease, immunosuppression), elective surgery should be postponed until 4 weeks after resolution of the infection. Conversely for mild or uncomplicated infections in otherwise healthy patients, it is reasonable to proceed with the planned surgery and avoid the inconvenience of a last-minute cancellation. The dilemma lies with patients between these two extremes, for whom decisions regarding the suitability to proceed should be made on an individualized basis.

### Cystic Fibrosis

Cystic fibrosis is an autosomal recessive disease caused by altered chloride and water transport across epithelial cells. This genetic disorder can result in progressive chronic airway disease characterized by airway obstruction, destruction, and frequent pulmonary infections. Affected individuals can also develop exocrine pancreatic insufficiency (i.e., malnutrition, diabetes mellitus, pancreatitis),

bowel obstruction, sinusitis, and liver disease (i.e., biliary cirrhosis, portal hypertension). The diagnosis is based on compatible clinical findings in at least one organ system (e.g., chronic airway disease, exocrine pancreatic insufficiency, chronic pansinusitis, cystic fibrosis) in a first-degree relative in combination with either biochemical (sweat chloride  $\geq 60$  mmol/L on two occasions) or genetic confirmation (presence of known disease-causing genetic mutations).<sup>255</sup>

The preoperative clinical evaluation should especially focus on respiratory, hepatic, and nutritional assessment. With respect to preoperative investigations, electrolyte levels, liver function tests, chest radiographs, and PFTs are useful. Collaborative perioperative management in conjunction with a pulmonologist or a cystic fibrosis specialist is ideal, with an important goal being optimization of pulmonary status (i.e., secretions, infections, bronchospasm) before surgery. Most medications for cystic fibrosis should be continued perioperatively.

### Postoperative Pulmonary Complications

Postoperative pulmonary complications encompass several important clinical entities and these have been further defined in a recent systematic literature review and consensus-based process. Abbott and colleagues identified four standard outcome measures that are appropriate for widespread use in clinical trials of postoperative pulmonary complications, namely, pneumonia, atelectasis, acute respiratory distress syndrome, and aspiration.<sup>256</sup> In addition, the investigators proposed a new definition of postoperative pulmonary complications that incorporates the severity of the complication based on the degree of therapy required (e.g., supplemental oxygen, positive pressure ventilation).<sup>256</sup> There is considerable variation in how pulmonary outcome complications are defined and this is reflected in the inconsistent reporting of outcomes across studies and hinders interpretation of research findings. Despite the reporting inconsistencies, a reasonable estimate is that these complications develop in about 5% of patients undergoing nonthoracic surgery.<sup>257,258</sup>

Established risk factors for pulmonary complications pertain to two general domains: patient-level risk factors and procedure-related risk factors (Box 31.10).<sup>218</sup> Patient-level factors include general health status (e.g., ASA physical status [ASA-PS], functional dependency), smoking history, advanced age, COPD, preexisting pulmonary disease (e.g., recent infection, low oxygen saturation) pulmonary hypertension, anemia, heart failure, preexisting sepsis, poor nutritional status (e.g., albumin concentration), and obesity (BMI  $> 30$  kg/m<sup>2</sup>).<sup>218,257,259,260</sup> Notably absent from this list of patient-related factors are asthma, arterial blood gas results, or PFT results. The risk of complications is surprisingly low in patients who have well-controlled asthma or preoperative corticosteroid treatment.<sup>214</sup> The risk is higher in asthmatic patients with recent exacerbations, prior postoperative pulmonary complications, recent hospitalizations, or endotracheal intubations for asthma. Arterial blood gases are useful in predicting pulmonary function after lung resection operations, but do not estimate perioperative pulmonary risk. Findings on PFTs, such as the degree of FEV<sub>1</sub>, are generally not predictive of pulmonary complications.<sup>218</sup> PFTs have clear roles in diagnosis ("Is

### BOX 31.10 Selected Risk Factors for Postoperative Pulmonary Complications

#### Potential Patient-related Risk Factor

- Advanced age
- ASA-PS Class 2 or more
- Congestive heart failure
- Functionally dependent
- Chronic obstructive pulmonary disease
- Weight loss
- Impaired sensorium
- Cigarette use
- Alcohol use
- Abnormal findings on chest examination

#### Potential Procedure-related Risk Factor

- Aortic aneurysm repair
- Thoracic surgery
- Abdominal surgery
- Upper abdominal surgery
- Neurosurgery
- Head-and-neck surgery
- Emergency surgery
- Vascular surgery
- General anesthesia
- Perioperative transfusion

#### Potential Laboratory Test Risk Factor

- Albumin concentration < 35 g/L
- Chest radiograph abnormalities
- BUN concentration > 7.5 mmol/L (> 21 mg/dL)

ASA-PS, American Society of Anesthesiologists Physical Status; BUN, blood urea nitrogen.

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

dyspnea caused by lung disease or heart failure?”) or informing management (“Can dyspnea or wheezing be improved further?”), but should not be used as a risk assessment tool or to deny a surgical procedure.<sup>10,218</sup> Procedure-related risk factors for pulmonary complications include the type of procedure (head-and-neck, thoracic, upper abdominal, aortic, neurosurgical), long-duration procedures, emergency procedures, general anesthesia, and residual neuromuscular blockade.<sup>218,257</sup>

Several preoperative clinical risk indices have been developed to estimate pulmonary risk.<sup>34,35,257,259,260</sup> Although these indices have reasonable predictive accuracy, they also have important limitations. Some only predict specific complication types (i.e., pneumonia vs. respiratory failure),<sup>34,35,259,260</sup> and others are too complex for easy clinical use.<sup>34,35</sup> The most straightforward, currently available index is likely the ARISCAT (Assess Respiratory Risk in Surgical Patients in Catalonia) score,<sup>257</sup> which has also been externally validated (Table 31.14).<sup>261</sup> The score classifies patients as low-risk, intermediate-risk, and high-risk strata.<sup>257</sup>

When high-risk patients are identified before surgery, the anesthesiologist has several available options to help decrease their perioperative pulmonary risk. These approaches include encouraging smoking cessation (see

**TABLE 31.14** Scoring Scheme for the ARISCAT\* Perioperative Pulmonary Risk Index

Components of ARISCAT Score	Points Assigned
Age	
■ ≤50 years	0
■ 51–80 years	3
■ >80 years	16
Preoperative oxygen saturation	
■ ≥96%	0
■ 91%–95%	8
■ ≤91%	24
Respiratory infection in prior month	17
Preoperative anemia (<100 g/L)	11
Surgical incision location	
■ Peripheral	0
■ Upper abdominal	15
■ Intrathoracic	24
Duration of surgery	
■ ≤2 h	0
■ >2–3 h	16
■ >3 h	23
Emergency procedure	8
<b>ARISCAT Score</b>	
Low-risk: < 26 points	1.6%
Intermediate risk: 26–44 points	13.3%
High-risk: ≥ 45 points	42.1%
<b>Risk of Pulmonary Complications<sup>†</sup></b>	

\*Estimates risk of composite endpoint of respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm, or aspiration pneumonitis.

ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia group.

<sup>†</sup>Three patients were excluded because of a missing value in some variable. From Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology.* 2010;113:1338–1350.

section on “Smokers and Second-Hand Smoke Exposure”), treatment of any recent asthma or COPD exacerbation, and treatment of any recent lower respiratory tract infection. These interventions may require medications (e.g., antibiotics, bronchodilators, corticosteroids), specialist referral (e.g., pulmonologists), or delay in the planned surgical procedure. There is accumulating evidence pointing to benefits from preoperative inspiratory muscle training and physiotherapy in high-risk patients undergoing cardiac or abdominal surgery.<sup>262,263</sup> The anesthesiologist can also use the preanesthesia evaluation to educate patients about the potential respiratory benefits of neuraxial anesthesia or analgesia,<sup>19,264,265</sup> and discuss options for less-invasive surgical procedures with the referring surgeon.

## ENDOCRINE DISORDERS

### Diabetes Mellitus

Diabetes mellitus afflicts about 420 million people worldwide.<sup>266</sup> The two main disease categories are type 1 diabetes (previously called “insulin-dependent diabetes” or “juvenile-onset diabetes”) and type 2 diabetes (previously called “non–insulin dependent diabetes” or “adult-onset diabetes”).<sup>267</sup> Type 1 diabetes, which accounts for about

5% to 10% of all cases of the disease, is the result of autoimmune destruction of pancreatic  $\beta$ -cells. Affected individuals have an absolute deficiency of insulin, but normal sensitivity to insulin. Since the disease has a typically early onset at a young age, and is often difficult to control, adults with type 1 diabetes are at risk of premature vascular disease, such as IHD, nephropathy, retinopathy, and peripheral neuropathy. They are also at risk of diabetic ketoacidosis. Type 2 diabetes is characterized by insulin resistance and a relative (but not absolute) deficiency in insulin. Most affected individuals are obese and seldom prone to ketoacidosis. Diabetes mellitus is associated with multiorgan dysfunction, including IHD, heart failure (independent of associated IHD), CVD, CKD, peripheral neuropathy, autonomic neuropathy (e.g., postural hypotension, gastroparesis), retinopathy, and reduced joint mobility (e.g., reduced cervical mobility affecting airway management). In the perioperative setting, diabetes mellitus is a risk factor for postoperative complications, including cardiac events,<sup>97</sup> acute kidney injury (AKI),<sup>268,269</sup> and surgical site infections.<sup>270</sup> Insulin therapy is the main treatment for type 1 diabetes mellitus, either as multiple daily injections or a continuous subcutaneous insulin infusion. In the case of type 2 diabetes, multiple treatment options are available, including nonpharmacologic therapy (i.e., diet, weight loss, exercise), metformin, sulfonylureas (e.g., glyburide, glipizide), repaglinide, glucagon-like peptide-1 (GLP-1) agonists (e.g., liraglutide), sodium-glucose cotransporter 2 (SGLT2) inhibitors (e.g., empagliflozin), dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin, saxagliptin, linagliptin, alogliptin), and insulin.

During the preoperative evaluation of a patient with diabetes mellitus, the anesthesiologist should document the disease type (i.e., type 1 vs. type 2), current usual glycemic control, history of hypoglycemic episodes, current therapy, and the severity of any end-organ complications. Given the effects of diabetes mellitus on other organ systems, the history and physical examination should especially focus on the cardiovascular, renal, and neurologic systems. Inquiries about postural dizziness, early satiety, and postprandial vomiting can help assess for any autonomic neuropathy. The physical examination should include an evaluation of pulses, skin breakdown, and joint (especially cervical spine) mobility. Informative preoperative laboratory tests include an ECG and blood sampling for electrolyte, creatinine, and blood glucose concentrations. To help better estimate renal function, an estimated GFR should be calculated (see section on “Kidney Disease”). Since patients are not typically fasting when they are evaluated in a preoperative evaluation clinic, glucose concentrations measured in the clinic cannot be used to evaluate general glycemic control. A diary of multiple glucose values (preprandial and postprandial) at varying times of the day is more informative for estimating the adequacy of therapy. Alternatively, a glycosylated hemoglobin (HbA<sub>1c</sub>) concentration can help characterize the average plasma glucose concentration within the prior 3 months. Among surgical patients, preoperative HbA<sub>1c</sub> is more informative than patients' self-reported history, fasting blood glucose concentrations, and random blood glucose concentrations in identifying preexisting poor glycemic control.<sup>271</sup> In the nonoperative setting, the American Diabetes Association recommends a target

HbA<sub>1c</sub> concentration under 7% for most diabetic patients. Although preoperative HbA<sub>1c</sub> is correlated with postoperative glycemic control,<sup>272</sup> its role as a predictor of postoperative complications is largely restricted to diabetic patients undergoing orthopedic or vascular surgery.<sup>273</sup> Recently updated guidelines from the National Institute for Health and Care Excellence (NICE) in the United Kingdom<sup>274</sup> recommend offering HbA<sub>1c</sub> testing to diabetic surgical patients who have not been tested in the prior 3 months, and ensuring the recent HbA<sub>1c</sub> test results be included in referral materials from patients' primary care providers.

In the perioperative setting, the goals of glycemic management are to avoid hypoglycemia, prevent ketoacidosis, and avoid marked hyperglycemia. Tight perioperative glucose control in the immediate perioperative period is controversial. While aggressive management of hyperglycemia may theoretically help decrease postoperative complications, these theoretical clinical benefits of intraoperative intensive glucose control have not been observed in randomized trials of surgical patients.<sup>275</sup> Ideally, all diabetic patients should have their surgery as an early morning case to minimize any disruption of their diabetic management fasting. Normal treatment regimen for most non-insulin diabetic medications (metformin, sulfonylureas, repaglinide, GLP-1 agonists, DPP-4 inhibitors) should be continued until (and inclusive of) the day before surgery but held on the morning of surgery. The possible exception pertains to SGLT2 inhibitors, which have been associated with euglycemic diabetic ketoacidosis in the postoperative setting.<sup>276</sup> Thus, some guidelines recommend that the medications be discontinued at least 24 hours before elective surgery.<sup>277</sup> Diabetic patients should discontinue *short-acting* insulin while fasting. The exception pertains to patients with continuous subcutaneous insulin infusion pumps. These individuals should continue their infusion at the lowest basal rate, which is usually the nighttime fasting rate. With respect to management of *intermediate-acting* or *long-acting* insulin on the day of surgery, there is no uniform consensus on optimal perioperative protocols. A reasonable approach is for patients with type 1 diabetes mellitus to take a small amount (one third to one half) of their usual morning dose of intermediate-acting or long-acting insulin (e.g., lente, isophane) to avoid diabetic ketoacidosis. Patients with type 2 diabetes mellitus can either take no insulin or up to one half of their usual dose of intermediate-acting, long-acting, or combination (e.g., 70/30 preparations) insulin on the morning of surgery.

### Thyroid Disease

Thyroid hormones are important for metabolism and its regulation. Mild to moderate thyroid dysfunction probably has minimal perioperative impact.<sup>278,279</sup> The major concern pertains to significant hyperthyroidism or hypothyroidism, which appears to increase perioperative risk. Symptoms and signs of hypothyroidism and hyperthyroidism can be subtle and nonspecific, especially with milder disease in older adults. Hyperthyroid individuals may manifest tachycardia, arrhythmias, palpitations, tremors, weight loss, and diarrhea. Patients with hypothyroidism may demonstrate hypotension, bradycardia, lethargy, weight gain, depressed cardiac function, pericardial effusions, and impaired ventilatory response to hypoxia or hypercarbia. Patients may

also have goiters with related symptoms such as dysphagia, dyspnea, wheezing, and orthopnea. Individuals with hyperthyroidism due to Graves disease may also demonstrate proptosis.

The preoperative evaluation should clarify the patient's current medical therapy as well as any recent changes. In patients with known thyroid disease, additional preoperative thyroid function testing is not needed if the patient is on a stable medication dose and was assessed as being euthyroid within the previous 6 months. If additional preoperative testing is clinically indicated, thyroid-stimulating hormone (TSH) assays are best to evaluate for hypothyroidism, while free triiodothyronine ( $T_3$ ), free thyroxine ( $T_4$ ), and TSH levels are useful in hyperthyroid patients. Surgery, stress, or illness can precipitate myxedema or thyroid storm in patients with untreated or severe thyroid dysfunction. In general, if a patient has moderate or worse hypothyroidism (i.e., elevated TSH and low free  $T_4$ —with or without associated symptoms), elective surgery should be postponed until the individual is euthyroid. Similarly, elective *non-thyroid* surgery should also be delayed to facilitate treatment of patients with overt hyperthyroidism (i.e., suppressed TSH with elevated free  $T_4$  or  $T_3$  concentrations—with or without associated symptoms). Consultation with an endocrinologist is necessary if surgery is urgent in patients with thyroid dysfunction. If surgery is urgent, hyperthyroid patients can be treated with  $\beta$ -adrenergic blockers, antithyroid medications (e.g., methimazole, propylthiouracil, potassium iodide), and corticosteroids. Other potentially useful tests include chest radiography or computed tomography scans to evaluate tracheal or mediastinal involvement by a goiter. All thyroid replacement therapy and antithyroid drugs should be continued on the day of surgery.

### Parathyroid Disease

Parathyroid hormone regulates calcium. Most cases of hyperparathyroidism are discovered based on an incidental elevated calcium level found during diagnostic testing. *Primary* hyperparathyroidism is caused by a primary disorder of the parathyroid glands (adenomas or hyperplasia). *Secondary* hyperparathyroidism is parathyroid gland hyperplasia induced by the hyperphosphatemia and hypocalcemia that occur during chronic renal failure. *Tertiary* hyperparathyroidism occurs when the parathyroid hyperplasia in secondary hyperparathyroidism functions autonomously. Hypercalcemia from parathyroid disease is associated with osteoporosis and bone loss. It is very unlikely that parathyroid glands become sufficiently enlarged to compromise the airway. Hypoparathyroidism is very uncommon, but it can be the consequence of a prior total parathyroidectomy.

### Hypothalamic-Pituitary-Adrenal Disorders

The hypothalamus releases corticotropin-releasing hormone, which regulates adrenocorticotrophic hormone (ACTH) release from the anterior pituitary gland. ACTH, in turn, regulates cortisol release from the adrenal cortex. Cortisol secretion varies with the circadian rhythm, with the highest release in the morning. Additionally, release increases with physical stress, psychological stress, fever, and hypoglycemia. Among physical stressors, surgery is one of the most potent activators of the hypothalamic-pituitary-adrenal axis. Although ACTH concentrations increase

with surgical incision and through the surgical procedure, the greatest ACTH secretion occurs during termination of anesthesia and the immediate postoperative period.<sup>280</sup> The magnitude and duration of the cortisol response reflects the degree of physiological stress imposed by the surgical stress. In procedures with minimal associated stress (e.g., inguinal hernia repair), increased cortisol secretion lasts for about 24 hours.<sup>280</sup> In more complicated procedures (e.g., major abdominal surgery), the response is larger in magnitude and lasts for about 5 days after surgery.<sup>280,281</sup>

Excess adrenal hormones result from endogenous cortisol associated with pituitary or adrenal tumors, or exogenous glucocorticoids used to treat disorders such as asthma or inflammatory diseases. Cushing syndrome refers to the combinations and symptoms due to chronic excess glucocorticoid exposure (either endogenous or exogenous). Cushing disease is the specific situation when the excess glucocorticoids are related to an ACTH-producing pituitary tumor. Other causes of Cushing syndrome include exogenous corticosteroids, adrenal tumors, adrenal hyperplasia, and neoplasms that secrete ectopic ACTH. The major manifestations of Cushing syndrome are obesity (with characteristic patterns of fat deposition causing "moon facies" and a "buffalo hump"), diabetes mellitus, female virilization, OSA, hypertension, elevated cardiovascular risk, elevated venous thromboembolism (VTE) risk, osteoporosis, striae, skin atrophy, and easy bruising. Airway management can be challenging in affected patients due to obesity and OSA. In addition, peripheral intravenous access can be difficult because of skin atrophy and obesity. These patients may require an ECG and blood sampling for electrolytes and glucose. Despite easy bruising, they have normal coagulation profiles.

An important issue for patients with chronic corticosteroid exposure is whether perioperative "stress-dose steroids" are needed. Both endogenous and exogenous glucocorticoids exert important negative feedback suppression on the hypothalamic-pituitary-adrenal axis. Thus, chronic exogenous corticosteroid exposure suppresses the adrenals and may blunt the normal cortisol hypersecretion associated with surgery—even if the patient does not demonstrate Cushing syndrome. Perioperative corticosteroid supplementation is needed only when a patient is likely to have suppression of the hypothalamic-pituitary-adrenal axis. Thus, supplementation is not required for individuals who have received less than 5 mg prednisone (or its equivalent) daily,<sup>282</sup> or less than 3 weeks of corticosteroids (regardless of dose).<sup>282</sup> These individuals should simply continue their usual long-term corticosteroid regimen through the perioperative period. Conversely, patients taking prednisone (or its equivalent) in daily doses exceeding 20 mg/day for more than 3 weeks, and patients with Cushing syndrome should have perioperative corticosteroid supplementation. The need for supplementation is unclear for patients who have taken prednisone (or its equivalent) at a daily dose of 5 to 20 mg for more than 3 weeks. The options are to simply empirically provide perioperative corticosteroid supplementation or refer the patient to an endocrinologist for formal evaluation of their hypothalamic-pituitary-adrenal axis. There is no clear consensus on the optimal perioperative corticosteroid supplementation regimen.<sup>284</sup> A proposed regimen that accounts for contemporary evidence and different stress-response profiles across surgical procedures is presented in Table 31.15.<sup>284</sup>

**TABLE 31.15** Recommendations for Perioperative Corticosteroid Coverage

Surgical Stress	Target Hydrocortisone Equivalent	Preoperative Corticosteroid Dose	Perioperative Corticosteroid Dose
Superficial procedure (e.g., biopsy, dental procedure)	8–10 mg/day	Usual daily dose	■ Then usual daily dose
Minor (e.g., inguinal hernia repair, colonoscopy, hand surgery)	50 mg/day	Usual daily dose	■ Hydrocortisone 50 mg IV before incision ■ Hydrocortisone 25 mg IV every 8 h for 24 h ■ Then usual daily dose
Moderate (e.g., colon resection, total joint replacement, lower extremity revascularization)	75–150 mg/day	Usual daily dose	■ Hydrocortisone 50 mg IV before incision ■ Hydrocortisone 25 mg IV every 8 h for 24 h ■ Then usual daily dose
Major (e.g., esophagectomy, pancreateoduodenectomy, major cardiac, major vascular, trauma)	75–150 mg/day	Usual daily dose	■ Hydrocortisone 100 mg IV before incision ■ Continuous IV infusion of 200 mg of hydrocortisone over 24 h ■ Then usual daily dose OR ■ Hydrocortisone 50 mg IV every 8 h for 24 h ■ Taper dose by 50% per day until usual daily dose is reached* ■ Then usual daily dose

\*Administer continuous IV fluids with 5% dextrose and 0.2% to 0.45% sodium chloride (based on degree of hypoglycemia).

IV, Intravenous.

From Liu MM, Reidy AB, Saatee S, et al. Perioperative steroid management: approaches based on current evidence. *Anesthesiology*. 2017;127:166–172.

Patients with adrenal insufficiency have weakness, weight loss, hypotension, orthostasis, hypovolemia, hyperpigmentation, and electrolyte abnormalities. Adrenal insufficiency results from destruction of the pituitary gland, destruction of the adrenal glands (e.g., autoimmune disease, tuberculosis, HIV infection), or long-term exogenous glucocorticoid administration (most common cause). To help establish the diagnosis and cause of adrenal insufficiency, patients require a morning cortisol concentration measurement, morning plasma ACTH concentration measurement, and often an ACTH stimulation test.<sup>285,286</sup> If the serum cortisol concentration is inappropriately low and a simultaneous plasma ACTH concentration is very high, primary adrenal insufficiency (i.e., primary adrenal disease) is the cause. Secondary (i.e., pituitary disease) or tertiary (i.e., hypothalamic disease) is the diagnosis if both serum cortisol and plasma ACTH concentrations are inappropriately low. Consultation with an endocrinologist is required if formal diagnostic testing for adrenal insufficiency is required, and to facilitate treatment of patients meeting the diagnostic criteria. Patients should continue their replacement corticosteroid therapy on the day of surgery and may need further supplementation based on the expected surgical stress response (see Table 31.15).

Importantly, aldosterone, although also produced by the adrenal cortex, is controlled instead by the renin-angiotensin system, not the hypothalamic-pituitary-adrenal axis. Aldosterone regulates volume and electrolytes (absorption of sodium and chloride; secretion of potassium and hydrogen ions).

### Multiple Endocrine Neoplasia Syndromes

Multiple endocrine neoplasia (MEN) syndromes are autosomal dominant inherited disorders. There are three types, namely MEN type 1, MEN type 2A, and MEN type 2B (Box 31.11). Although rare (2 in 100,000 for MEN type 1, and 3 in 100,000 for MEN type 2), recognition is important to facilitate treatment of the affected patient and evaluation of family members. MEN type 1 is characterized by the “3 Ps,” namely tumors of the parathyroid glands, anterior

### BOX 31.11 Types of Multiple Endocrine Neoplasia Syndromes

#### Multiple Endocrine Neoplasia Type 1

1. Primary hyperparathyroidism
2. Enteropancreatic tumor (e.g., gastrinoma, insulinoma, nonfunctioning)
3. Anterior pituitary tumor (e.g., prolactinoma)
4. Others
  - (a). Foregut carcinoid tumor (e.g., thymus, gastric enterochromaffin-like tumor)
  - (b). Adrenal cortical tumor (nonfunctioning)
  - (c). Lipomas
  - (d). Facial angiofibromas
  - (e). Collagenomas

#### Multiple Endocrine Neoplasia Type 2A

1. MEN2A classical syndrome (i.e., medullary thyroid cancer, pheochromocytoma, primary hyperparathyroidism)
2. MEN2A with cutaneous lichen amyloidosis
3. MEN2A with Hirschsprung disease
4. Familial medullary thyroid cancer (no pheochromocytoma or parathyroid hyperplasia)

#### Multiple Endocrine Neoplasia Type 2B

1. Medullary thyroid cancer
2. Pheochromocytoma
3. Others
  - (a). Mucosal neuromas
  - (b). Intestinal ganglioneuromas
  - (c). Marfanoid habitus

pituitary, and pancreatic islet cells. Hyperparathyroidism is the most common manifestation of MEN type 1, with 90% penetrance by the age of 40 years. Affected individuals are also predisposed to other tumors, including gastrinomas (usually in the duodenum), carcinoid tumors (thymus or bronchi), enterochromaffin cell-like gastric tumors, adrenocortical adenomas, and lipomas. Individuals

with gastrinomas can develop Zollinger-Ellison syndrome, which is characterized by multiple peptic ulcers due to gastrin hypersecretion. While testing for MEN type 1 gene mutations is possible,<sup>287</sup> there is little evidence that early detection improves the disease prognosis.

Within MEN type 2A, there are four subtypes, namely classical MEN type 2A, MEN type 2A with cutaneous lichen amyloidosis, MEN type 2A with Hirschsprung disease, and familial medullary thyroid cancer (see [Box 31.11](#)). Hyperparathyroidism in MEN type 2A is often mild or asymptomatic. Since pheochromocytoma (see section on “Pheochromocytoma”) is present in about 50% of MEN type 2 cases, this diagnosis must be considered as a possible component of MEN type 2 syndrome. Furthermore, if a pheochromocytoma is present, it should be removed before any other tumor resections. Extraadrenal pheochromocytoma tumors are rare in MEN type 2, but bilateral adrenal disease is common. It is unusual for pheochromocytoma to precede a medullary thyroid carcinoma or be the initial manifestation of MEN type 2. In contrast to MEN type 1, early diagnosis of MEN type 2 through genetic screening is very important. This genetic testing predicts the clinical disease phenotype (e.g., age of onset, aggressiveness), guides surveillance for associated tumors, and informs timing of prophylactic thyroidectomy to prevent medullary thyroid carcinoma.

### Pheochromocytoma

Pheochromocytomas are catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla. Similar tumors arising from sympathetic ganglia are termed catecholamine-secreting paragangliomas or extraadrenal pheochromocytomas. Nonetheless, the term “pheochromocytoma” is often used to refer to either type of tumor. These rare tumors (incidence ~1 per 100,000 person-years)<sup>288</sup> occur most commonly between ages 40 and 60 years, with equal incidence in males and females. About 40% of cases occur as part of a familial disorder (i.e., von Hippel-Lindau syndrome, MEN type 2, neurofibromatosis type 1). These tumors tend to present at a younger age and are more likely to be bilateral adrenal pheochromocytomas or paragangliomas.

Pheochromocytomas are usually discovered when patients present with consistent symptoms, suggestive family history, or incidental adrenal mass. About half of patients have symptoms, which are typically paroxysmal. The classic triad of associated symptoms are episodic headaches (90% of symptomatic patients), sweating (60%-70% of symptomatic patients), and tachycardia. About half of patients have paroxysmal hypertension, 5% to 15% have normal blood pressure, and the remainder have what appears to be essential hypertension. Other manifestations include orthostatic hypotension, psychiatric disorders (i.e., panic attacks), pallor, blurred vision, weight loss, hyperglycemia, and cardiomyopathy. A diagnosis of pheochromocytoma should be considered if any of the following features is present.<sup>289</sup>

- Triad of episodic headaches, sweating, and tachycardia
- Hyperadrenergic spells (e.g., nonexertional palpitations, diaphoresis, headache, tremor)
- Hypertension that is difficult to control, or occurs at a young age
- Hypertension associated with new-onset or atypical diabetes mellitus
- Idiopathic dilated cardiomyopathy

- Family history of pheochromocytoma or suspicious familial syndrome (von Hippel-Lindau syndrome, MEN type 2, neurofibromatosis type 1)
- A history of gastric stromal tumors or pulmonary chondromas
- Incidentally discovered adrenal mass

Measurements of fractionated metanephrine and catecholamine concentrations in the urine and plasma generally establish the diagnosis of pheochromocytoma, with recent guidelines focusing on initial testing with either plasma-free metanephrines or urinary fractionated metanephrines.<sup>290</sup> Nonetheless, since testing algorithms vary considerably across hospitals and regions, a referral to an appropriate specialist (e.g., endocrinologist) should be made to facilitate a formal diagnosis in an individual with suspicious findings.

Patients scheduled for pheochromocytoma resection should undergo surgery at centers with experienced teams of anesthesiologists and surgeons. They also require about 10 to 14 days of medical preparation before surgery to mitigate perioperative risks. The overarching goals of this preparation are to control hypertension, control tachycardia, and normalization of intravascular volume status. The mainstay of medical therapy is preoperative  $\alpha$ -adrenergic blockade started 7 to 14 days before surgery.<sup>290</sup> The preferred drug at many centers is phenoxybenzamine, which is an irreversible, long-acting, nonspecific  $\alpha$ -adrenergic blocking drug. The initial dose is 10 mg once or twice daily, and the dose is increased by 10 to 20 mg every 2 to 3 days as needed. Most patients eventually need doses ranging from 20 to 100 mg daily. The arterial blood pressure target is less than 130/80 mm Hg in the seated position, with systolic pressure less than 90 mm Hg while standing. Typical side effects include orthostatic dizziness, fatigue, and nasal congestion. Given these side effects, as well as higher rates of postoperative hypotension after preoperative phenoxybenzamine treatment, some centers instead use selective  $\alpha_1$ -adrenergic blocking drugs (e.g., prazosin, terazosin, doxazosin).<sup>291</sup> These agents are also preferable when long-term pharmacologic treatment is indicated (e.g., metastatic pheochromocytoma). The disadvantage of selective  $\alpha_1$ -adrenergic blocking drugs is their incomplete degree of  $\alpha$ -adrenergic blockade, thus resulting in more episodes of intraoperative hypertension.<sup>291</sup>

After adequate  $\alpha$ -adrenergic blockade,  $\beta$ -adrenergic blockade may be started cautiously with short-acting drugs. As an example, 10 mg of propranolol every 6 hours can be used. After 24 to 48 hours, a long-acting preparation (e.g., metoprolol, atenolol) can be substituted, provided that the patient tolerates  $\beta$ -adrenergic blockade. The dose is then adjusted to achieve a heart rate between 60 and 80 beats/min.  $\beta$ -Adrenergic blockade should *never* be initiated before  $\alpha$ -adrenergic blockade.<sup>290</sup> In the setting of unopposed  $\alpha$ -adrenergic receptor stimulation, blockade of vasodilatory peripheral  $\beta$ -adrenergic receptors worsen hypertension, while acute depression of cardiac function can precipitate acute heart failure. In addition, initiation of  $\beta$ -adrenergic blockade may unmask a catecholamine-induced cardiomyopathy, with resulting acute pulmonary edema.

Alternatives to perioperative  $\alpha$ -adrenergic blockade include calcium channel blockers and metyrosine.<sup>290</sup>

Nicardipine is the most commonly used calcium channel blocker for this indication, with a starting oral dose of 30 mg twice daily (sustained release preparation). The main role for calcium channel blockers is likely to supplement  $\alpha$ - and  $\beta$ -adrenergic blockade when blood pressure control is inadequate, or to treat patients with intolerable side effects from usual therapy. Monotherapy with calcium channel blockers is not recommended.<sup>290</sup> Metyrosine, which inhibits catecholamine synthesis, has many side effects (e.g., sedation, diarrhea). As a consequence, it is also reserved for cases where conventional treatment is insufficient or not tolerated.

The preoperative evaluation of a patient with known pheochromocytoma should focus on the cardiovascular system (including orthostatic vital signs) and current medical treatment for pheochromocytoma (including adequacy of treatment). Laboratory testing includes an ECG, as well as blood sampling for a CBC, electrolyte concentrations, creatinine concentrations, and glucose concentrations. The patient may also warrant echocardiography or a cardiology consultation.

## KIDNEY DISEASE

During preoperative evaluation, it is important to establish the severity, type, and underlying cause of preoperative renal impairment. Based on the Kidney Disease Improving Global Outcomes (KDIGO) guideline group, CKD is defined as a GFR less than 60 mL/min/1.73 m<sup>2</sup> for at least 3 months, regardless of the underlying cause.<sup>292</sup> Chronic kidney failure is defined as a GFR less than 15 mL/min/1.73 m<sup>2</sup> or the need for renal replacement therapy (i.e., dialysis). End-stage renal disease generally refers to chronic kidney failure that requires either dialysis or transplantation. GFR decreases with age; the renal reserve of a normal 80-year-old person is less than half that of a 40-year-old person. Thus, creatinine concentration is often not an accurate indicator of renal function, especially in older individuals.<sup>293</sup> The GFR can be reduced by 50% without a rise in creatinine concentration, while creatinine concentration does not exceed normal limits until GFR has fallen to less than 50 mL/min. Consequently, it is preferable to estimate renal function using an estimated GFR (eGFR) equation, such as the Cockcroft-Gault,<sup>294</sup> Modification of Diet in Renal Disease,<sup>295</sup> and current CKD-EPI equations.<sup>296</sup> Online calculators to estimate renal function are available (e.g., [www.kidney.org/professionals/kdoqi/gfr\\_calculator](http://www.kidney.org/professionals/kdoqi/gfr_calculator)). Calculating an eGFR is especially important in patients who are older, have elevated creatinine concentrations, or have other risk factors for CKD.<sup>293</sup> Given the inaccuracy of these equations at lower creatinine concentrations, values of eGFR that are greater than 60 mL/kg/min/1.73 m<sup>2</sup> should simply be reported as “>60 mL/kg/min/1.73 m<sup>2</sup>.” In the United States, the leading causes of end-stage renal disease are diabetes mellitus and hypertension.

AKI is a sudden decrease in renal function with the possible decrease in urine output. Episodes of AKI can occur in individuals with or without CKD. Several consensus-based criteria for classifying AKI have been developed, including the RIFLE classification scheme,<sup>297</sup> the Acute Kidney Injury Network classification scheme,<sup>298</sup> and the current KDIGO criteria.<sup>299</sup> AKI may be reversible if precipitating factors are

identified and corrected. Classifying AKI into prerenal, renal, and postrenal causes allows for a systematic approach. Prerenal causes can often be differentiated by calculating the blood urea nitrogen-to-creatinine ratio. A ratio more than 20 suggests prerenal etiologies, with hypovolemia or hypotension the most common. A fractional excretion of sodium (FENa) less than 1% also suggests prerenal disease (in the absence of concomitant diuretic administration) and can be calculated using the following formula:

$$\text{FENa} = \frac{P_{\text{Cr}}/\text{U}_{\text{Cr}}}{P_{\text{Na}}/\text{U}_{\text{Na}}}$$

Obstruction, which results in dilated ureters and enlarged kidneys, should always be considered in the differential diagnosis of AKI. Prompt identification with ultrasound should lead to attempts to decompress the outflow tract.

Patients with CKD have many associated comorbidities, both related to the underlying diseases that led to CKD and its resulting end-organ complications. Cardiovascular issues include hypertension, IHD, ventricular dysfunction (diastolic and systolic), heart failure, CVD, PAD, pericarditis, pericardial effusions, and valvular heart disease (valvular calcification with resulting regurgitation or stenosis). Pulmonary hypertension and increased cardiac output occur in patients with arteriovenous fistulas. CKD is also associated with chronic anemia due to reduced erythropoietin production by the kidneys. While treatable with erythropoiesis stimulating agents, complete “normalization” of hemoglobin concentration (i.e., 135 g/L vs. 113 g/L) may actually increase morbidity and vascular events.<sup>300</sup> Hence, current KDIGO guidelines recommend using erythropoiesis stimulating agents to treat hemoglobin concentrations less than 90 g/L, but avoid increasing the concentration to above 130 g/L.<sup>301</sup> Other hematological abnormalities include platelet dysfunction and increased bleeding, despite normal platelet counts, prothrombin times, and activated partial thromboplastin time (aPTT). Once dialysis is begun, patients become more prone to hypercoagulable states. Patients with CKD can develop autonomic and peripheral (sensory and motor) neuropathies. Unsurprisingly, CKD is associated with many electrolyte disturbances. Chronic metabolic acidosis is common, but it is usually mild and compensated for by chronic hyperventilation. Hyperkalemia is the most serious electrolyte disturbance. Hypocalcemia is common in patients undergoing dialysis, although with long-term disease, secondary and tertiary hyperparathyroidism eventually develops. Chronically elevated troponin concentrations are common in end-stage renal disease, which does influence interpretation of any postoperative troponin elevations.<sup>302</sup> Since insulin is metabolized by the kidneys, worsening renal function should be suspected in diabetic patients with end-stage renal disease who develop improved glycemic control or unexpected hypoglycemia.

Preexisting CKD is a risk factor for increased postoperative complications, including cardiac complications,<sup>97</sup> AKI,<sup>303,304</sup> acute stroke,<sup>305</sup> and death.<sup>99</sup> Risk factors for postoperative AKI have also been identified. In cardiac surgery, several simple preoperative risk indices have been developed to predict postoperative AKI requiring dialysis.<sup>268,269</sup> Important risk factors in these indices include complex surgery, nonelective surgery, CKD, diabetes

mellitus, heart failure, female sex, and COPD. In noncardiac surgery, identified risk factors for AKI include increased age, male sex, symptomatic heart failure, hypertension, liver disease (including ascites), CKD, PAD, COPD, non-elective surgery, and intraperitoneal surgery.<sup>303,304</sup> Preoperative identification of at-risk patients can facilitate care, such as preoperative hydration and avoidance of hypovolemia. Nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors interfere with renal perfusion autoregulation and should be avoided or discontinued in patients with CKD. In contrast, these drugs do not increase the risk of postoperative AKI in patients with normal renal function.<sup>306</sup> Many drugs are also metabolized or cleared by the kidneys. Drugs with particular perioperative implications are the LMWHs since there is no easy method to monitor their anticoagulation effects. LMWHs are cleared by the kidneys and are not removed during dialysis; thus, they have a prolonged duration of action in patients with CKD. Similarly, dosing of DOACs have to be adjusted in CKD (see Table 31.11).

The preoperative evaluation of patients with CKD should emphasize the cardiovascular system, cerebrovascular system, intravascular volume status, and electrolyte status. The early stages of CKD typically cause no symptoms. The anesthesiologist should inquire about the cardiovascular systems (i.e., chest pain, orthopnea, paroxysmal nocturnal dyspnea), urine output, associated comorbidities, medications, dialysis schedules, and any hemodialysis catheter problems (e.g., infection, thrombosis). Information on the patient's target and current weight may be helpful for assessing volume status. Patients with CKD need an ECG and blood sampling to measure electrolyte, calcium, glucose, albumin, and creatinine concentrations. Further evaluation is needed if the ECG shows LVH (hypertension), peaked T waves (hyperkalemia), flattened T waves, a prolonged PR interval, or a prolonged QT interval (hypokalemia). A chest radiograph (infection, volume overload), echocardiogram (murmurs, heart failure), and cardiology evaluation may be necessary in some cases. Venous access sites or blood draws from the brachial, cephalic (antecubital), and central veins in the nondominant upper extremity should be avoided in patients who may eventually need fistulas in those locations for dialysis.

Preoperative renal replacement therapy (dialysis) schedules should be coordinated with the timing of the planned surgery. Dialysis is important for correct volume overload, hyperkalemia, and acidosis before planned surgery. Ideally, elective surgery should be performed about 24 hours after dialysis. Performance of surgery shortly after dialysis should be avoided, because of the risks of acute volume depletion and electrolyte alterations. Specifically, dialysis leads to fluid shifts and electrolyte (i.e., sodium, potassium, magnesium, phosphate) imbalance, especially related to shifting of electrolytes between intracellular and extracellular compartments.

### Contrast-Induced Nephropathy

Contrast-induced nephropathy is defined as AKI that occurs after radiocontrast administration. Typically, the creatinine concentration increases within 24 to 48 hours after contrast exposure, after which it typically declines to baseline levels within 3 to 7 days. Recent (<24 hours)

preoperative contrast exposure is also a risk factor for AKI following cardiac surgery.<sup>307</sup> Even when renal function returns to normal, patients with contrast-induced nephropathy experience elevated risks of short-term and long-term mortality.<sup>308</sup> Risk factors for contrast-induced nephropathy are CKD (especially diabetic nephropathy), heart failure, hypovolemia, and certain contrast exposure characteristics (i.e., high volume, ionic agents, hyperosmolar agents). Preventative strategies include avoiding volume depletion, discontinuing NSAIDs for 24 to 48 hours, using a low-risk contrast administration protocol (i.e., low volume of a low-osmolal or iso-osmolal agent), and periprocedure intravenous volume administration with normal saline. Despite initial promising results for N-acetylcysteine and sodium bicarbonate in relatively small randomized trials, a large trial with more than 5000 high-risk participants found that neither approach prevented contrast-induced nephropathy.<sup>309</sup>

### HEPATIC DISORDERS

Liver disease can affect the hepatocytes and/or biliary system, thereby impacting protein synthesis (e.g., coagulation factors, albumin), bile regulation, and metabolism of drugs or toxins. Hepatocellular diseases, such as hepatitis (viral, alcoholic, autoimmune hepatitis) and hepatocellular carcinoma, affect hepatocytes and liver synthetic function. Obstructive disorders, including choledocholithiasis, bile duct tumors (extrahepatic), primary biliary cirrhosis (intrahepatic), and primary sclerosing cholangitis (extrahepatic and intrahepatic), cause bile stasis. Most drug-induced liver disease, as well as some forms of viral hepatitis, affect both hepatocytes and the biliary system.

The preoperative history typically reveals the underlying disease etiology, disease severity, therapies, and associated complications. Some patients with liver disease may be asymptomatic, whereas others may complain of fatigue, weight loss, dark urine, pale stools, pruritus, right upper quadrant pain, bloating, and jaundice. The physical examination should assess for weight, vital signs (including oxygen saturation), jaundice, bruising, ascites, pleural effusions, peripheral edema, hepatomegaly, splenomegaly, and altered mental status. The presence of encephalopathy, coagulopathy, ascites, volume overload, and infection should be determined before surgery. The bilirubin concentration generally must exceed 25 g/L before icterus is evident in mucous membranes and sclerae. If new-onset or worsening encephalopathy is identified, precipitating factors should be sought, such as infection, drug effects, bleeding, or electrolyte disturbances.

Baseline testing includes an ECG and blood sampling for CBC, electrolyte concentration, creatinine concentration, liver function tests, albumin concentration, and INR. Patients suspected of having hepatitis may require screening for the hepatitis A immunoglobulin M (IgM) antibody, the hepatitis B surface and core antigens, the hepatitis B surface antibody, and the hepatitis C antibody. A chest radiograph can help identify any suspected effusions. Coagulopathy can be a result of vitamin K deficiency (from cholestasis), factor deficiency (from loss of synthetic function), or thrombocytopenia (from splenomegaly and portal hypertension). Thus, therapy to correct coagulopathy should be directed at the

cause. Vitamin K, fresh frozen plasma, or platelets may correct deficiencies. Vitamin K, taken at 1 to 5 mg orally or subcutaneously daily for 1 to 3 days, may correct a prolonged PT and carries minimal risk. The coagulopathy in patients with synthetic failure is not likely to correct, thus necessitating fresh frozen plasma transfusion aiming for an INR less than 1.5. Limited evidence suggests that lactulose (30 mL orally every 6 hours for 3 days preoperatively) with the last dose within 12 hours of surgery, or oral bile salts with intravenous hydration beginning the night before the operation, may reduce perioperative AKI in patients at risk.<sup>310</sup> Reduction of ascites preoperatively may decrease the risk of wound dehiscence and improve pulmonary function. Sodium restriction (in diet and intravenous solutions), diuretics (especially spironolactone), and paracentesis are useful for reducing ascites. If ascites fluid is aspirated, it should also be analyzed for infection. Encephalopathy is frequently precipitated by an additional acute insult such as infection, gastrointestinal bleeding, hypovolemia, or sedatives. It is therefore important to determine reversible factors and treat them accordingly. Lactulose (30 mL every 6 hours orally) is first-line therapy. Addressing nutritional deficiencies with enteral or parenteral supplementation may have benefits, especially in alcoholic patients. Patients who abuse alcohol may be at risk for neurologic deterioration (i.e., Wernicke-Korsakoff syndrome) if thiamine, folate, and vitamin B<sub>12</sub> supplements are not provided, especially when these patients are given nutrition or glucose. These same patients are also at risk of alcohol withdrawal syndromes.

The perioperative risk of patients with chronic hepatitis or cirrhosis is predicted by histologic severity, portal hypertension, and impairment of liver function. Patients with severe liver disease have increased perioperative morbidity and mortality; common adverse events are bleeding, infection, liver failure, and hepatorenal syndrome. Predictors of poor perioperative outcome in patients with liver disease include the following:

- Child-Turcotte-Pugh class C cirrhosis, which is calculated using bilirubin concentration, albumin concentration, PT, ascites severity, and encephalopathy severity (Table 31.16)
- Model for end-stage liver disease (MELD)<sup>311</sup> score of 15 or more (the MELD score is calculated using serum bilirubin concentration, INR, and serum creatinine concentrations)

**TABLE 31.16** Child-Turcotte-Pugh Classification

Parameter	1 point	2 points	3 points
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–2.5	<2.8
Prothrombin time (seconds over control)	<4	4–6	>6
Encephalopathy	None	Grade 1–2	Grade 3–4

Class A: <7 points.  
Class B: 7–9 points.  
Class C: >9 points.

- Acute hepatitis (viral or alcoholic)
- Chronic active hepatitis with jaundice, encephalopathy, coagulopathy, or elevated liver enzymes
- Abdominal surgical procedures
- PT prolongation of 3 seconds or more that is refractive to vitamin K therapy

The MELD score can be calculated as shown below (where creatinine and bilirubin concentrations are expressed in mg/dL):

$$\text{MELD} = 6.43 + [3.78 \times \log_e (\text{bilirubin})] + [11.2 \times \log_e (\text{INR})] + [9.57 \times \log_e (\text{creatinine})]$$

Online calculators are also available to calculate MELD scores readily (e.g., [www.unos.org](http://www.unos.org)). In some cases, it may be appropriate to delay elective surgery until an acute episode of hepatitis (or exacerbation of chronic disease) has resolved, or until a diagnosis is established for newly discovered hepatic dysfunction. Elective surgery is contraindicated in patients with acute or fulminant liver disease. High-risk patients are best managed collaboratively with a liver specialist.

## Hepatitis

Hepatitis, which is defined as hepatocyte inflammation, can be caused by drugs, alcohol, viruses (hepatitis A, B, C, D, and E), and autoimmune diseases (see also Chapter 16). These disorders generally have an initial acute phase, as well as a subsequent chronic phase that can progress to cirrhosis. Risk factors for hepatitis are alcohol use, sexual activity (i.e., multiple partners, sex industry workers, sex with sex industry workers, men who have sex with men), intravenous drug use, blood transfusions before 1992, obesity (i.e., nonalcoholic steatohepatitis [NASH]), tattoos, body piercing, and travel to developing countries. Hepatitis A is caused by contaminated food, contaminated water, or contact with an infected person. Since it rarely progresses beyond the acute illness, a remote history of hepatitis A has no perioperative significance. Hepatitis B is transmitted by sexual activity or contact with blood (rarely after implementation of screening in 1986). It varies in severity and can advance to cirrhosis; this has become much less common due to widespread hepatitis B vaccination. Additionally, antiviral therapy can treat the infection, albeit with variable efficacy. Hepatitis C is transmitted primarily through blood exposure (all blood has been screened since 1992), especially among intravenous drug users. Many patients are unaware of infection because the acute phase is often asymptomatic. While hepatitis C infection can advance to cirrhosis, currently available antiviral therapy can now eliminate infection in almost all patients. Hepatitis D occurs only in conjunction with hepatitis B infection, whereas hepatitis E is less common in high-income countries. Hepatitis D can progress to cirrhosis, while hepatitis E rarely progresses beyond the acute illness. Alcoholic hepatitis generally occurs after at least 20 years of moderate to heavy daily alcohol intake (>100 g/day) and may progress to cirrhosis. Autoimmune hepatitis primarily affects young females and has an as yet unknown etiology. Many different drugs (including herbal and over-the-counter preparations) can also cause hepatitis, with examples being statins, isoniazid, and acetaminophen.

## Obstructive Jaundice

Extrahepatic bile duct obstruction may be caused by gallstones, tumors (e.g., pancreatic, gallbladder, bile duct, ampulla of Vater), or scarring. Patients can present with jaundice, pruritus, and abdominal pain. Risk factors for postoperative mortality in these patients include a hemoglobin concentration less than 100 g/L, serum bilirubin exceeding 20 mg/dL, and serum albumin lower than 25 g/L.<sup>312</sup> These patients are at elevated risk for postoperative AKI, which may be prevented using bile salts or lactulose.<sup>310</sup>

## Miscellaneous Liver Diseases

Wilson disease, hemochromatosis, and  $\alpha_1$ -antitrypsin deficiency are uncommon hereditary causes of liver disease. All three conditions can eventually lead to end-stage liver disease. In contrast, another hereditary liver disease, Gilbert disease, is characterized by a mildly elevated bilirubin level and no perioperative significance. NASH, also known as “fatty liver,” progresses to liver fibrosis, cirrhosis, and end-stage liver disease (sometimes necessitating liver transplantation). The condition is associated with obesity, hypertension, dyslipidemia, and diabetes mellitus. Following a more than doubling in disease prevalence over the past two decades in the United States,<sup>313</sup> NASH is now the most common cause of chronic liver disease and the second most common indication for liver transplantation.<sup>314,315</sup> Primary biliary cirrhosis (or primary biliary cholangitis) is an autoimmune disorder characterized by intrahepatic biliary obstruction and antimitochondrial antibodies. Affected patients are predominantly female (>90%), may have other autoimmune disorders (e.g., Sjögren syndrome, autoimmune thyroid disease, limited cutaneous scleroderma, rheumatoid arthritis), and can progress to end-stage liver disease. Primary sclerosing cholangitis is characterized by bile duct destruction that can progress to cirrhosis and end-stage liver disease. The disease mainly affects males and may be idiopathic or associated with inflammatory bowel disease (i.e., ulcerative colitis, Crohn disease).

## Unexpected Elevated Liver Function Tests

Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentration reflect hepatocyte damage. Bilirubin concentration measures the liver's ability to conjugate and excrete bile salts. Alkaline phosphatase (ALP) rises with impaired hepatic excretion, whereas albumin and INR measure the synthetic function of the liver. Routine preoperative laboratory screening may identify about 1 in 700 surgical patients as having unexpected liver diseases, most of which are not severe.<sup>316</sup> Nonetheless, if abnormal liver function test values are unexpectedly found, further testing or referral may be necessary in some cases. Elevated AST or ALT concentrations should prompt hepatitis screening with hepatitis A IgM antibody, hepatitis B antigens (surface and core), hepatitis B surface antibody, and hepatitis C antibody. Elevated concentrations of ALP or bilirubin, especially in association with normal or mild to moderate increased transaminase levels, may indicate obstruction in the biliary system. In these cases, abdominal ultrasound, computed tomography scans, or endoscopic retrograde cholangiopancreatography may establish a diagnosis.

## Cirrhosis

Cirrhosis is defined as irreversible liver fibrosis and is the end result of most hepatotoxic conditions. This fibrosis leads to portal hypertension, impaired synthetic function (i.e., synthesis of proteins such as clotting factors), and impaired metabolic functions (i.e., clearance of toxins and drugs). Portal hypertension can lead to splenomegaly, esophageal varices, ascites, dependent edema, and pleural effusions. Patients with ascites may also develop spontaneous bacterial peritonitis, which is associated with increased perioperative mortality. Other complications include hepatic encephalopathy, bleeding, thrombocytopenia, low albumin concentrations, and prolonged INR. Hepatopulmonary syndrome may develop, resulting in hypoxemia and pulmonary hypertension because of pulmonary shunts. Jaundiced patients in particular are at risk for developing hepatorenal syndrome, which is renal insufficiency associated with hepatic disease but without any primary renal disease. The condition may be related to renal hypoperfusion. Patients with end-stage liver disease also develop a high–cardiac output state, characterized by decreased systemic vascular resistance. The Child-Turcotte-Pugh classification can predict perioperative morbidity and mortality, with especially high risks in patients assigned to class C (see Table 31.16). The MELD score also predicts perioperative risks, perhaps better than the Child-Turcotte-Pugh classification,<sup>317</sup> with scores exceeding 14 indicative of increased perioperative risk.

## HEMATOLOGIC DISORDERS

### Anemia

Anemia is a very common preoperative hematologic disorder with multifactorial etiology. It is strictly defined as a reduced number of circulating red blood cells (RBCs), however, more commonly it is defined based on the value of reduced hemoglobin concentration or reduced hematocrit. For example, the World Health Organization defines anemia as a hemoglobin level less than 130 g/L in adult men and less than 120 g/L in adult women. Anemia can be classified based on the underlying mechanisms as being related to decreased RBC production (e.g., bone marrow disorders, nutritional deficiencies), increased RBC destruction (e.g., hemolytic anemia, intravascular hemolysis), and blood loss (e.g., gastrointestinal blood loss). Anemia may also be classified morphologically based on the associated RBC size, which is itself characterized by the mean corpuscular volume (MCV). Based on this approach, anemia can be classified as microcytic (MCV < 80 femtoliter [fL]), macrocytic (MCV > 100 fL), or normocytic (MCV between 80 and 100 fL). Common causes of microcytic anemia are iron deficiency (including chronic blood loss), thalassemia minor, and anemia associated with inflammatory disease. Common causes of macrocytic anemia include alcoholism, liver disease, hypothyroidism, and vitamin B<sub>12</sub> deficiency. Common causes of normocytic anemia are CKD, heart failure, and cancer.

Preexisting anemia is a consistently recognized risk factor for postoperative death and complications, including AKI, stroke, and infections.<sup>318</sup> Furthermore, this risk is proportional to the degree of anemia and independent of

the patient's other comorbidities.<sup>101,102,319</sup> Nonetheless, there are some important caveats for consideration. First, it remains unclear whether anemia is the causal mechanism for these complications, or instead simply a marker of a high-risk patient. The limited available perioperative data generally suggest that anemia treatment strategies (e.g., erythropoiesis-stimulating agents) can improve hemoglobin concentrations and reduce transfusion requirements, but without convincing evidence for the prevention of death or complications.<sup>320-322</sup> These perioperative data are also generally consistent with findings in nonsurgical populations, such as patients with heart failure.<sup>323-327</sup> Second, there is no consistent hemoglobin concentration threshold that defines elevated perioperative risk. While data from noncardiac surgery performed in Jehovah's Witness patients suggest that risk increases substantially once preoperative hemoglobin concentrations fall below 100 g/L (especially in the presence of concomitant IHD),<sup>328</sup> simply increasing hemoglobin concentrations to this threshold with RBC transfusion is not consistently beneficial. Importantly, transfusion itself has also been associated with poor outcomes in observational studies.<sup>329</sup> In a multicenter randomized trial of 2016 patients undergoing hip fracture surgery, a strategy of transfusing in response to a 100 g/L threshold in hemoglobin concentration was not superior to a strategy of transfusing in response to a 80 g/L threshold or symptoms of anemia.<sup>330</sup> Similarly, in a multicenter randomized trial of 5243 patients undergoing cardiac surgery, a strategy of transfusing in response to a 75 g/L threshold was noninferior to a strategy of transfusing in response to a 95 g/L threshold.<sup>331</sup> These data suggest that the optimal perioperative hemoglobin concentration threshold varies between 75 g/L and 100 g/L across individuals, with interindividual differences largely explained by comorbid conditions (e.g., cardiopulmonary disease).

During the preoperative evaluation of known or suspected anemia, the overarching goals are to determine its etiology, duration, stability, related symptoms, and therapy. Thus, it is important to inquire about any history of anemia (including family history of anemia), colon cancer, gastrointestinal bleeding, genitourinary bleeding, menorrhagia, chronic infections, inflammatory diseases, nutritional deficiencies, and prior weight reduction procedures (e.g., bariatric surgery). The anesthesiologist should also consider the type of surgical procedure, anticipated blood loss, and comorbid conditions that may either affect oxygen delivery or be affected by decreased oxygen delivery (i.e., pulmonary, renal, hepatic, cerebrovascular, cardiovascular disease). In addition, an accurate determination of the patient's medications is helpful, especially because anemia has implications for the risk-to-benefit profile of some perioperative medications, such as  $\beta$ -adrenergic blockers.<sup>103,104</sup>

Patients with anemia or suspected anemia must have a CBC. In general, collaboration with a primary care physician or hematologist is helpful for further evaluation of newly diagnosed anemia. Usual initial studies include peripheral smear and MCV; subsequent studies, such as iron studies (i.e., ferritin, transferrin saturation), vitamin B<sub>12</sub>, or folate levels, are guided by findings on the smear and the MCV.<sup>332</sup> The MCV is high and the vitamin B<sub>12</sub> or folate levels are low in macrocytic anemia associated with these deficiencies. Low values in MCV, ferritin (<30 g/ $\mu$ L),

and transferrin saturation (<20%) are indicative of iron deficiency anemia. In some cases of iron deficiency anemia, transferrin saturation may still be low (<20%) but ferritin concentrations are in an indeterminate zone (i.e., 30-100 g/ $\mu$ L). Conversely, ferritin and transferrin saturation are normal or high in anemia associated with chronic disease.

Blood type and screening may be necessary based on the level of preoperative anemia and anticipated degree of surgical blood loss. Elective procedures should be postponed in patients with significant anemia, regardless of the anticipated surgical blood loss. This delay allows for evaluation of the underlying cause, such as occult blood loss, vitamin deficiency, or undiagnosed chronic conditions (e.g., CKD). When delay in elective surgery is possible, updated 2015 guidelines from the ASA suggest preoperative treatment with an erythropoiesis-stimulating agent and iron in some patient subgroups (e.g., CKD, anemia of chronic disease, patient's refusal to receive blood transfusions), especially for anemic individuals scheduled for procedures with significant expected blood loss.<sup>333</sup> Similarly, preoperative iron therapy may be considered in patients with known iron deficiency anemia, when time permits.<sup>333</sup>

### Sickle Cell Disease

Sickle cell disease is a hereditary hemoglobinopathy with associated vasoocclusive episodes that are responsible for most associated complications. Patients homozygous for hemoglobin S (HbS) have symptomatic disease; they are at risk for major morbidity and have a shortened life expectancy. Patients with SC disease, who have both HbS and HbC, have a much less severe clinical course with moderate anemia. Heterozygous patients (HbS and HbA) have sickle cell trait and rarely have any related consequences. Preoperative assessment should focus on evidence of organ dysfunction and recent patterns of acute exacerbations.<sup>334</sup> Patients may have CKD, loss of renal concentration ability (and therefore are prone to dehydration), splenomegaly, pulmonary hypertension, pulmonary infarctions, CVD, and heart failure. They are at risk for infections because of splenic infarctions. Predictors of perioperative vasoocclusive complications include recent increases in hospitalizations, advanced age, preexisting infections, and pulmonary disease.<sup>334</sup>

The preoperative examination focuses on the frequency, severity, and pattern of vasoocclusive crises. In addition, the anesthesiologist should evaluate the degree of pulmonary, cardiac, renal, and central nervous system damage. Useful tests include an ECG, chest radiograph, and blood sampling for CBC and creatinine concentration. Additional testing (e.g., echocardiogram, arterial blood gases) may be needed. Preoperative prophylactic transfusion is increasingly used in patients with sickle cell anemia who are undergoing any surgical procedure—other than short minor procedures (e.g., biopsy, myringotomy).<sup>335</sup> The objective of any red cell transfusion is to reduce the proportion of abnormal hemoglobin in the affected patient. A prior randomized trial found that prophylactic transfusion to a hemoglobin concentration greater than 100 g/L resulted in fewer adverse events following intermediate-risk surgery.<sup>336</sup> This simpler approach of transfusing to a hemoglobin concentration threshold (>100 g/L) is as effective as a more aggressive approach of transfusing to decrease

HbS concentration to under 30% (while also increasing hemoglobin concentration to  $\geq 100$  g/L)<sup>337</sup> in the setting of intermediate-risk surgery. It is likely that a more aggressive strategy (i.e., decreasing HbS concentration to  $< 30\%$ ) is preferable for high-risk surgery such as major cardiovascular or intracranial procedures. In general, the decision to transfuse preoperatively should be made only in concert with a hematologist familiar with the disease. Additionally, if the person with sickle cell is managed by a specialist sickle cell service, it is best to liaise with this team before surgery. The patient's surgical admission should be planned to minimize preoperative dehydration (e.g., minimize fasting period, schedule procedure as an early morning case).

### Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase deficiency is a hereditary Coombs-positive hemolytic anemia. Since it is an X-linked hereditary condition, affected individuals are typically males. Hemolysis may be triggered by drugs (e.g., antipyretics, nitrates, sulfonamides), food (e.g., fava beans), infection, hypoxia, hypothermia, or blood products. Lists of potentially triggering medications are available online (e.g., [www.g6pd.org](http://www.g6pd.org), [www.g6pddeficiency.org](http://www.g6pddeficiency.org)). The severity of the hemolysis varies across individuals and the underlying genetic defects. Treatment involves avoidance of triggers, folic acid supplementation, and management of acute hemolytic episodes (i.e., hydration, red cell transfusion for severe anemia). The preoperative evaluation should focus on previous hemolysis episodes, predisposing factors, and current hematocrit.

### Coagulopathies

Hypocoagulable states may be either inherited (e.g., hemophilia) or acquired (e.g., liver disease, malnutrition, drug exposure). To determine the diagnosis and associated bleeding risk, the anesthesiologist should inquire about known diagnoses, tests, treatments, previous bleeding episodes, and family history. A history of excessive bruising, prolonged bleeding after cuts, heavy menstrual cycles, and bleeding gums is sensitive but not specific. A *change* in these symptoms is likely more meaningful than a long-term history (because what one individual considers excessive may actually be normal). Excessive bleeding after previous procedures or childbirth (especially if transfusions were unexpectedly required) is more definitive but not diagnostic. Petechiae, multiple bruises, hematomas, jaundice, and frank bleeding are important findings. Diagnostic testing may include a CBC (including platelet count), INR, and aPTT; however, *routine* preoperative screening for coagulopathies is not indicated. Clinical indications include a known bleeding disorder, hepatic disease, and anticoagulant use.<sup>5</sup> National guidelines in the United Kingdom also recommend coagulation testing only in patients who are (1) ASA physical status class III or IV; (2) undergoing intermediate, major, or complex surgical procedures; and (3) known to take anticoagulant medications or have chronic liver disease.<sup>274</sup> If a specific cause of bleeding is suspected or known (e.g., liver disease, malnutrition), then additional targeted testing (e.g., liver function tests, protein, albumin) may be needed.

Patients may occasionally have abnormal INR or aPTT results on preoperative screening bloodwork. In patients

without a history of vitamin K antagonist use, the most common causes of a prolonged INR are laboratory error, liver disease, and malnutrition. Consequently, the test should initially be repeated. If the repeat test result remains abnormal, both liver function tests and a hepatitis panel are warranted, with possible referral to a hematologist. A trial of oral vitamin K (1-5 mg daily for 3 days) can also be implemented. A prolonged aPTT can result from both hypocoagulable and hypercoagulable (e.g., factor V Leiden, anticardiolipin antibody, lupus anticoagulant, antiphospholipid antibody syndrome) conditions. The first steps are to repeat the test and ascertain possible exposure to heparin. Even small amounts of heparin in indwelling catheters can prolong the aPTT, especially if the blood is drawn from that site. Other than heparin exposure, other causes of a prolonged aPTT include von Willebrand disease (vWD; see section on von Willebrand Disease) and hemophilias (see section on "Hemophilias"). Mixing studies (in which normal blood is mixed with the subject's blood) allows for differentiation between factor deficiencies (aPTT will be corrected) versus inhibitors (no correction). Elective surgical procedures should be postponed until the etiology of abnormal tests is determined and corrections are made.

**Hemophilias.** Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) are X-linked recessive inherited disorders that almost exclusively manifest in males. Hemophilia B is also referred to as "Christmas disease." Hemophilia C is an autosomal recessive deficiency of factor XI (also called Rosenthal syndrome) that tends to affect individuals of Ashkenazi Jewish descent. Hemophilia A has a six-fold higher incidence than Hemophilia B (1 in 5000 male births vs. 1 in 30,000 male births). The severity of bleeding varies across individuals but is similar among relatives (who have the same underlying genetic mutation) and is directly related to the degree of factor deficiency. Severe hemophilia is characterized by less than 1% factor activity, moderate hemophilia by 1% to 5% activity, and mild hemophilia by more than 5% to under 40% activity. Increased disease severity is characterized by an early onset of bleeding episodes, as well as higher risks of both severe and spontaneous bleeding. About two thirds of hemophilia A cases are severe, while the proportion is 50% for hemophilia B. Patients with hemophilia have a prolonged aPTT, but a normal INR and platelet count.

A hematologist must be involved in the perioperative care of patients with hemophilia. A detailed plan to both measure and replace deficient factors is paramount. Current guidelines recommend that, in the setting of major surgery, factor replacement be used to increase preoperative levels to 80% to 100% for hemophilia A and 60% to 80% for hemophilia B.<sup>338</sup> After surgery, the target factor level is 50%, until the surgical wound is healed. The specific required dose of recombinant factor is informed by the targeted increase in factor levels, clinical expertise of the consulting hematologist, individual patient-level factors (e.g., history of previous bleeding episodes), and hospital protocols. The dose required to increase factor VIII levels is:

$$\text{Factor VIII dose} = \text{weight (kg)} \times 0.5 \times (\text{desired absolute \% increase in factor levels})$$

The typical required dose for factor IX replacement is:

$$\text{Factor IX dose} = \text{weight (kg)} \times (\text{desired absolute \% increase in factor levels})$$

To rapidly increase factor levels to close to 100%, the usual dose required is 50 units/kg for factor VIII and 100 to 120 units/kg for factor IX.<sup>339</sup> Intramuscular injections are to be avoided in these patients.

**von Willebrand Disease.** vWD is an inherited disorder of von Willebrand factor (vWF) that affects both sexes. It is the most common congenital coagulopathy, occurring in approximately 1% of individuals.<sup>340</sup> Several types (1, 2A, 2B, 2M, 2N) are autosomal dominant, while type 3 is autosomal recessive (Table 31.17). vWD can result from both quantitative and qualitative vWF deficiencies. Most affected patients have a normal INR and platelet count (although type 2B can have a mild thrombocytopenia), but typically elevated aPTT (although patients with mild disease may have normal aPTT). Indeed, vWD is the most common cause of a prolonged aPTT in patients not taking heparin. The condition is diagnosed by measuring plasma vWF functional activity (ristocetin cofactor, which causes platelet aggregation), plasma vWF antigen levels, and factor VIII levels. Most patients with vWD have a history of bleeding, but some do not receive a diagnosis until a challenge to coagulation occurs with major surgery or antiplatelet drug exposure (e.g., aspirin, NSAIDs).

A hematologist should be involved in the care of patients with vWD. Treatment options for vWD include desmopressin acetate (1-desamino-8-d-arginine vasopressin [DDAVP]) and vWF replacement therapy. DDAVP increases the release of factor VIII, vWF, and plasminogen activator from endothelial cells. It is contraindicated in patients with type 2B disease because it increases abnormal vWF release and may cause thrombocytopenia. In addition, it is not recommended in patients with type 3 disease (since there is minimal to no vWF available to be released from endothelial cells). In other cases, an intravenous dose of 0.3 µg/kg (given over 15-30 minutes to minimize hypotension, flushing, and tachycardia) typically raises vWF concentrations by three- to four-fold. Nonetheless, considerable variation in response exists among individuals. Hence, an initial test of DDAVP should be conducted prior to any bleeding episodes (e.g., surgery), while monitoring changes in vWF and factor VIII concentrations over the 4 hours after drug administration. DDAVP

is also available as a nasal spray (150 µg for individuals under 50 kg, and 300 µg for individuals weighing 50 kg or more). For individuals who cannot be treated adequately with DDAVP, vWF preparations should be used instead. A variety of preparations are available, including vWF-containing factor VIII concentrates, purified vWF concentrates, and recombinant vWF products. These options, if available, are preferable to cryoprecipitate (which can be used nonetheless, but is associated with higher risks of viral transmission).

**Thrombocytopenia.** Thrombocytopenia is defined as a platelet count less than 150,000/mm<sup>3</sup>. It may be the result of decreased production, increased destruction, or sequestration. Causes include malignant diseases, primary immune thrombocytopenia (ITP), drug-induced thrombocytopenia (e.g., quinine, sulfonamides, ampicillin), rheumatological autoimmune disorders (e.g., SLE, rheumatoid arthritis), pregnancy (i.e., gestational thrombocytopenia, preeclampsia), chronic liver disease (i.e., hypersplenism), alcohol, nutritional deficiencies, infection (e.g., hepatitis C, sepsis), hereditary disease, and disseminated intravascular coagulation. If a patient has an unexpectedly low platelet count, the initial steps are to repeat the test, examine the peripheral smear, and collect blood for the platelet count in a tube without ethylenediaminetetraacetic acid. This chemical is a chelating agent often used to prevent clotting in tubes used for determining CBC, but it can also cause clumping of platelets (termed pseudothrombocytopenia). ITP is a chronic autoimmune disorder characterized by autoantibodies that cause platelet destruction. Usual treatment includes corticosteroids, splenectomy (eliminates the major site of platelet removal), and intravenous immunoglobulin. Patients with ITP often have less bleeding than expected, even at very low platelet levels, likely because of increased platelet turnover with a resulting predominance of young platelets. A patient with newly discovered thrombocytopenia may require a hematology consultation before elective surgery.

Thrombocytopenia within the context of recent heparin exposure should raise a concern regarding potential heparin-induced thrombocytopenia (HIT), which generally occurs within 5 to 10 days after heparin exposure.<sup>341</sup> HIT is an immune-mediated disorder characterized by antibodies directed against platelet factor 4 complexed with heparin. While HIT is characterized by thrombocytopenia, affected patients are at risk for arterial thromboses,

**TABLE 31.17** Classification of von Willebrand Disease

Type	Characteristics	Initial Treatment
1	80% of cases; quantitative defect	Desmopressin*
2A	Quantitative and qualitative defect	Desmopressin*
2B**	Rare; quantitative and qualitative defect, autosomal dominant	Cryoprecipitate or factor VIII concentrates with vWF
2M	Qualitative defect	Desmopressin*
2N	Qualitative defect; vWF levels normal; factor VIII reduced	Desmopressin* effect may be too short-lived
3	Rare; low to undetectable levels of vWF	Desmopressin* usually not effective

\*Desmopressin acetate (DDAVP).

\*\*With type 2B desmopressin acetate may cause thrombocytopenia. If desmopressin is not effective, factor VIII concentrates containing vWF may be used. vWF, von Willebrand factor.

venous thromboses, stroke, skin necrosis, limb gangrene, and organ infarction. Since the results of definitive laboratory testing for HIT antibodies (i.e., immunoassay and/or functional assay for HIT antibodies) typically takes several days, the initial presumptive diagnosis is based on clinical presentation and available laboratory tests (e.g., decreasing platelet counts). This initial diagnosis can be aided with validated clinical prediction tools, such as the “4 Ts” score.<sup>342</sup> While waiting for the results of antibody testing in patients with suspected HIT, any heparin therapy (including LMWH) should be immediately discontinued and alternative anticoagulation therapy (e.g., danaparoid, argatroban, bivalirudin, fondaparinux, DOACs) instituted.

In otherwise healthy individuals (i.e., no other basis for elevated bleeding risks) neuraxial anesthesia is generally considered safe once the platelet count exceeds 50,000 to 80,000 per mm<sup>3</sup>.<sup>343-346</sup> Surgery can be safely performed in patients with platelet counts higher than 50,000/mm<sup>3</sup>.<sup>346</sup> The risk of bleeding increases progressively as the count falls further, to less than 50,000/mm<sup>3</sup>. When platelet transfusions are used to treat thrombocytopenia, the platelet count generally rises by 10,000/mm<sup>3</sup> for every unit transfused.

**Thrombocytosis.** Thrombocytosis is a platelet count more than 450,000/mm<sup>3</sup>. It may be physiologic (i.e., exercise, pregnancy), primary (e.g., myeloproliferative disorder), or secondary (e.g., iron deficiency, neoplasm, surgery, chronic inflammation). Increasing levels of thrombocytosis can increase risks for thrombotic events, such as strokes, myocardial infarction, pulmonary emboli, mesenteric emboli, and venous clots. Conversely, patients with primary thrombocytosis (also known as essential thrombocythemia) also have a tendency toward increased bleeding, which may be due to qualitative alterations in platelet function and an acquired von Willebrand syndrome associated with very high platelet counts (>1,000,000/mm<sup>3</sup>). Treatments include medications (e.g., hydroxyurea, anagrelide, pegylated interferon) that decrease platelet production and thereby reduce platelet counts over 7 to 10 days. Plasmapheresis, which removes platelets from the circulation, can be used if an immediate lowering in platelet count is required. In cases of secondary thrombocytosis, treatment of the underlying disorder usually results in normalization of the platelet count.

**Polycythemia.** Polycythemia is characterized by an increased number of circulating RBCs and increased hemoglobin concentration. It can be defined based on hematocrit (>48% in females and >49% in males) and hemoglobin concentration (>160 g/L in females and >165 g/L in males). Polycythemia can be a primary disorder (i.e., polycythemia vera) or secondary to conditions typically associated with chronic hypoxia (e.g., COPD, high altitude, cyanotic congenital heart disease). A steep increase in blood viscosity occurs once the hematocrit increases to more than 50%, resulting in an increased thrombogenic risk. High hematocrits are associated with increased atherosclerosis (e.g., carotid

stenosis, stroke) and cardiac disease (e.g., heart failure, myocardial infarction). Reports on whether polycythemia increases perioperative risk are contradictory. For example, a hematocrit more than 51% was associated with increased postoperative mortality in a retrospective cohort study of more than 310,000 patients.<sup>102</sup> Conversely, a previous smaller study of 200 patients did not find an increased rate of perioperative complications in individuals with secondary polycythemia.<sup>347</sup>

The preoperative evaluation should focus on the pulmonary and cardiovascular systems. On physical examination, the anesthesiologist should examine for cyanosis, clubbing, wheezing, murmurs, and oxygen saturation (via pulse oximetry). Useful laboratory tests include an ECG, arterial blood gases, and chest radiograph. An unexpected finding of polycythemia should prompt an investigation for possible causes, which if not readily apparent, should raise the possibility of polycythemia vera. In such cases, elective surgery should be postponed pending a consultation by a hematologist.

**Venous Thromboembolic Disorders.** VTE is an important potential risk in hospitalized patients, including surgical patients.<sup>348</sup> Primary VTE prophylaxis is beyond the scope of this chapter and is covered extensively in specialty society practice guidelines.<sup>11,12</sup> Nonetheless, patients should be stratified preoperatively for their risks of perioperative VTE to inform the appropriate selection of prophylactic measures. The expected risk of postoperative VTE depends on both patient-related (e.g., inflammatory bowel disease, acute illness, smoking, malignant disease, obesity, increased age, prior VTE, estrogen use, hypercoagulable state, inherited thrombophilia) and procedure-related (e.g., invasiveness, trauma, immobilization) factors. A reasonable approach for estimating perioperative VTE risk is to use a validated clinical prediction index, a widely used example being the Modified Caprini Risk Assessment Model (Box 31.12).<sup>11,349</sup> A Caprini score of zero indicates very low VTE risk (0.5% risk in the absence of thromboprophylaxis), scores of 1 to 2 indicate low VTE risk (1.5% risk in the absence of thromboprophylaxis), scores of 3 to 4 indicate moderate VTE risk (3.0% risk in the absence of thromboprophylaxis), and scores of 5 or more indicate high VTE risk (6.0% risk in the absence of thromboprophylaxis).

Some subgroups of patients are at considerably higher risk for perioperative VTE, namely those with very recent VTE (i.e., within prior 3 months) and those with a history of VTE associated with a high-risk inherited thrombophilia.<sup>350</sup> For individuals with a very recent VTE episode, elective surgery should be delayed until 3 or more months have elapsed since the episode (during which time they should be anticoagulated).<sup>351</sup> Specifically, the risk of recurrent VTE is highest during the first 3 to 4 weeks after the initial episode; this risk then decreases over the next 2 months. Hereditary high-risk thrombophilias include Factor V Leiden, anti-thrombin III deficiency, protein C deficiency, protein S deficiency, prothrombin gene mutation, and antiphospholipid antibodies. Factor V Leiden and prothrombin gene mutations are the most common causes, together comprising up to 60% of cases.<sup>352</sup>

### BOX 31.12 Modified Caprini Risk Assessment Model for Venous Thromboembolism

#### 1 Point Each

- Age 41–60 years
- Minor surgery
- BMI > 25 kg/m<sup>2</sup>
- Swollen legs
- Varicose veins
- Pregnancy or postpartum
- History of unexplained or recurrent spontaneous abortion
- Oral contraceptives or hormone replacement
- Sepsis (<1 month)
- Serious lung disease, including pneumonia (<1 month)
- Abnormal pulmonary function
- Acute myocardial infarction
- Heart failure (<1 month)
- History of inflammatory bowel disease
- Medical patient at bed rest

#### 3 Points Each

- Age ≥ 75 years
- History of VTE
- Family history of VTE
- Factor V Leiden mutation
- Prothrombin 20210A mutation
- Lupus anticoagulant
- Anticardiolipin antibodies
- Elevated serum homocysteine
- Heparin-induced thrombocytopenia
- Other congenital or acquired thrombophilia

#### 2 Points Each

- Age 61–74 years
- Arthroscopic surgery
- Major open surgery (>45 min)
- Laparoscopic surgery (>45 min)
- Malignancy
- Confined to bed (>72 h)
- Immobilizing plaster cast
- Central venous access

#### 5 Points Each

- Stroke (<1 month)
- Elective arthroplasty
- Hip, pelvis, or leg fracture
- Acute spinal cord injury (<1 month)

BMI, Body mass index; VTE, venous thromboembolism.

From Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practical guidelines. *Chest*. 2012; 141: e227S–e277S.

Patients having minor procedures such as dental, endoscopic, cataract, or superficial operations usually do not require interruption of anticoagulant therapy. In other individuals, withholding warfarin for 5 days typically allows the INR to decrease to normal if the baseline INR is in the usual therapeutic target (2.0 and 3.0). A longer interval may be needed if the baseline INR is higher (see section on “Preoperative Anticoagulant Therapy”). During the time without warfarin, patients may be at risk for recurrent thromboembolism; however, the risk is relatively small in all but the highest-risk patients (i.e., VTE in prior 3 months, or VTE with high-risk inherited thrombophilia). The decision to bridge with intravenous unfractionated heparin or with LMWH subcutaneously in high-risk patients must be made collaboratively with the treating physician.

**Preoperative Anticoagulant Therapy.** Outpatient oral anticoagulant therapy includes vitamin K antagonists (e.g., warfarin) and DOACs. These agents increase perioperative bleeding, except in the case of very minor procedures. Thus, they should only be continued perioperatively if an individual does not have patient-related risk factors for bleeding (e.g., liver disease, abnormal renal function, prior bleeding complications), is scheduled for procedures without important bleeding risk (e.g., dental extraction, simple cutaneous procedures, cataract surgery without bulbar blocks), and is

not being considered for neuraxial anesthesia. Otherwise, anticoagulant therapy must be temporarily discontinued before surgery.

Typically, vitamin K antagonists should be stopped 5 days before surgery, with consideration for a longer discontinuation period if the initial INR value is more than 3.0. Ideally, the INR should be rechecked within 24 hours before surgery,<sup>195</sup> and a low dose of oral vitamin K (1 to 5 mg administrated orally or subcutaneously) administered for any INR result greater than 1.5. Vitamin K has an effect within 6 to 10 hours after oral or subcutaneous administration (more predictable with oral administration), and it peaks within 24 hours to 48 hours.<sup>353</sup> Administration of higher doses may lead to warfarin resistance when therapy is initiated again. Some patients undergoing elective lower extremity joint replacement surgery may also receive an initial dose of warfarin before surgery for perioperative thromboprophylaxis. The 2018 American Society of Regional Anesthesiologists (ASRA) guidelines state that neuraxial anesthesia can still be performed in these patients when only a single dose of warfarin has been administered within a period of 24 hours or less before surgery.<sup>196</sup>

Patients are increasingly receiving DOACs for long-term anticoagulation, typically for nonvalvular atrial fibrillation, although some individuals may be prescribed low-dose DOAC therapy for IHD.<sup>91</sup> The timing of preoperative

discontinuation of DOACs should be guided by the specific drug prescribed, expected procedural bleeding risk, renal function (based on estimated GFR), and planned use of neuraxial anesthesia. Some proposed approaches for preoperative DOAC discontinuation are outlined in Tables 31.11 and 31.12.<sup>195-197</sup>

Patients may require temporary bridging therapy during the intervening period between discontinuation of vitamin K antagonist therapy and the date of surgery. Such bridging therapy is generally not needed after interruption of DOACs because of their relatively short half-lives. Most patients with nonvalvular atrial fibrillation do not require bridging therapy if their anticoagulant therapy is temporarily discontinued before surgery (see section on "Atrial Fibrillation").<sup>195,198</sup> Conversely, many patients with mechanical heart valves will require bridging therapy, with the decision based on the location of the mechanical heart valve and nature of planned surgery (see Box 31.4).<sup>173</sup> Additionally, some patients who are at very high risk for recurrent VTE (e.g., VTE episode within prior 3 months) may also require bridging therapy. In general, decisions to use bridging therapy with intravenous unfractionated heparin or LMWH must be individualized, account for patients' risks of bleeding while on bridge therapy, and be made collaboratively with the treating physician.

If bridging is planned, either LMWH or intravenous unfractionated heparin can be started 2 or more days after the last administered dose of vitamin K antagonist (e.g., warfarin). Bridging therapy should be started once the INR drops to under 2.0.<sup>195</sup> There are several available options for LMWH (e.g., enoxaparin, dalteparin). The specific choice and dose should be selected based on consultation with a hematologist or the patient's treating physician. For patients with impaired renal function (eGFR < 30 mL/min), intravenous heparin bridging is preferable, although some LMWH dosing adjustments remain possible if eGFR is in the range between 15 and 30 mL/min.<sup>195</sup> Intravenous unfractionated heparin is usually discontinued approximately 6 hours before the surgery to allow for normal intraoperative coagulation. The last dose of bridging dose LMWH should be given 24 hours preoperatively to allow normalization of coagulation by the time of surgery (based on an assumption of normal renal function). Both unfractionated heparin and LMWH are contraindicated in patients with an allergy to heparin or a history of HIT. Options for bridging therapy in such patients include argatroban (intravenous infusion), bivalirudin (intravenous infusion), fondaparinux (subcutaneous), or oral DOACs. The specific management strategy should be selected following consultation with a hematologist.

Based on the 2018 ASRA guidelines,<sup>196</sup> recommendations for management of preoperative anticoagulant therapy are more conservative if perioperative neuraxial techniques are being considered. These guidelines recommend that warfarin should be discontinued 5 or more days before surgery, and a repeat preoperative INR should confirm a normalized value before neuraxial blocks are performed.<sup>196</sup> The recommended intervals for timing of neuraxial blocks after discontinuing DOAC therapy are outlined in Table 31.11. The last prophylactic dose of

LMWH should be 12 or more hours before any planned neuraxial block, whereas the last therapeutic dose (including bridging therapy) of LMWH should be 24 or more hours beforehand. Preoperative unfractionated intravenous heparin should be stopped 6 or more hours before planned spinal or epidural anesthesia.<sup>196</sup> In addition, return to normal coagulation can be monitored using aPTT or anti-factor Xa activity. Though the safety of performing neuraxial techniques in the presence of low-dose subcutaneous unfractionated heparin (i.e., 5000 units twice daily) has been described,<sup>354</sup> the 2018 ASRA guidelines include a Grade 2C recommendation for waiting 4 to 6 hours after subcutaneous injection before performing neuraxial blocks in patients receiving subcutaneous unfractionated heparin (i.e., 5000 units 2 or 3 times daily).<sup>196</sup> This Grade 2C rating indicates that the recommendation was relatively weaker ("conflicting evidence or opinion on the usefulness") and based entirely on case reports or expert opinion.<sup>196</sup> Any patients receiving fibrinolytic and thrombolytic drugs should not receive neuraxial anesthesia.

**Preoperative Antiplatelet Therapy.** Traditionally, aspirin has been discontinued before surgery (often 7-10 days before surgery) because of concern about increased bleeding. A withdrawal period of 7 to 10 days is likely excessive, especially because new platelets formed after aspirin discontinuation (half-life ≈15 minutes) are not inhibited. Since 10% of platelets are turned over every 24 hours, and about 50,000/mm<sup>3</sup> of normal functioning platelets are needed to control surgical bleeding, it is likely that aspirin need only be stopped 3 days before surgery to mitigate risks of increased bleeding. Continuation of aspirin until the time of surgery leads to increased bleeding during major noncardiac surgery,<sup>136</sup> but not during cardiac surgery.<sup>355</sup> Withdrawing aspirin itself has important theoretical risks with respect to a rebound hypercoagulable state and increased cardiac risk,<sup>141,356</sup> however, these theoretical risks have not been supported by data from large randomized trials.<sup>136,355</sup> Therefore, a reasonable standard approach for most surgical patients is to discontinue aspirin temporarily 3 days before surgery, with some notable exceptions. Specifically, aspirin should be continued in any patient with a prior PCI,<sup>144</sup> high-grade IHD, or high-risk CVD (e.g., stroke within prior 9 months).<sup>212</sup> Continuation of aspirin is not a contraindication to performance of neuraxial blocks.<sup>196</sup>

P2Y<sub>12</sub> inhibitors are the other relatively common type of antiplatelet medications that might be encountered during preoperative evaluation, especially among patients with known IHD or CVD. These medications include oral medications (clopidogrel, ticagrelor, prasugrel, ticlopidine) and an intravenous formulation (cangrelor). Aside from the case of patients with a recent PCI (see section on "Coronary Stents"), P2Y<sub>12</sub> inhibitor therapy should be temporarily discontinued before elective surgery. The usual recommended time interval for discontinuing these medications before surgery (including cases where neuraxial blocks are planned) is 5 to 7 days for clopidogrel, 5 to 7 days for ticagrelor, 7 to 10 days for prasugrel, 10 days for ticlopidine, and 3 hours for cangrelor.<sup>196</sup>

Some patients with either PAD or CVD may be on long-term therapy with dipyridamole, which causes vasodilation and impairment of platelet function. The drug is available as an immediate-release formulation, as well as an extended-release formulation combined with aspirin (i.e., Aggrenox). There are minimal data on the safety of continuing dipyridamole in patients undergoing surgery; current ASRA guidelines recommend discontinuing extended-release dipyridamole 24 hours before performing any neuraxial block.<sup>196</sup> Information on the perioperative safety of other antiplatelet therapies (e.g., glycoprotein IIb/IIIa inhibitors) is also limited. Platelet glycoprotein IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, tirofiban) exert profound effects on platelet aggregation. Following administration, the time to restoration of normal platelet aggregation is 24 to 48 hours for abciximab, and 4 to 8 hours for eptifibatide and tirofiban. Neuraxial techniques should be avoided until platelet function has recovered after platelet glycoprotein IIb/IIIa inhibitor administration.<sup>196</sup>

## NEUROLOGIC DISEASE

The preoperative history in a patient with neurologic disease should focus on recent exacerbations, prior investigations, and therapy (both current and prior). The basic neurologic examination should evaluate mental status, speech, cranial nerves, gait, motor function, and sensory function. This baseline determination also allows for comparison of any new postoperative deficits.

### Cerebrovascular Disease

The major clinical manifestation of CVD is acute stroke with more than 10 million new strokes per year worldwide. In addition, about 6.5 million individuals die annually from stroke, making it the second leading cause of death globally.<sup>357</sup> The two main categories of stroke are hemorrhagic stroke and ischemic stroke. Hemorrhagic stroke is largely related to either intracerebral hemorrhage or subarachnoid hemorrhage. Common causes of intracerebral hemorrhage include hypertension, trauma, coagulopathies, illicit drug use (i.e., amphetamines, cocaine), and arteriovenous malformations (AVMs). Causes of subarachnoid hemorrhage are bleeding from aneurysms and AVMs (see section on “Aneurysms and Arteriovenous Malformations”). Ischemic stroke may be related to thrombosis of an artery through several different mechanisms (e.g., atherosclerosis, arterial dissection), embolism (e.g., related to atrial fibrillation), or systemic hypoperfusion (e.g., cardiac arrest). The other major manifestation of CVD is a TIA, which is a transient episode of neurologic dysfunction caused by focal ischemia in the brain, spinal cord, or retina, but without infarction.<sup>358</sup>

CVD has important perioperative implications. It is a risk factor for postoperative complications, including cardiac events,<sup>97</sup> stroke,<sup>132,359,360</sup> and death.<sup>77</sup> Furthermore, the risks of postoperative cardiac complications and recurrent stroke are particularly increased when elective noncardiac surgery is performed within 9 months after a prior stroke<sup>212</sup> or when surgical aortic valve replacement is performed within 3 months after a prior stroke.<sup>212</sup> Importantly, if emergency surgery needs to be performed after a stroke, it may be preferable to *not* delay surgery. Specifically, while the risks of postoperative cardiovascular complications

are very high when emergency surgery is performed within 2 weeks after an ischemic stroke, these risks were reduced when surgery proceeded within 72 hours after the stroke.<sup>361</sup> This temporal pattern may be explained by progressively worsening cerebral autoregulation during the first 5 days after an ischemic stroke (which then recovers over the next 3 months).<sup>362</sup>

The preoperative evaluation should focus on the timing, presentation, etiology, and treatment of prior strokes or TIAs. It is important to document the etiology in order to distinguish carotid stenosis (i.e., atherosclerosis) from cardioembolic disease. Causes of cardiac emboli include stasis (i.e., atrial fibrillation, severe cardiomyopathy, ventricular aneurysm), thrombogenic (i.e., valvular heart disease, prosthetic heart valve), and paradoxical venous source (e.g., patent foramen ovale). The physical examination should include a brief neurologic exam to identify any preexisting deficits, auscultation for carotid bruits, and a precordial assessment to assess for murmurs or extra heart sounds. Depending on the underlying basis for CVD (i.e., atherosclerosis, atrial fibrillation), patients may be on long-term therapy with aspirin, P2Y<sub>12</sub> inhibitors (e.g., clopidogrel), vitamin K antagonists, and DOACs. Both vitamin K antagonists and DOACs should be temporarily discontinued before surgery (see section on “Atrial Fibrillation”). Similarly, P2Y<sub>12</sub> inhibitor therapy should be interrupted before surgery, with the possible exception of cases with very recent coronary stent implantation (see section on “Coronary Stents”). Continuing aspirin perioperatively does not prevent cardiovascular complications,<sup>136</sup> but leads to an increased risk of major bleeding (a risk factor for perioperative stroke).<sup>132</sup> Nonetheless, selective continuation of aspirin can be considered in patients with high-risk atherosclerotic CVD or recent stroke (i.e., previous 9 months).<sup>212</sup> In other cases, aspirin should be temporarily held 72 hours before surgery.<sup>136</sup> In addition, concomitant CVD should be carefully considered in any decision to initiate new β-adrenergic blocker therapy in a patient awaiting noncardiac surgery. Although β-blockade does decrease perioperative cardiac risk, it also significantly increases the risk for acute postoperative stroke.<sup>132,133</sup>

### Asymptomatic Carotid Bruit

The presence of a carotid bruit significantly increases the likelihood of a significant lesion (i.e., 70%-99% stenosis) in both symptomatic or asymptomatic patients.<sup>26</sup> Thus, a newly discovered carotid bruit should prompt a careful search for any evidence of prior strokes or TIA, especially if the planned surgical procedure involves neck manipulation. At-risk individuals include those with risk factors for CVD (e.g., hypertension, smoker, diabetes mellitus, hyperlipidemia, IHD, PAD), as well as patients with prior head and neck radiation exposure. Patients may not volunteer pertinent symptoms until they are specifically probed, especially if the symptoms were transient. The anesthesiologist should specifically inquire about *amaurosis fugax*, dysphagia, dysarthria, and other symptoms of cerebrovascular insufficiency. Carotid Doppler ultrasound studies are simple, effective tools to evaluate suspicious carotid bruits. Significant abnormalities on Doppler studies may entail a referral to a neurologist or vascular surgeon. The risk of stroke in patients who have truly asymptomatic bruits is 1% to 2% per year, with most strokes preceded by transient

symptoms.<sup>363</sup> No evidence indicates that truly asymptomatic bruits increase the risk of perioperative stroke.<sup>364</sup>

### Seizure Disorder

The seizure type (e.g., *grand mal*, absence) and specific symptoms (e.g., staring, focal findings) are important to document in the preoperative evaluation. For example, absence (previously *petit mal*) seizures may be particularly difficult to recognize after surgery because they lack generalized motor signs. Hence, typical symptoms, such as staring and obtundation, may be misinterpreted as residual anesthetic effects in the postoperative period. It is important to determine the etiology of the seizure disorder because of possible associated morbidities, which include brain tumors, aneurysms, AVMs, classic epilepsy, drug toxicity, electrolyte disorders, infections, CVD, sickle cell disease, and SLE.

The anesthesiologist should document the anticonvulsant dosing regimen and adequacy of seizure control. Routine measurement of serum drug levels of anticonvulsants is not indicated unless there are concerns about drug toxicity or ongoing breakthrough seizures. Indeed, patients with good control of seizures may have levels outside the therapeutic range. Drug levels are highly influenced by when the blood draw occurs relative to the timing of drug administration. In general, trough levels should be measured. Anti-seizure medications have multiple side effects (e.g., bone marrow suppression, macrocytic anemia, leukopenia, hyponatremia), and testing may be needed based on suspected abnormalities. The most commonly ordered tests are CBC and electrolyte concentrations. All anticonvulsant therapy should be continued perioperatively. A patient with poorly controlled or new-onset seizures should be evaluated by a neurologist before any non-emergent surgery.

### Multiple Sclerosis

Multiple sclerosis is believed to be an inflammatory immune disorder with two general clinical patterns: exacerbating-remitting and chronic progressive. Symptoms can include ataxia, motor weakness, sensory deficits, autonomic dysfunction, emotional lability, bladder or bowel dysfunction, and visual disturbances. Exacerbations of multiple sclerosis can be triggered by stress, infections, pregnancy, and elevated temperatures. Various treatments have been tried, including corticosteroids, immunosuppressants, monoclonal antibodies, plasmapheresis, benzodiazepines, and baclofen. The preoperative evaluation should document the history and pattern of disease, especially symptoms and physical deficits affecting the respiratory system (including oxygen saturation). Medications, previous triggers, and preexisting neurologic deficits should be documented. Testing is generally directed toward associated disturbances (e.g., chest radiography and CBC if pulmonary infection is suspected) and any medication side effects. For example, azathioprine can suppress bone marrow or affect liver function, cyclophosphamide may cause electrolyte abnormalities, and corticosteroids can cause hyperglycemia. Patients with stable minor disease require no special testing. Related medications should be continued on the day of surgery. No clear association has been shown between the type of anesthetic or a specific anesthetic drug and disease exacerbations. Nonetheless, regional anesthesia may offer theoretical advantages for patients with respiratory compromise or cognitive dysfunction.

### Aneurysms and Arteriovenous Malformations

Aneurysms and AVMs can occur in the cerebral and spinal vascular beds. These lesions may be intact, ruptured, symptomatic, or incidental asymptomatic findings. Associated risk factors include polycystic kidney disease, fibromuscular dysplasia, type IV Ehlers-Danlos syndrome, and a family history. Some AVMs become large enough to exert a mass effect. The risk of aneurysmal bleeding, and possibly AVM bleeding, increases during pregnancy. Most patients have minimal symptoms before a rupture. A rupture can result in altered mental status, syncope, increased intracranial pressure, inappropriate antidiuretic hormone (ADH) secretion, and hemodynamic changes (i.e., bradycardia, tachycardia, ectopic beats). Typical testing includes an ECG and blood sampling to measure electrolyte, glucose, and creatinine concentrations. Chest radiography, echocardiography, and neurologic imaging (e.g., computed tomography scan) are also often needed. Importantly, the ECG changes seen following a rupture, which often include ST-segment and T-wave changes, mimic those seen with myocardial ischemia. In addition, troponin concentrations are often elevated, while echocardiography may reveal significant cardiac dysfunction with depressed contractility and wall motion abnormalities. Although the bleeding may be primarily responsible for these cardiovascular changes, concomitant IHD or preexisting cardiomyopathy should also be considered. Measures aimed at controlling increased intracranial pressure, arterial blood pressure, and blood glucose are important.

### Parkinson Disease

Parkinson disease is a degenerative disorder of the basal ganglia characterized by failure of dopamine secretion and diminished inhibition of the extrapyramidal motor system. Patients typically have diminution of spontaneous movements, rigidity (cogwheel rigidity is classic), resting tremor, masked facies, difficulty speaking, difficulty walking, depression, and dementia. Autonomic dysfunction (including orthostatic hypotension), excessive salivation, and impaired thermoregulation may also occur. Patients are at risk of pulmonary complications resulting from difficulty swallowing, altered mental status, increased aspiration risk, and ventilatory muscle dysfunction. Pharmacologic treatments include levodopa, dopamine agonists (e.g., bromocriptine, pramipexole, ropinirole, rotigotine), monoamine oxidase type B inhibitors (e.g., selegiline, rasagiline, safinamide), anticholinergic agents (e.g., trihexyphenidyl, benztrapine), amantadine, and catechol-O-methyl transferase inhibitors (tolcapone, entacapone). Levodopa can cause dyskinesias (i.e., dystonic and myoclonic involuntary movements). Some individuals also undergo implantation of deep brain stimulators to manage their symptoms.

Preoperative evaluation should assess the pulmonary system, signs of dysphagia, and degree of disability. Evidence of significant pulmonary symptoms or possible infection requires chest radiography, pulmonary consultation, and possible delay of the procedure for improvement. All associated medications should be continued. Abrupt withdrawal of levodopa may exacerbate symptoms (especially dysphagia and chest wall rigidity) or precipitate neuroleptic malignant syndrome. The latter disorder is characterized by autonomic instability, altered mental status, rigidity, and

fever. Some medications encountered in the perioperative setting, such as metoclopramide and phenothiazines, may exacerbate symptoms of Parkinson disease by interfering with dopamine. Individuals with deep brain stimulators require deactivation of the devices before any procedures in which electrocautery will be used. The specific device should be identified, along with the severity of disease symptoms when the device is turned off. Perioperative management of the device ideally should be coordinated with the surgeon and the clinician managing the device.

### **Neuromuscular Junction Disorders**

Myasthenia gravis is an autoimmune disorder of skeletal muscle neuromuscular junctions that is caused by antibodies against nicotinic acetylcholine receptors. The disease is characterized by skeletal muscle weakness that worsens with activity and improves with rest. Cardiac and smooth muscle function is unaffected. Weakness is exacerbated by stress, infections, hypokalemia, medications (e.g., aminoglycosides, propranolol, ciprofloxacin, clindamycin), and surgery. A classification system for severity of myasthenia gravis is presented in **Box 31.13**. Patients with myasthenia gravis commonly have other autoimmune diseases, such as rheumatoid arthritis, polymyositis, and thyroid disorders.

Ocular symptoms (i.e., diplopia, ptosis) are almost always present; often, they are the presenting complaint or sole complaint. Cranial nerve and bulbar involvement are common, with an associated aspiration risk related to pharyngeal and laryngeal muscle weakness. Affected individuals may have thymic hyperplasia and tumors. Since the thymus is located in the anterior mediastinum, thymic enlargement has potential implications for anesthesia care (see section on “Mediastinal Masses”). Patients are usually treated with thymectomy, acetylcholinesterase inhibitors (e.g., pyridostigmine, neostigmine), immunosuppressants (corticosteroids, azathioprine, mycophenolate, cyclosporine), plasmapheresis, and intravenous immunoglobulins. Worsening symptoms may reflect worsening disease (i.e., myasthenic crisis) or excessive acetylcholinesterase inhibitor treatment (i.e., cholinergic crisis). A short-acting anticholinesterase (edrophonium) can help distinguish the two states, since only a myasthenic crisis improves with more anticholinesterase. Plasmapheresis and intravenous

immunoglobulins have been used to treat myasthenic crises and prepare patients for surgery, but still require several days to weeks to produce improvement.

All medications (with associated doses) should be documented and continued perioperatively. These drugs may also have implications themselves. For example, patients taking azathioprine require a CBC and liver function tests because of drug-induced bone marrow suppression and liver dysfunction. Patients treated with corticosteroids need measurement of blood glucose concentration, as well as possible perioperative corticosteroid supplementation. Since ventilatory function can be compromised, preoperative PFTs may also be indicated for selected patients, particularly those suspected of having severely affected ventilatory function. PFTs may be particularly helpful if patients are being considered for ambulatory surgery, especially in free-standing surgical centers. Drugs that can exacerbate myasthenic symptoms should also be avoided.

Lambert-Eaton syndrome is similar to myasthenia gravis, with muscle weakness including oculobulbar involvement and dysautonomia. It is caused by antibodies against voltage-gated calcium channels that result in decreased acetylcholine release. It is not associated with thymic abnormalities, but commonly occurs with malignant diseases, especially small cell lung cancer and gastrointestinal tumors. The other distinguishing feature of this disorder is that the muscle weakness classically improves with activity and is worse after inactivity. In addition to acetylcholinesterase inhibitors, typical treatments include 3,4-diaminopyridine, which is a selective potassium channel blocker. Preoperative evaluation and management are similar to those for myasthenia gravis. All related medications should be continued perioperatively.

### **Muscular Dystrophies and Myopathies**

Muscular dystrophies and myopathies are inherited disorders that affect the neuromuscular junction. They share many similarities but do have a few differences. The hallmark of these disorders is progressive skeletal muscle weakness that commonly leads to respiratory failure. No effective therapy is available. Many individuals have associated cardiomyopathies and possible association with malignant hyperthermia.

Duchenne and Becker muscular dystrophies are X-linked recessive disorders that occur primarily in males. Affected individuals have elevated creatine phosphokinase levels, often preceding the onset of symptoms. Male patients with a family history of either Duchenne or Becker muscular dystrophy should be considered at risk (even when they have not been formally tested), and they require precautions similar to those in patients with diagnosed disease. Cardiomyopathy and respiratory failure are the usual causes of death. Female carriers of the abnormal gene may have dilated cardiomyopathy despite having no other manifestations of the disease. The preoperative evaluation should focus on the cardiovascular (e.g., palpitations, dyspnea, chest pain, syncope, orthopnea, dependent edema) and pulmonary (e.g., aspiration, pneumonia) systems. Potentially helpful additional preoperative tests include ECGs, PFTs, and echocardiography. Facioscapulohumeral muscular dystrophy (also known as faciohumeroscapular or Landouzy-Dejerine muscular dystrophy) is an autosomal dominant disorder

#### **BOX 31.13 Osserman Classification System for Myasthenia Gravis Clinical Classification System**

**Class I:** Ocular myasthenia

**Class IIA:** Mild generalized myasthenia with slow progression: no crises, responsive to drugs

**Class IIB:** Moderately severe generalized myasthenia: severe skeletal and bulbar involvement but no crises; drug response less than satisfactory

**Class III:** Acute fulminating myasthenia: rapid progression of severe symptoms, with respiratory crises and poor drug response

**Class IV:** Late severe myasthenia, same as III but progression over 2 years from class I to II

Data from Osserman KE, Genkins G. Studies in myasthenia gravis: review of a twenty-year experience in over 1200 patients. *Mt Sinai J Med*. 1971;38:497–537.

that affects both sexes and causes a slow, progressive weakness of muscles in the shoulders and face. Cardiomyopathy occurs much less frequently than in other dystrophies, but arrhythmias have been reported. Limb-girdle dystrophies have a variable genetic inheritance pattern and primarily affect the muscles of the shoulders and pelvis. Conduction abnormalities are present in some patients, although frank cardiomyopathies are less frequent. The preoperative evaluation is largely similar to that described previously for Duchenne muscular dystrophy.

**Myotonic Dystrophies.** Myotonia is characterized by prolonged contraction and delayed relaxation of muscles. It is a common symptom of several dystrophies, including classic myotonic dystrophy, congenital myotonic dystrophy, myotonia congenital, and central core disease. Myotonic dystrophy, which is the most common of these conditions, is an autosomal dominant inherited disorder affecting both sexes. Congenital myotonic dystrophy is a severe form of this disease that manifests in infancy, often in the children of affected mothers. The classic findings are severe muscle wasting, typically involving the diaphragm, face, hands, pharynx, and larynx. Cold temperatures can often trigger myotonia. The disease severity is variable, with symptoms often not apparent until the second or third decade of life; hence, a family history is important. Cardiomyopathies, arrhythmias, and conduction abnormalities are common, while some patients also have cardiac valvular abnormalities. Cardiac involvement may not correlate with the degree of atrophy or weakness in skeletal muscle. Once an affected individual shows any evidence of second- or third-degree AV block, a pacemaker should be implanted (even if the patient is asymptomatic) because an unpredictably rapid progression of conduction disease may occur. Given this potential for rapid disease progression, pacemaker placement may be considered in patients with first-degree AV block, regardless of symptoms. Affected individuals are also at risk for aspiration, pneumonia, respiratory failure, and postoperative pulmonary complications. Central core disease is a rare disorder caused by deficiency of mitochondrial enzymes. The name derives from findings of muscle biopsies, which reveal “cores” of abnormalities. Affected individuals have proximal muscle weakness, scoliosis, and sometimes cardiomyopathies. As with myotonic dystrophy, patients are at risk for respiratory failure and aspiration. Myotonia congenita is a hereditary disorder that involves only skeletal muscles, causes less severe symptoms, and does not cause cardiac abnormalities.

Myotonia was historically thought to predispose patients to malignant hyperthermia, however, current evidence indicates that they are *not* at increased risk.<sup>365</sup> Nonetheless, succinylcholine should still be avoided in these patients because it may cause diffuse muscle contraction. Symptomatic treatments for myotonic contractions include corticosteroids, quinine, and procainamide; otherwise, these diseases have no cure. These treatments should be continued perioperatively. The preoperative evaluation focuses on the cardiopulmonary system, with special emphasis on evaluating for pulmonary infection, heart failure, syncope, conduction abnormalities, and valvular abnormalities. Preoperative testing includes an ECG, echocardiogram (except for myotonia congenita), and chest radiograph (if

symptoms of pulmonary disease are present). Evidence of a conduction abnormality on ECG should trigger a cardiology consultation. Myotonia is not inhibited by regional anesthesia, but local anesthetic infiltration into muscle may provide symptomatic relief.

### Central Nervous System Tumors

Pituitary tumors are classified as functioning (associated with endocrine abnormalities) versus nonfunctioning, as well as benign (adenomas are the most common pituitary lesion) versus malignant. The tumor can have mass effects that lead to associated symptoms, such as headaches, visual field defects, and increased intracranial pressure (with resulting gait disturbances, vomiting, cranial nerve deficits, bladder incontinence, bowel incontinence). Other symptoms may be related to pituitary insufficiency (e.g., hypoadrenalinism, hypothyroidism, infertility) or overactivity. Manifestations of pituitary overactivity include Cushing syndrome from ACTH-secreting tumors; acromegaly from growth hormone secretion; hyperthyroidism from TSH production; and gynecomastia, lactation, and sex hormone-related changes from prolactin and gonadotropin (follicle stimulating and luteinizing hormones) secretion. These hormones are all produced by the anterior lobe of the pituitary and are controlled by a feedback loop from the hypothalamus. The posterior pituitary stores and secretes vasopressin and oxytocin, which are synthesized in the hypothalamus.

Acromegaly results in enlargement of connective tissue, bone, and visceral organs. Affected individuals have an enlarged jaw (i.e., macroglossia), nose, feet, hands, pharyngeal tissue, and laryngeal tissue (including macroglossia and enlarged epiglottis). Affected individuals have increased risks of sleep apnea (both central and obstructive), neuropathies (from nerve entrapment), hypertension, diastolic dysfunction, and cardiac valvular abnormalities. IHD, heart failure, diabetes mellitus, hypothyroidism, and difficult airway management (i.e., mask ventilation, laryngoscopy, intubation) may also occur. The preoperative evaluation should document any chest pain, dyspnea, snoring, numbness, polydipsia, headaches, and visual disturbances. The physical examination focuses on blood pressure, airway examination, murmurs, neurologic findings, and peripheral edema. It is important to plan for possible difficult airway management and inform the patient about the possible use of awake fiberoptic intubation. Preoperative testing may include an ECG and blood sampling for electrolyte concentration, glucose concentration, and thyroid function tests. TSH increases production of thyroid hormones ( $T_3$  and  $T_4$ ) by the thyroid gland (see section on “Thyroid Disease”). Prolactin- and gonadotropin-secreting tumors have little impact on anesthetic management, but their symptoms may alert clinicians to an undiagnosed pituitary tumor.

Posterior pituitary tumors result in failure to secrete vasopressin or ADH, which regulates renal water excretion. A deficiency results in diabetes insipidus, which is characterized by excessive urine output from a failure to reabsorb water. Unless treated with DDAVP, these patients may develop hypernatremia and volume depletion. The anesthesiologist should therefore carefully evaluate patients' intravascular volume status and conduct blood sampling for

electrolyte concentrations and creatinine concentrations. Patients with pituitary tumors, pituitary apoplexy (hemorrhage into pituitary, which is associated with hypertension, trauma, or pregnancy), or previous pituitary tumor resection may require hormone replacement therapy (i.e., corticosteroids, thyroid replacement, DDAVP). These medications must not be interrupted during the perioperative period. The adequacy of replacement therapy can be determined based on the clinical evaluation, as well as blood sampling for electrolyte concentrations, creatinine concentrations, and thyroid function tests.

Other intracranial tumors include gliomas (45% of tumors), astrocytomas, ependymomas, medulloblastomas, oligodendrocytomas (malignant and highly lethal), benign meningiomas (15% of tumors), schwannomas, craniopharyngiomas, and dermoid tumors. Metastatic lesions (6% of intracranial tumors) can also occur with virtually all types of primary malignant diseases. Common sources of metastatic intracranial lesions include breast, colorectal, and lung cancers. Most intracranial tumors are detected either incidentally, or when patients develop seizures or symptoms related to mass effect. Symptoms of mass effect include headaches, strokelike symptoms, vomiting, visual disturbances, altered cognitive function, and ataxia. If the intracranial pressure becomes elevated, hypertension, bradycardia, arrhythmias, ECG abnormalities, and brainstem herniation may occur. Careful assessment of neurologic deficits is important. For patients with metastatic lesions, issues pertaining to the primary malignant disease and previous treatment (e.g., chemotherapy, radiation, corticosteroids, anticonvulsants) must be clarified. Continuation of preexisting corticosteroids (to treat cerebral edema) and anticonvulsant medications is important.

## MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

These disorders are characterized by musculoskeletal deformities and chronic inflammation. Assessment of deformities is important because of their potential implications for airway management and regional anesthesia technique. Chronic inflammation—which occurs with rheumatoid arthritis, SLE, and systemic sclerosis—can cause vasculopathy and multiorgan dysfunction. Affected organ systems may include cardiovascular, pulmonary, renal, hematologic, integumentary, gastrointestinal, central nervous, and peripheral nervous systems.

### Rheumatoid Arthritis

Rheumatoid arthritis is a chronic autoimmune disorder that primarily affects joints, but it often also affects multiple organ systems. The disease affects approximately 1% of the population, and women are 2 to 3 times more likely to be affected as are men.<sup>366</sup> Distal joints are involved more often than proximal, often in a symmetric pattern. Joint involvement is characterized by inflammation that can progress to severe deformity, although the disease course can vary dramatically. The temporomandibular joints and cricoarytenoid cartilage can be involved, resulting in limited mouth opening, hoarseness, and possible difficulties with airway management. Atlantodens subluxation and instability of the cervical spine can also occur. Subluxation, which is

caused by ligamentous laxity, as opposed to joint disease, may also occur, although the prevalence appears to be decreasing with the advent of improved disease modifying agents. Cervical spine disease can be asymptomatic. IHD, pericardial effusions, aortic regurgitation, and conduction abnormalities may be present in affected individuals. Symptoms of myocardial ischemia may be masked in patients with rheumatoid arthritis because of impairment of functional status by concomitant joint disease. In addition, exertional dyspnea because of heart failure may be confused with pulmonary involvement. Pulmonary manifestations include restrictive lung disease secondary to decreased thoracic mobility, pulmonary fibrosis, and pleural effusions. Patients have an increased risk of renal dysfunction secondary to both vasculitis and long-term NSAID use. Peripheral neuropathy can result from vasculitis or entrapment. Anemia, leukocytosis, thrombocytosis (from chronic inflammation), and thrombocytopenia (from splenomegaly) may be present. Patients may also have rheumatoid nodules that occur subcutaneously (usually over extensor joints) or in the lungs.

The preoperative examination must document symptoms related to the many organ systems affected by rheumatoid arthritis. Special detail is directed to the neurologic, airway, pulmonary, and cardiovascular systems. Documentation of deformities and neurologic deficits is important to establish a baseline level of function. Significant hoarseness should prompt an evaluation by an otolaryngologist to assess the mobility of the vocal cords and the presence of cricoarytenoid arthritis. A careful history may elicit neurologic deficits, neck pain, upper extremity pain, or crunching sound with neck movement. Indications for preoperative cervical spine radiographs include neurologic findings, long-standing severely deforming disease, or procedures requiring prone positioning or manipulation of the cervical spine. The specific radiographs required are anteroposterior and lateral cervical spine films with flexion, extension, and open-mouth odontoid views.<sup>367</sup> Significant abnormalities (i.e., anterior atlas-dens interval  $>9$  mm or posterior interval  $<14$  mm) require consultation with a neurologist or neurosurgeon. Notably, disease duration, severity, and symptoms do not correlate with cervical spine subluxation. New or worsening pulmonary symptoms should prompt further evaluation with pulse oximetry, chest radiographs, PFTs, or possibly a pulmonary consultation. Muffled heart sounds, pericardial rubs, and low voltage on an ECG suggest a pericardial effusion, which necessitates an echocardiogram. Any suspicious murmur merits an echocardiogram in these patients. Because rheumatoid arthritis is associated with a very high prevalence of IHD, patients may require ECGs and possible cardiac stress testing (with subsequent cardiology referral as indicated). Other preoperative tests include blood sampling for CBC and creatinine concentrations.

Advanced planning for management of potential difficult airways is important, including discussion of regional anesthetic options and possible awake fiberoptic intubation. When possible, corticosteroids, analgesics, and non-biological disease modifying agents (e.g., methotrexate, leflunomide, hydroxychloroquine, sulfasalazine) should be continued, although consideration can be given to stopping NSAIDs 2 to 3 days before surgery. There are more concerns regarding whether biological disease modifying agents (i.e.,

tumor necrosis factor alpha antagonists) should be stopped before surgery, especially since continued treatment may predispose patients to postoperative infections. Several guidelines recommend holding these agents before surgery,<sup>368,369</sup> although there is uncertainty regarding when treatment should be stopped relative to surgery. Especially since these drugs have different dosing cycles, patients with complex immunosuppressant therapy are best managed collaboratively with their rheumatologist, primary care physician, and surgeon. Stress-associated adrenal insufficiency may occur in patients taking preoperative corticosteroid therapy. Details on which patients warrant perioperative stress dose corticosteroids, as well as a suggested dosing regimen, are presented in the section on "Hypothalamic-Pituitary-Adrenal Disorders" and Table 31.15.

### Ankylosing Spondylitis

Ankylosing spondylitis is a progressive inflammatory arthropathy that primarily affects the spine and sacroiliac joints, although peripheral joints may also be involved. It usually occurs in males. Ankylosing spondylitis can have important extraarticular manifestations, including uveitis, vasculitis, aortitis, and aortic insufficiency. Affected individuals may develop restrictive lung disease related to pulmonary fibrosis or chest wall movement restriction (joint fixation and kyphosis). Kyphosis can be so extreme that patients are unable to face forward, thereby making mask ventilation, direct laryngoscopy, and intubation very difficult. The patient's preoperative evaluation should focus on the cardiovascular, pulmonary, and musculoskeletal systems, with the physical examination including measurement of oxygen saturation on room air. The presence of a murmur on physical examination warrants an echocardiogram. If ventilatory compromise is suspected or present, a chest radiograph and PFTs are necessary. Most analgesic medications and non-biological disease modifying agents (e.g., sulfasalazine) can be continued preoperatively, although consideration can be given to stopping NSAIDs 2 to 3 days before surgery. Several guidelines recommend holding biological disease modifying agents (i.e., tumor necrosis factor alpha antagonists) before surgery,<sup>368,369</sup> although there is uncertainty regarding when treatment should be stopped relative to surgery. Especially since these drugs have different dosing cycles, patients with complex immunosuppressant therapy are best managed collaboratively with their rheumatologist, primary care physician, and surgeon. It is important to plan for perioperative airway management and inform the patient about the possibility of awake fiberoptic intubation. Peripheral nerve blocks are an option, but neuraxial anesthesia is often unsuccessful in the presence of severe spinal involvement.

### Systemic Lupus Erythematosus

SLE is a systemic autoimmune disease that is predominantly caused by vasculitis. It has a variable course with flares and remission periods. SLE is more likely to affect females (i.e., seven-fold higher prevalence in adults), as well as individuals with East Asian or African-American ethnic backgrounds.<sup>370</sup> The multiorgan disease has musculoskeletal, cardiovascular, pulmonary, renal, neurological, dermatological, hematological, gastrointestinal, and

constitutional manifestations. Common constitutional symptoms are fever and chronic fatigue. The fevers may be explained by disease activity itself, as well as frequent infections related to disease-induced immune dysfunction and immunosuppressant treatment. The musculoskeletal findings are typically a migratory arthritis of the small joints in the hands and feet. Many patients have dermatologic conditions including alopecia, photosensitivity, and a typical "butterfly rash" across the cheeks and nose. Vasospasm of the digits (i.e., Raynaud phenomenon), often associated with atrophy of nails and fingernails, can make it difficult to obtain pulse oximetry readings. Pulmonary manifestations include interstitial lung disease, pleural effusions, frequent respiratory infections, and pulmonary hypertension. Pulmonary hypertension, which can result from recurrent pulmonary emboli, pulmonary vasculopathy, and interstitial lung disease, carries a high risk of perioperative complications.<sup>371</sup> Cardiovascular involvement includes hypertension (often difficult to control), premature IHD, pericarditis, myocarditis, coronary artery vasculitis, cardiomyopathy, aseptic endocarditis, and pleural effusions. Neurologic disease includes cerebral vasculitis, stroke, CVD, cognitive dysfunction, seizures, peripheral neuropathy, headache, neuropsychiatric manifestations, and affective disorders. Lupus nephritis is a common end-organ complication that carries a poor prognosis and often results in ESRD. Patients with SLE may have anemia, leukopenia, thrombocytopenia, and antiphospholipid antibodies. Individuals with these antibodies typically have a prolonged aPTT, but are predisposed to pulmonary emboli, stroke, and recurrent venous or arterial thromboses.

The preoperative evaluation should assess all major organ systems and relevant medications. Patients with severe disease, infections, or exacerbations are best managed collaboratively with their rheumatologist or primary physician. The history should cover details on typical disease flairs (manifestations, timing, treatment), fevers, cardiovascular symptoms (e.g., dyspnea, chest pain, orthopnea), neurologic symptoms (e.g., stroke, seizures), renal disease, prior thromboembolic events, and fevers. Given the prevalence of IHD and CVD in these patients, the evaluation should include reviewing results of any previous relevant diagnostic studies (e.g., cardiac stress testing, echocardiography, computed tomography, MRI). The preoperative physical examination concentrates on the pulmonary (rales, decreased breath sounds), cardiac (pericardial rubs, murmurs, arrhythmias, jugular venous distention, peripheral edema), and nervous (motor deficits, sensory deficits, visual disturbances) systems. Helpful preoperative tests include an ECG and blood sampling for CBC, electrolyte concentrations, glucose concentrations, creatinine concentrations, and aPTT (unless the patient has a known antiphospholipid syndrome). Significant ECG abnormalities (e.g., conduction delays, arrhythmias, Q waves, low voltage) should prompt consideration for further testing, cardiology consultation, or pulmonology consultation. Other tests that may be considered include an INR (patients receiving warfarin), echocardiogram (murmurs, suspected heart failure, suspected effusion), chest radiograph (pulmonary symptoms or suspected heart failure), and PFTs (worsening or undiagnosed dyspnea). Patients with advanced cardiomyopathy, decompensated heart failure, pulmonary hypertension, systemic

vasculitis, and recent or recurrent thromboembolism are considered to be at high risk, and they are best managed in concert with the appropriate specialists. Most medications, including corticosteroids and non-biological disease-modifying agents (e.g., hydroxychloroquine, cyclosporine, azathioprine, tacrolimus) should be continued. Patients on long-term corticosteroid therapy may need perioperative stress dose corticosteroids. Details on patient selection for such therapy, as well as a suggested dosing regimen, are presented in the section on “Hypothalamic-Pituitary-Adrenal Disorders” and Table 31.15. Medications that require temporary preoperative discontinuation include anticoagulant therapy; consultation with a hematologist may be necessary to plan perioperative anticoagulation management, including the possible need for bridging therapy. Similarly, patients with complex biological immunosuppressant therapy for SLE (e.g., belimumab) are best managed collaboratively with their rheumatologist.

### Systemic Sclerosis

Systemic sclerosis (previously known as scleroderma) is an autoimmune multisystem disease that is characterized by excessive fibrosis. It occurs more commonly in females.<sup>372</sup> Aside from skin thickening, the most common skin manifestation is Raynaud phenomenon. Scleroderma has several variants, which are differentiated based on the extent of skin and internal organ involvement. *Localized scleroderma* involves just the skin, and no other organs. *Limited systemic sclerosis* has cutaneous manifestations “limited” to face and upper extremities, as well as systemic involvement in the gastrointestinal tract (e.g., dysphagia, reflux) and lungs (e.g., interstitial lung disease, pulmonary hypertension). *Diffuse systemic sclerosis* is characterized by generalized skin involvement and multiple end-organ damage. Manifestations include myocardial fibrosis, pericarditis, heart failure (right-sided and left-sided), coronary artery fibrosis, severe hypertension, ESRD, dysphagia, fatigue, weight loss, and gastroesophageal reflux. Pulmonary hypertension, which may result from interstitial lung disease or vasculopathy, is a leading cause of death in systemic sclerosis and is associated with increased perioperative risk.<sup>371</sup>

The preoperative evaluation focuses on the organ systems in the manner outlined previously in the section on SLE, with special attention to evidence of pulmonary hypertension (see section on “Pulmonary Hypertension”). The history should evaluate for any evidence of pulmonary disease (e.g., cough, dyspnea) or cardiac disease (e.g., dyspnea, orthopnea, chest pain). Patients may develop limited mouth opening, limited neck mobility, poor dentition, and oropharyngeal lesions secondary to skin involvement. Careful airway evaluation and planning for airway management are essential in such individuals, especially because they may also be at high risk for aspiration secondary to gastroesophageal reflux. Dermal involvement, edema, and contractures may also make venous access and regional anesthesia technically challenging. Thus, it is helpful to discuss central venous access and possible awake fiberoptic intubation during the preoperative assessment; in some cases, consideration should be given to arranging for interventional radiology to place intravenous lines.

Patients with systemic sclerosis usually need an ECG, and blood sampling for CBC (especially if receiving

immunosuppressant therapy) and creatinine concentration. A chest radiograph and PFTs can be useful if interstitial lung disease or pulmonary fibrosis is suspected. Echocardiography (i.e., right ventricular size, right ventricular function, estimated right ventricular systolic pressure) may be useful to screen patients with suspected pulmonary hypertension. Antihypertensive agents (including calcium channel blockers for Raynaud phenomenon) and immunosuppressant therapy should be continued.

### Raynaud Phenomenon

Raynaud phenomenon is an exaggerated vascular response to cold or emotional stress that results in color changes of the digits (typical sequence is pallor to cyanosis to rubor).<sup>373</sup> It is classified as primary (termed *Raynaud disease*) or secondary (termed *Raynaud phenomenon*). Raynaud phenomenon is associated with connective tissue diseases, autoimmune disorders, drugs, and use of vibrating tools. Connective tissue diseases associated with Raynaud phenomenon include systemic sclerosis, Sjögren disease, SLE, and possibly rheumatoid arthritis. Raynaud phenomenon most often affects the hands, typically resulting in a sudden onset of cold digits with sharply demarcated pallor or cyanosis. Cutaneous vasospasm is also common in other sites, such as the face and ears, where it causes pain and numbness. Criteria for the diagnosis of Raynaud disease include symmetric episodic attacks, absence of PAD, absence of tissue injury (or gangrene), normal nail fold capillary examination, normal erythrocyte sedimentation rate, and negative anti-nuclear antibody test. Raynaud disease requires no special additional preoperative evaluation. Secondary Raynaud phenomenon should prompt an assessment for associated disease states. It is also important to distinguish Raynaud phenomenon from PAD, especially given the difference in associated comorbidities. Calcium channel blockers are useful treatments in many patients and should be continued in the perioperative period.

### Inherited Connective Tissue Disorders

Ehlers-Danlos syndrome is a disorder of collagen synthesis. It consists of several subtypes that have various manifestations but are almost all characterized by joint hypermobility. Type IV disease is more serious because affected individuals may have vascular fragility and skin fragility, as well as predisposition to vascular rupture, visceral rupture, and pneumothorax. Patients with type VI Ehlers-Danlos syndrome have muscle weakness, scoliosis, ocular fragility, skin fragility, and osteopenia.

Marfan syndrome is characterized by tall stature, arachnodactyly (i.e., long digits), scoliosis, pectus excavatum, valvular disease (e.g., aortic insufficiency, mitral valve prolapse, mitral regurgitation), arrhythmias, and ascending aortic dilatation. These patients are at risk for aortic dissection. Ocular (e.g., ectopia lentis, strabismus, glaucoma) and pulmonary (e.g., spontaneous pneumothorax) complications can also occur.<sup>374</sup> Other manifestations include retrognathia and high arched palates. Careful auscultation for the diastolic murmur of aortic insufficiency is important (see Table 31.8). If such a murmur is detected, subsequent tests should include an echocardiogram and chest radiograph. The most distinguishing feature of osteogenesis imperfecta is the propensity for fractures from extremely fragile bones.

These patients may have blue sclerae, short stature, scoliosis, joint hypermobility, hearing loss, muscle weakness, mitral valve prolapse, aortic insufficiency, and platelet dysfunction. An ECG and echocardiogram are necessary if physical examination reveals a murmur. Epidermolysis bullosa is distinguished by blistering, skin fragility, and scarring caused by abnormal epidermal-dermal anchoring. Even noninvasive blood pressure measurement may cause skin blistering and breakdown in an affected individual.

### Kyphoscoliosis

Kyphoscoliosis is a curvature of the spine in both lateral and posterior directions. It can involve the thoracic region, the lumbar region, or both. Kyphoscoliosis may occur alone or as a manifestation of other diseases (e.g., collagen vascular disorders, Marfan syndrome, neurofibromatosis, muscular dystrophies, cerebral palsy). Therefore, the preoperative evaluation should also focus on identifying any coexisting abnormalities. Severe thoracic deformity may cause cardiopulmonary compromise as a consequence of restrictive lung disease, pulmonary hypertension, heart failure, tracheobronchial compression, or cardiac compression. The history should focus on assessing cardiopulmonary symptoms. The ability of the patient to lie supine (to facilitate airway access and management) must also be determined. The physical examination should evaluate vital signs (including oxygen saturation), pulmonary system (rales, decreased air entry), and cardiovascular system (murmurs, additional heart sounds, edema, jugular venous distention). A CBC, as well as a blood type and screen, is required in any patient scheduled to undergo spine correction surgery for kyphoscoliosis. Additionally, an ECG and chest radiograph may be useful. If heart failure is suspected based on clinical evaluation, a preoperative echocardiogram should be performed. Any reversible lung disease or heart failure must be optimized preoperatively.

## CANCERS AND TUMORS IN PREOPERATIVE PATIENTS

### Patients With Cancer

Patients with cancer may have complications related to both the disease itself and its treatment (e.g., chemotherapy, radiation therapy). Typically, patients are aware of the side effects of their cancer treatments. It is helpful to ask them whether any unexpected complications occurred during treatment, or whether chemotherapy or radiation therapy had to be interrupted because of adverse effects. A hypercoagulable state is also common in cancer, particularly advanced disease, primary brain tumors, ovarian adenocarcinoma, pancreatic cancer, colon cancer, gastric cancer, lung cancer, prostate cancer, and kidney tumors. The risk of thromboembolic events is increased six-fold in patients with cancer, with active cancer accounting for 20% of new cases of thromboembolism.

The preoperative evaluation focuses on cardiac, pulmonary, neurologic, and hematologic systems. Previous head and neck irradiation may cause carotid artery disease, hypothyroidism, or difficulty with airway management. Auscultation for bruits, thyroid function tests, and carotid Doppler studies are therefore recommended. Mediastinal, chest wall, or left breast irradiation can cause pericarditis,

conduction abnormalities, cardiomyopathy, valvular heart disease, and premature IHD (even in the absence of traditional cardiovascular risk factors).<sup>375</sup> Thus, younger patients with a history of radiation therapy should be assessed for cardiac symptoms and undergo an ECG—even if they may not otherwise be at risk for heart disease. Based on these initial results, stress testing and echocardiography may be indicated. Previous irradiation to the lungs, breast, or mediastinum may also cause radiation pneumonitis. In such individuals, an oxygen saturation measurement and chest radiograph may be required, with consideration for PFTs if appropriate.

Other important chemotherapy-associated side effects include cardiomyopathy with trastuzumab and anthracyclines (e.g., doxorubicin); pulmonary toxicity with bleomycin; nephrotoxicity with cisplatin; hemorrhagic cystitis with cyclophosphamide; and peripheral neuropathy with vincristine or cisplatin. Many chemotherapeutic agents are toxic to the bone marrow, and patients commonly exhibit preoperative anemia. Patients who received corticosteroids as part of their cancer treatment may be at risk for adrenal insufficiency. These individuals may require supplemental perioperative corticosteroids; details on patient selection for such therapy, as well as a suggested dosing regimen, are presented in the section on “Hypothalamic-Pituitary-Adrenal Disorders” and Table 31.15. Other chemotherapy drugs result in impaired postsurgical wound healing, especially antiangiogenic agents (e.g., bevacizumab, sunitinib, sorafenib, pazopanib, vandetanib, cabozantinib, axitinib). Consequently, elective major surgery should be scheduled after temporary discontinuation of these agents, whenever feasible. The time interval for preoperative discontinuation varies across these agents from 28 days (bevacizumab) to 1 week (sunitinib, sorafenib, pazopanib, vandetanib, cabozantinib) to 48 hours (axitinib). Based on the type of chemotherapy, an ECG, chest radiograph, and blood sampling for CBC, electrolyte concentrations, creatinine concentration, and liver function tests may be needed. In some cases, consideration may be given to delaying the surgical procedure to allow resolution of neutropenia and thrombocytopenia. In general, advance planning of blood component replacement (including type and screening in the preoperative clinic) can avoid delays on the day of surgery.

The direct effects of cancers depend on the specific organ systems involved. Issues pertaining to intracranial tumors are discussed in the section on “Central Nervous System Tumors”. Bone and liver involvement with metastases can commonly occur in patients with breast, colorectal, lung, and head and neck tumors. These bony lesions can in turn cause hypercalcemia or pancytopenia. Head and neck tumors, and their associated therapy (e.g., surgery, radiation), may cause thyroid dysfunction and difficulty with airway management. Lung cancer can cause airway problems, compromised pulmonary function, or mediastinal masses (see section on “Mediastinal Masses”). In these cases, computed tomography scans of the head, neck, or chest may be indicated. Paraneoplastic syndromes can complicate almost any type of malignant disease but are most commonly seen with lung cancer. Typical manifestations of these syndromes include hypercalcemia, inappropriate ADH secretion, Lambert-Eaton syndrome, Cushing syndrome, and neuropathies.

Patients who are receiving opioids on a long-term basis for cancer pain are likely to require larger than usual doses of medication for postoperative pain control (see the later section on “Planning for Postoperative Pain Management”). On the day of surgery, these patients typically take their usual analgesic medications, with the exception of NSAIDs (which, if possible, should be stopped 2-3 days before surgery).

### Mediastinal Masses

Tumors that may occur in the anterior mediastinal space include lymphomas, thymomas, teratomas, thyroid goiters, and metastatic tumors. Anterior mediastinal masses can obstruct the great vessels (i.e., aorta, pulmonary arteries, pulmonary vein, superior vena cava), heart, trachea, and bronchi. Patients may complain of dyspnea, dysphagia, stridor, wheezing, coughing (especially when recumbent), and orthopnea. Compression of the superior vena cava can result in superior vena cava syndrome, which is characterized by jugular venous distention as well as edema in the face, neck, chest, and upper extremities. Affected individuals may also develop increased intracranial pressure and airway compromise. Imaging of the chest (with computed tomography or MRI) and echocardiography are needed if airway, cardiac, or vascular compression is suspected. Flow-volume loops may also be useful to assess the location (extrathoracic vs. intrathoracic) and degree of airway obstruction. Patients with tracheobronchial, cardiac, or major vessel compression require special anesthetic precautions, including possible awake fiberoptic intubation.

### Von Hippel–Lindau disease

von Hippel–Lindau disease is an autosomal dominant inherited disorder characterized by a variety of benign and malignant tumors. Associated tumors include hemangioblastomas, retinal angiomas, clear cell renal cell carcinomas, pheochromocytomas, and neuroendocrine tumors of the pancreas. During preoperative evaluation, the anesthesiologist should assess for symptoms suggestive of a pheochromocytoma or neuroendocrine tumor (see relevant sections of this Chapter), as well as evaluate the patient’s renal function. Any further testing (e.g., electrolytes, ECG, creatinine, glucose) should be guided by findings from the initial clinical evaluation.

### Carcinoid Tumors

Carcinoid tumors are rare neuroendocrine tumors that release mediators. They are associated with MEN type 1. These tumors typically occur in the gastrointestinal tract and are the most common neoplasms of the appendix; in addition, they can also occur in the pancreas and bronchi. Carcinoid syndrome is caused by vasoactive amines (e.g., serotonin, norepinephrine, histamine, dopamine), polypeptides (e.g., bradykinin, somatostatin, vasoactive intestinal peptide, glucagon), and prostaglandins released by the tumors. Typical manifestations include flushing, tachycardia, arrhythmias, diarrhea, malnutrition, bronchospasm, and carcinoid heart disease. Nonetheless, most patients are asymptomatic because the liver inactivates the bioactive products of carcinoid tumors. Consequently, patients with gastrointestinal carcinoid tumors have manifestations of carcinoid syndrome only if they have hepatic metastases.

Carcinoid heart disease is characterized by endocardial fibrosis of pulmonic and tricuspid valves. Affected individuals may then develop tricuspid regurgitation, pulmonic stenosis, pulmonic regurgitation, right-sided heart failure, peripheral edema, and hepatomegaly. They may also develop *carcinoid crisis*, which is associated with profound flushing, bronchospasm, tachycardia, and hemodynamic instability. These life-threatening episodes can occur with induction of anesthesia, intraoperative handling of a tumor, or other invasive procedure on a tumor (e.g., tumor embolization).<sup>376</sup>

The preoperative clinical evaluation should focus on dyspnea, orthopnea, wheezing, edema, arrhythmias, and murmurs; subsequent diagnostic tests are guided by the initial assessment. Patients with chronic diarrhea need measurement of electrolyte and creatinine concentrations. Patients with cardiac involvement must have an ECG and echocardiogram. Malnourished patients need an ECG, as well as measurement of electrolyte and albumin concentrations. Predictors of perioperative adverse events in these patients are carcinoid heart disease and elevated urinary 5-hydroxyindoleacetic acid concentrations.<sup>377</sup> The mainstay of pharmacologic treatment of carcinoid syndrome are somatostatin analogues, namely octreotide and lanreotide. Preoperative treatment with octreotide (300-500 µg intravenous or subcutaneously) helps mitigate the risks of intraoperative carcinoid crises.<sup>378</sup> An alternative approach for high-risk major procedures is to start a continuous intravenous 50 µg /hour infusion of octreotide 12 hours before surgery and continue it for at least 24 to 48 hours after surgery.<sup>376</sup>

## Special Issues in Preoperative Evaluation

### PSEUDOCHOLINESTERASE DEFICIENCY

A personal or family history of pseudocholinesterase, or butyrylcholinesterase, deficiency should be identified preoperatively (see Chapter 35). Pseudocholinesterase, which is found in the plasma, liver, pancreas, heart, and brain, is distinct from acetylcholinesterase, which is found in erythrocytes. Patients with an “allergy to succinylcholine” should be suspected of having either this disorder or malignant hyperthermia. Previous anesthetic records may help clarify an uncertain history. Additionally, inquiring whether the patient was intubated postoperatively, gravely ill, or in need of intensive care may be helpful.

Pseudocholinesterase activity may be permanently reduced because of abnormal genotypes, or transiently altered because of disease, drugs, pregnancy, or infancy. In patients with a history suggestive of pseudocholinesterase deficiency, recommended testing includes plasma cholinesterase activity, dibucaine number, and fluoride number. Plasma cholinesterase activity is a quantitative measure of enzyme activity, whereas the dibucaine number and fluoride number are qualitative measures. Plasma cholinesterase activity should not be confused with acetylcholinesterase activity, which is an assessment of erythrocyte cholinesterase. The *dibucaine number* represents the percentage inhibition of the enzyme by the local anesthetic dibucaine, and

the fluoride number represents the percentage inhibition by fluoride. Normal individuals—who are homozygous for the wild-type gene—have a dibucaine number of 80 because their plasma cholinesterase is 80% inhibited by dibucaine. Individuals who are homozygous for the atypical genes have a dibucaine number of 20 (corresponding to 20% inhibition) and can be paralyzed for 4 to 8 hours after receiving succinylcholine. In heterozygous individuals who have a dibucaine number of 60 (corresponding to 60% inhibition), the duration of action of succinylcholine is prolonged by 50% to 100%. The combination of dibucaine number and plasma cholinesterase activity therefore differentiates genetic from acquired causes of prolonged apnea after succinylcholine administration. Patients with known or suspected pseudocholinesterase deficiency should be encouraged to obtain proper medical alert identification. Additionally, they should be educated that the enzyme also metabolizes ester-linked local anesthetics.

## MALIGNANT HYPERTHERMIA

A known history or suggestive history (e.g., hyperthermia or rigidity during anesthesia) of malignant hyperthermia in a patient or family member must be clearly documented in the preoperative assessment. This information must also be communicated to the surgeon and eventual anesthesia provider—especially to ensure that appropriate arrangements are made preoperatively (see [Chapter 35](#)). Individuals who are genetically predisposed to malignant hyperthermia are asymptomatic until they are exposed to triggering agents. Certain neuromuscular diseases are also associated with elevated risks of malignant hyperthermia, including some muscular dystrophies (i.e., Duchenne, Becker, myotonic), King-Denborough syndrome, central core disease, periodic paralysis, osteogenesis imperfecta, myelomeningocele, and strabismus.

## MORBIDLY OBESE PATIENTS

The morbidly obese patient presents special preoperative risks. Obesity is associated with several important comorbidities, including diabetes mellitus, hypertension, cardiovascular disease, CVD, cancer, OSA (see the earlier section on “Obstructive Sleep Apnea”), and poor functional capacity. Obese individuals are also at risk for NASH, which can result in abnormal liver function tests, liver fibrosis, and end-stage liver disease. In addition, patients with extreme obesity are at risk for right-sided heart failure and pulmonary hypertension. Such individuals can have obesity-hypoventilation syndrome (OHS), also known as Pickwickian syndrome. OHS is characterized by impaired central ventilatory drive and is distinct from OSA. It is associated with awake, chronic hypoxemia ( $\text{PaO}_2 < 65 \text{ mm Hg}$ ) without a diagnosis of COPD or primary lung disease. In the perioperative setting, obese patients experience higher rates of difficult bag-mask ventilation and difficult tracheal intubation.

The preoperative evaluation focuses on relevant coexisting diseases, airway, cardiopulmonary system, and vital signs (including pulse oximetry). When measuring blood pressure, the cuff should have a width that is approximately two thirds of the arm and a length that can adequately

encircle the extremity. Assessment of neck circumference can also identify individuals at risk for difficulty with endotracheal intubation. It is also helpful to determine both actual body weight and ideal body weight. Determination of ideal body weight may be helpful in dose selection for certain medications (e.g., neuromuscular blockers),<sup>379</sup> and for determining optimal intraoperative mechanical ventilation settings. Treatments for obesity can have important perioperative implications. For example, drugs or other weight reduction methods (e.g., purging, diuretics, laxatives, gastric bypass procedures) may result in electrolyte abnormalities, vitamin deficiencies, malnutrition, anemia, and cardiopulmonary disorders. Two previously available antiobesity medications, fenfluramine and dexfenfluramine (both were withdrawn from the market in 1997), had significant cardiac side effects, including regurgitant valvular lesions and pulmonary hypertension. Any individual who was ever exposed to these drugs should undergo a cardiovascular evaluation, including an echocardiogram.

## PATIENTS WITH TRANSPLANTED ORGANS

The number of patients with transplanted organs who require nontransplant surgical procedures increases yearly. During preoperative evaluation, these patients present special issues relating to transplant function, allograft denervation, immunosuppression, and other posttransplant physiologic and pharmacologic issues. Close interaction with the transplant team is one of the most important steps in the perioperative care of these patients. Clinicians performing the preoperative assessment should ensure that the transplant care providers are made aware of the upcoming procedure and are given an opportunity to make recommendations.

Some general preoperative considerations apply to all transplant recipients, as well as additional concerns based on the specific organ transplanted. In all transplant recipients, the level of function of the transplanted organ and the presence of any rejection should be evaluated. The dosage regimen of all immunosuppressant medications should be noted, and patients should be instructed to continue these medications perioperatively. However, these drugs can modify the pharmacology of many other agents administered during the perioperative period, as has been extensively summarized in the literature.<sup>380,381</sup> Patients should also be assessed for complications related to immunosuppressant therapy. These complications include the following: hyperglycemia and adrenal suppression (corticosteroids); increased risks of infection, hypertension, and renal insufficiency (corticosteroids, cyclosporine, tacrolimus); and myelosuppression causing anemia, thrombocytopenia, and leukopenia (azathioprine, sirolimus). Although transplant recipients are at increased risk for postoperative infections, no evidence indicates that higher doses of antibiotic prophylaxis provide added benefit. Instead, usual preoperative recommendations for antibiotic prophylaxis should be followed. Stress-associated adrenal insufficiency may occur in patients taking long-term corticosteroid therapy. Details on which patients warrant perioperative stress dose corticosteroids, as well as a suggested dosing regimen, are presented in the section on “Hypothalamic-Pituitary-Adrenal Disorders” and [Table 31.15](#).

Cardiac evaluation is important in all transplant recipients because they are at increased risk for cardiovascular disease. The basis for this increased risk includes the underlying diseases that led to organ failure (e.g., diabetes mellitus, hypertension) and the potential for drug regimens, transplantation, and rejection episodes to create or worsen traditional cardiovascular risk factors. Preoperative renal function should also be assessed because long-term immunosuppressive regimens often lead to CKD. Although the effects of transplantation and immunosuppressive regimens on intravascular coagulation are controversial, thromboprophylaxis should be considered in all transplant recipients.

Kidney transplant recipients present some specific issues for preoperative evaluation. Despite the presence of a normal creatinine concentration, GFR in these individuals is generally decreased. This impairment in renal function predisposes these patients to electrolyte abnormalities and altered drug metabolism. Nephrotoxic drugs, such as NSAIDs and COX-2 inhibitors, should be avoided in all renal transplant recipients. In addition, their risk for cardiovascular disease is increased to approximately twice that of the general population. Careful preoperative cardiovascular evaluation is essential.

Successful liver transplantation usually resolves the hepatic and other end-organ effects of end-stage liver disease. Nonetheless, some pretransplant pulmonary problems may not resolve after transplantation, thus necessitating careful evaluation of pulmonary function. These disturbances can include hepatopulmonary syndrome, which involves hypoxemia from intrapulmonary vascular shunting. Other patients may continue to demonstrate ventilation-perfusion mismatch related to pulmonary effusions, ascites, or diaphragmatic dysfunction, as well as diffusion abnormalities resulting from interstitial pneumonitis or impaired hypoxic pulmonary vasoconstriction.

Following successful lung transplantation, recipients may require months to achieve peak pulmonary function. Compared with all other allografts, the transplanted lung is especially susceptible to infection and rejection as a result of its exposure to the external environment. Careful preoperative evaluation with PFTs should be considered in all lung transplant recipients, with postponement of elective surgery when allograft rejection or infection is suspected. Other perioperative considerations include airway hyperresponsiveness, loss of the cough reflex, and potential for injury to the airway anastomosis with intubation. These patients are also at increased risk for pulmonary edema, which has been attributed to disrupted lymphatic drainage in the transplanted lung.

Most issues relating to heart transplant recipients relate to the absence of autonomic innervation in the transplanted heart. This denervation has multiple physiologic effects, such as a higher than normal resting heart rate (from absence of vagal tone); the absence of cardiac baroreflexes; and the lack of response to carotid sinus massage, Valsalva maneuver, laryngoscopy, or tracheal intubation. Denervation also affects responses to medications; the allograft demonstrates a normal or augmented response to direct-acting drugs (e.g., epinephrine), a blunted response to indirect-acting agents (e.g., ephedrine), and no response to vagolytic agents.

Chronic allograft rejection can manifest as accelerated IHD, and ventricular dysfunction (both systolic and diastolic). Because allograft denervation causes any myocardial ischemia to be silent, typical clinical manifestations include fatigue, ventricular dysrhythmias, heart failure, and ECG evidence of a silent myocardial infarction. Should preoperative evaluation raise clinical suspicions of worsening rejection, recent cardiac testing must be reviewed. Heart transplant recipients undergo routine periodic evaluation for IHD (cardiac stress testing or coronary angiography) and ventricular function (e.g., echocardiogram). The ECGs of these patients may reveal conduction abnormalities, and two P waves (a small nonconducted P wave from the native atria and a normal-sized conducted P wave from the donor atria). Many heart transplant recipients also require permanent pacemakers, and pacemaker function should be confirmed during the preoperative evaluation.

## PATIENTS WITH ALLERGIES

The patient's preoperative evaluation record should carefully document any history of allergies and adverse drug reactions. True anaphylactic reactions should be distinguished from adverse side effects (e.g., nausea with opioid use), especially because a patient's definition of an allergy may differ significantly from the true clinical definition. In some cases, patients may incorrectly attribute previous perioperative difficulties to "allergies" to anesthetic or analgesic medications. The reported incidence of perioperative anaphylaxis is about 1 in 10,000 to procedures in large countrywide epidemiological studies, with consistent estimates based on studies from 2 different countries (France vs. United Kingdom) and time periods (2004 vs. 2016).<sup>382,383</sup> The overall incidence appears similar in these two epidemiological studies; however the common precipitating agents differ. In the older French study, the most common causes were neuromuscular blocking agents (58%), latex (20%), and antibiotics (13%).<sup>383</sup> Conversely, in the more recent United Kingdom study, the most common precipitating agents were antibiotics (53%), neuromuscular blocking agents (33%), and chlorhexidine (9%).<sup>382</sup> The mortality associated with an individual episode of anaphylaxis is about 4%,<sup>384</sup> but anaphylaxis accounts for up to 3% of perioperative deaths that are totally or partially related to anesthesia.<sup>385</sup> A careful history (including a review of records of prior allergic events and any associated laboratory tests) generally allows for avoidance of precipitating agents. In selected cases in which the clear diagnosis of a specific allergy is required to guide perioperative management, referral to an allergy specialist and possible skin testing (if the allergic reaction is believed to be immunoglobulin E [IgE]-mediated) may be considered.

Allergic reactions to neuromuscular blocking drugs (NMBDs) are relatively more frequent in Europe as compared to North America. These differences have been attributed, in part, to the use of cough suppressants containing pholcodine in many European countries. Exposure to pholcodine is associated with development of IgE antibodies to NMBDs.<sup>386</sup> Confirmatory testing for an allergy to NMBDs can involve both skin testing and in-vitro assays for NMBD-specific IgE.

Although the rate of latex sensitization continues to increase, the development of better ways to identify at-risk patients has led to a decreased incidence of latex-induced anaphylaxis,<sup>387</sup> as evidenced by the absence of any latex-associated episodes in the recent epidemiological study from the United Kingdom.<sup>382</sup> The diagnosis of a latex allergy during preoperative evaluation is based on a careful history. Risk factors for latex allergy include a history of multiple surgeries, occupational exposure to latex (e.g., healthcare workers, food handlers), and an atopic history. This history may be supplemented with skin testing and latex-specific IgE antibody serology. When latex allergy is identified during the preoperative evaluation, the operative team should be notified in advance to ensure that all appropriate equipment is available. The ASA Task Force outlines detailed intraoperative considerations for these patients.<sup>388</sup> Among antibiotics, penicillins and cephalosporins are the most common causes of anaphylaxis. A small risk of cross-reactivity exists between penicillins and cephalosporins, but most of these reported reactions involve rashes, not anaphylaxis. Reported allergies to vancomycin should be distinguished from “red man syndrome.” This histamine-induced side effect, which is associated with rapid injection of vancomycin, consists of flushing, pruritus, erythematous rash, and hypotension. With respect to other medications commonly encountered in the perioperative setting, anaphylactic reactions to amide local anesthetics are extremely rare. Most true anaphylactic reactions following exposure to ester local anesthetics do not involve an allergy to the local anesthetic, but rather to associated preservatives (e.g., *para*-aminobenzoic acid). Patients may incorrectly interpret adverse side effects from epinephrine in local anesthetic solutions as allergies, especially with dental procedures. Such reports should be carefully distinguished from true allergies. Similarly, true allergies to opioids are rare, with most reports of such “allergies” being simply opioid-related side effects, such as nausea and vomiting.

The scientific status of idiopathic environmental intolerance syndrome (formerly called multiple chemical sensitivity disorder) is very controversial. These individuals report chronic, diffuse, nonspecific symptoms with low levels of multiple chemical substances. Symptoms involve multiple organ systems and include fatigue, headache, memory loss, palpitations, and gastrointestinal symptoms. The symptoms are not generally accompanied by biologic test abnormalities or changes on physical examination, but they are frequently associated with psychiatric symptoms, notably depression and anxiety.<sup>389</sup> Preoperative evaluation of these patients can be extremely challenging because they have significant concerns about the multiple exposures involved during the perioperative period and the potential impact on their symptoms. No current recommendations are available on the perioperative care of these patients.

## HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Acute infection with HIV causes a mononucleosis-like illness, which then progresses to chronic lymphadenopathy (lasting 3–5 years). Infection can culminate in cell-mediated immune deficiency characterized by opportunistic infections, malignant diseases (e.g., Kaposi sarcoma, non-Hodgkin lymphoma), and death (usually secondary from

infections, wasting, or cancer). The prognosis of untreated HIV infection and acquired immunodeficiency syndrome (AIDS) is very poor.<sup>390</sup> Nonetheless, outcomes have now improved substantially in individuals compliant with highly active antiretroviral therapy.<sup>391</sup> Risk factors for HIV infection include sexual contact with an infected individual, bloodborne contamination, men who have sex with men, sexual workers, and those having contact with sexual workers. Most infection transmitted by blood exposure occurs in intravenous drug users, whereas infection through blood product transfusion in the United States is very rare (1 per 1.5–2 million blood transfusions). Mothers can transmit the disease to infants, which occurs usually during breastfeeding or delivery.<sup>392</sup> Many patients infected with HIV are unaware of their status.

HIV infection is a multisystem disease.<sup>393</sup> Cardiac complications include myocarditis, dilated cardiomyopathy, valvular disease, pulmonary hypertension, pericardial effusions, and cardiac tamponade. Pulmonary effects include lymphoid interstitial pneumonitis, as well as drug-resistant infections with *Pneumocystis jiroveci*, *Mycobacterium avium*, or *Mycobacterium tuberculosis*, cytomegalovirus, and *Cryptococcus*. Nervous system manifestations include central nervous system tumors, infections, aseptic meningitis, and AIDS-related dementia. Malignant diseases can occur, such as lymphomas, Kaposi sarcoma, and cervical cancer. These tumors can also have direct consequences for anesthetic management. For example, supraglottic or intraoral Kaposi sarcoma may interfere with ventilation and intubation, whereas non-Hodgkin lymphoma can cause mediastinal masses. Gastrointestinal manifestations include dysphagia, diarrhea, and esophagitis, which can in turn cause malnutrition, dehydration, and electrolyte imbalance. Renal complications include acute tubular necrosis, glomerulonephritis, renovascular disease, and HIV-associated nephropathy with nephritic syndrome. Antiretroviral medications used to treat HIV infection also have important side effects. The major classes of antiretroviral medications include nucleoside reverse transcriptase inhibitors (e.g., lamivudine, zidovudine, tenofovir, abacavir), nonnucleoside reverse transcriptase inhibitors (e.g., nevirapine, efavirenz, rilpivirine), protease inhibitors (e.g., atazanavir, darunavir, lopinavir, fosamprenavir, saquinavir), attachment inhibitors (e.g., maraviroc), and integrase strand transfer inhibitors (e.g., raltegravir).<sup>394</sup> Side effects of relevance to anesthesiologists include lactic acidosis (nucleoside reverse transcriptase inhibitors), hepatotoxicity (nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors), hyperlipidemia (protease inhibitors), insulin resistance (protease inhibitors), premature IHD (protease inhibitors),<sup>395</sup> cardiac conduction abnormalities (protease inhibitors), and bone marrow suppression (all classes).

If the preoperative evaluation of a relatively young, otherwise healthy individual elicits a history of thrush, fever of unknown origin, chronic diarrhea, lymphadenopathy, or herpes zoster in more than one dermatome, these findings should raise concern of undiagnosed HIV infection. In these cases, the enzyme-linked immunosorbent assay (ELISA) is the primary initial screening test. It demonstrates very high sensitivity exceeding 99% but yields a high number of false-positive results. The Western blot technique is used as the

confirmatory test following an initial positive ELISA result. Patients with known HIV infection frequently require further evaluation, including an ECG, a chest radiograph, and blood sampling for CBC, electrolyte concentration, creatinine concentration, and liver function tests. If the patient shows evidence of malnourishment or nephrotic syndrome, further blood tests for albumin, total protein, and magnesium concentrations may be beneficial. The patient's perioperative prognosis may be estimated based on the CD4 lymphocyte count and viral load, which reflect the patient's immunologic status during the previous 3 months. In general, rates of postoperative complications and mortality are higher among patients with CD4 counts lower than 200 cells/mm<sup>3</sup> and viral loads greater than 10,000 copies/mL.<sup>396,397</sup> Patients' antiretroviral therapy must be continued through the perioperative period.

## PATIENTS WITH A HISTORY OF SUBSTANCE ABUSE

A patient with a history of current or previous alcohol or drug addiction presents special challenges for the perioperative team. The lifetime prevalence of these addictions is significant; for example, about 14% of the United States population suffers from alcohol addiction.<sup>398</sup> In a suggested classification system, abused drugs can be categorized as central nervous system depressants (e.g., opioids, alcohol, sedatives, hypnotics), stimulants (e.g., cocaine, amphetamines), and other psychotropic substances (e.g., cannabis).<sup>399</sup> Importantly, many addicts are polysubstance abusers. Thresholds for defining high-risk alcohol consumption are 5 or more standard drinks in a day (>14 drinks per week on average) for males under 65 years of age, and 4 or more standard drinks in a day (>7 drinks per week on average) for all females and males 65 or more years of age. Addictive disease should be considered *permanent* even in patients who have had long periods of abstinence. Some patients in the process of recovery from addiction may be receiving specific medications to maintain recovery. For example, previous opioid abusers may be receiving methadone (long-acting opioid agonist), buprenorphine (partial  $\mu$ -agonist), or naltrexone (opioid antagonist).

Substance abuse disorders are risk factors for poor outcomes in the perioperative setting. For example, individuals with histories of alcohol misuse experience elevated rates of postoperative complications.<sup>72,400-402</sup> In addition, they are at risk for postoperative withdrawal, acute intoxication, and altered tolerance of anesthetic or opioid medications. Consequently, it is worthwhile to incorporate screening for substance abuse disorders into the preoperative evaluation. Several simple validated screening questionnaires for alcohol abuse disorders are available, including the four-item CAGE questionnaire,<sup>403</sup> the three-item AUDIT-C questionnaire,<sup>404</sup> and the U.S. National Institute on Alcohol Abuse and Alcoholism 2- and 4-question tests (NIAAA-2Q/4Q).<sup>405</sup> These screening tools appear to be more sensitive when administered through a computer-based self-assessment questionnaire than during an in-person interview with a nurse or anesthesiologist.<sup>406</sup> The accuracy of these questionnaires can be further augmented with additional screening laboratory tests, namely gamma glutamyl transferase and carbohydrate-deficient

transferrin.<sup>6,407</sup> The preoperative evaluation is also an opportunity to obtain a detailed history of known addiction (drug type, routes of administration) and recovery (periods of abstinence, pharmacotherapy for addiction). The dosage of any pharmacotherapy should be documented and verified. Patients in recovery may also have heightened anxiety regarding upcoming surgical procedures because of concerns about relapse into addiction, and inadequate pain treatment (given their history of addiction). Such concerns may be appropriate. Patients receiving opioid substitution therapy do experience normal pain responses to nociceptive stimuli but require additional analgesia for control of post-procedural pain.<sup>408</sup> These patients should therefore be reassured that anxiety and pain will be adequately treated. The clinicians performing preoperative evaluation may have prejudicial attitudes and lack the educational background to formulate appropriate perioperative pain management plans. For example, pain medication may be under dosed and inappropriately restricted because of concerns about provoking relapses. Early involvement of the acute pain service and addiction specialists to assist in the management of these at-risk patients may be helpful.

The preoperative period should be used to develop appropriate management plans based on the types of abused drugs. All pertinent preoperative information and management plans should be transmitted to members of the perioperative team. Individuals addicted to alcohol, sedatives, or hypnotics may require stabilization with benzodiazepines, whereas heroin addicts may require substitution with methadone. It is important to document the dosage of opioids consumed by individuals abusing these drugs, especially to help guide postoperative pain management. To avoid inadequate analgesia (which could potentially activate addiction) in these patients, the preoperative evaluation should be used to discuss and plan the optimal use of nonopioid analgesics and regional techniques. Patients actively abusing cocaine and amphetamines are at especially high risk during anesthesia because of the potential for intraoperative hemodynamic instability. Urine testing may be helpful to rule out abused substances in such patients, but the results should be interpreted based on drug pharmacokinetics. For example, the half-life of cocaine is about 1.5 hours but its inactive metabolites may still be detectable in the urine for 14 days after consumption.<sup>409</sup> A history of intravenous drug use should prompt an evaluation for cardiovascular, pulmonary, neurologic, and infectious complications such as endocarditis, abscesses, osteomyelitis, hepatitis, and HIV infection. Opioid (including heroin) users have a tolerance to narcotics. Patients with alcoholism are at risk for delirium tremens, a potentially life-threatening form of withdrawal characterized by autonomic instability and hyperpyrexia. These patients may also have liver disease (alcoholic hepatitis, cirrhosis, portal hypertension, end-stage liver disease), alcohol-induced cardiomyopathy, arrhythmias, seizures, neuropathies, dementia, Wernicke-Korsakoff syndrome (ataxia and cognitive dysfunction secondary to thiamine deficiency), macrocytic anemia, and coagulopathies (from hepatic dysfunction or vitamin K deficiency). Cocaine and amphetamine addicts can develop cerebrovascular accidents, cardiomyopathy, and arrhythmias. Additionally, cocaine and amphetamines inhibit the uptake of sympathomimetic neurotransmitters, thereby

increasing risks for hypertension, tachycardia, paranoia, anxiety, seizures, and myocardial ischemia. Long-term use can result in ventricular hypertrophy, myocardial infarction, and nasal septal perforation. Solvents can cause cardiac dysrhythmias, pulmonary edema, cerebral edema, diffuse cortical atrophy, and hepatic failure. Hallucinogens, such as lysergic acid diethylamide, can cause autonomic dysregulation and paranoia. Ecstasy, or more specifically 3,4-methylenedioxymethamphetamine, can cause excessive thirst that results in hyponatremia, pulmonary edema, or cerebral edema. Acute marijuana use can cause tachycardia, vasodilatation, and increased cardiac output. The risk of pulmonary complications in patients who smoke marijuana is similar to that of individuals who smoke tobacco.<sup>410</sup>

During the preoperative evaluation interview, patients who abuse alcohol or drugs may not give a reliable history. The subsequent physical examination should include careful measurement of vital signs, including temperature. For example, cocaine and amphetamines may cause hypertension and tachycardia, whereas acute opioid use may result in a slow respiratory rate. Acute opioid use may also manifest as lethargy and pinpoint pupils, and recent alcohol consumption can often be detected by smell. Especially in individuals suspected of being intravenous drug abusers, it is important to examine venous access sites for signs of abscesses and infections. In addition, careful auscultation for murmurs is essential because of the risk of bacterial endocarditis. Cocaine or alcohol abusers can also exhibit findings in their cardiovascular examination consistent with heart failure or arrhythmias. Long-term alcohol abuse may manifest with physical findings of chronic liver disease. In addition to identifying the presence of substance abuse and its related complications, clinicians should ascertain whether, and for how long, patients can stop consuming alcohol or addictive drugs. If patients do stop consumption occasionally, it is especially important to determine what complications, if any, occur. When an alcoholic patient reports previously interrupting drinking for several days, the interviewer should inquire whether agitation, seizures, delirium tremens, or other signs of withdrawal developed. Any testing is largely informed by findings on the preoperative clinical evaluation, as well as the specific drug being abused. For example, an ECG may be warranted to assess for previous myocardial infarction in an individual with a history of cocaine abuse or in an individual receiving methadone (which prolongs the QT interval).

Ideally, patients with drug or alcohol dependence should be drug free well before elective surgical procedures. The availability of randomized trial data is limited and suggest that preoperative alcohol cessation programs can help prevent postoperative complications.<sup>411</sup> Preanesthesia clinic staff should therefore be prepared to refer patients to addiction specialists or to prescribe medications to prevent withdrawal in the preoperative period if patients agree to abstinence. For example, benzodiazepines can be useful in preventing or treating alcohol withdrawal symptoms.

Some medications used to manage withdrawal or facilitate recovery have specific perioperative considerations.<sup>412</sup> Patients taking methadone should continue maintenance doses in the perioperative period. Patients who are taking disulfiram because of a history of alcohol abuse may

have an altered response to sympathomimetic drugs; some authors therefore suggest that disulfiram be discontinued 10 days before the surgical procedure.<sup>412</sup> If disulfiram is continued, users can experience flushing, nausea, and tachycardia in response to small amounts of alcohol, such as amounts encountered in skin preparations or medications. For patients taking naltrexone for a history of alcohol abuse, consideration should be given to discontinuing it 3 days preoperatively.<sup>412</sup> Naltrexone alters responses to opioid analgesics and may make postoperative pain management very challenging. Buprenorphine-containing medications (i.e., Suboxone), which are used to treat opioid addiction (as well as chronic pain), also alter responses to opioid analgesics. In the case of relatively minor surgery with minimal levels of anticipated postoperative pain, it is reasonable to continue buprenorphine perioperatively and maximize the use of nonopioid analgesic approaches (e.g., regional anesthesia, NSAIDs). In other cases, the perioperative management of buprenorphine should be coordinated with the patient's addiction specialist.

## BREASTFEEDING PATIENTS

There are limited data to help guide recommendations for the safety of anesthetics and medications in babies of breastfeeding mothers who receive these agents. For elective surgery, women should be advised to pump and store milk preoperatively; this milk can be used in the first 24 hours after anesthesia administration, or for the duration of breast milk exposure to potentially harmful agents. The mother should discard milk produced within the first 24 hours after anesthesia, and then generally resume breastfeeding after this period. Very young or premature babies, especially those susceptible to apnea, may be at risk if the mothers continue to take opioid or sedating drugs. Mothers should be advised to discuss the safety of breastfeeding while taking medications with their child's pediatrician.

## PATIENTS WITH DO NOT RESUSCITATE ORDERS

Some patients scheduled for procedures have advance directives or a do-not-resuscitate (DNR) status.<sup>413</sup> The ASA adopted guidelines for the care of these patients and updated them in 2013 (Box 31.14).<sup>414</sup> Frequently, in circumstances with DNR orders, care providers are focused on a procedure-directed approach (i.e., do not intubate, do not administer resuscitative drugs). This approach is problematic in the perioperative period because much of anesthesia care involves such procedures. Within the context of anesthesia care, a better approach is to discuss DNR status in a goal-directed approach (i.e., from the perspective of the patient's values and objectives, such as quality-of-life concerns).<sup>415</sup> The ideal time to have this emotional and complex discussion is during the preoperative evaluation. Short discussions in the preoperative clinic have been shown to foster dialogue among patients, their proxies, and physicians regarding advance directives concerning end-of-life care, as demonstrated by a randomized trial of patients at a preoperative evaluation clinic.<sup>416</sup> In this trial, individuals who received the information session were significantly more likely to complete a durable power-of-attorney (27%

### BOX 31.14 Do-Not-Resuscitate Orders in the Perioperative Period

Policies automatically suspending DNR orders or other directives that limit treatment before procedures involving anesthetic care may not sufficiently address a patient's rights to self-determination in a responsible and ethical manner. Such policies, if they exist, should be reviewed and revised, as necessary, to reflect the content of these guidelines.

1. *Full Attempt at Resuscitation:* The patient or designated surrogate may request the full suspension of existing directives during the anesthetic and immediate postoperative period, thereby consenting to the use of any resuscitation procedures that may be appropriate to treat clinical events that occur during this time.
2. *Limited Attempt at Resuscitation Defined With Regard to Specific Procedures:* The patient or designated surrogate may elect to continue to refuse certain specific resuscitation procedures (for example, chest compressions, defibrillation or tracheal intubation). The anesthesiologist should inform the patient or designated surrogate about which procedures are (1) essential to the success of the anesthesia and the proposed procedure, and (2) which procedures are not essential and may be refused.
3. *Limited Attempt at Resuscitation Defined With Regard to the Patient's Goals and Values:* The patient or designated surrogate may allow the anesthesiologist and surgical team to use clinical judgment in determining which resuscitation procedures are appropriate in the context of the situation and the patient's stated goals and values. For example, some patients may want full resuscitation procedures to be used to manage adverse clinical events that are believed to be quickly and easily reversible, but to refrain from treatment for conditions that are likely to result in permanent sequelae, such as neurologic impairment or unwanted dependence upon life-sustaining technology.

DNR, Do-not-resuscitate.

Modified from Committee on Ethics, American Society of Anesthesiologists: Ethical guidelines for the anesthesia care of patients with do-not-resuscitate orders or other directives that limit treatment, 2013. Available at <http://www.asahq.org/For-Members/Standards-Guidelines-and-Statements.aspx>.

vs. 10%) and discuss end-of-life care with their proxy decision makers (87% vs. 66%).

## Preoperative Laboratory and Diagnostic Studies

The value of preoperative diagnostic testing is a central issue in delivering cost-effective health care to surgical patients. The role of preoperative testing to screen for disease and evaluate patients' fitness for surgery has been extensively studied. This research has largely concluded that routine preoperative testing in all surgical patients (i.e., without consideration for their demographics or comorbidities) cannot be justified. Routine preoperative testing in asymptomatic healthy patients has very poor diagnostic yield, provides little to no additional prognostic information, and has not shown any beneficial effect on outcomes.<sup>274,417-420</sup> Unnecessary testing is also expensive, and may lead to costly evaluation of borderline or false-positive test abnormalities. Aside from potentially causing operating room delays or cancellations, these unnecessary follow-up tests

may pose risks to patients that are attributable to follow-up tests and any associated interventions. Therefore, the targeting of testing in appropriate patients has both clinical and economic benefits. At some hospitals where surgeons and primary care physicians order all preoperative tests, the common practice has been to order tests without any diagnostic focus, other than speculation that the anesthesiologist may "require them" for surgery to proceed without delay or cancellation. Other justifications offered for nonselective ordering of tests include routine screening for disease states, establishment of a diagnostic baseline, personal habit (e.g., "standard" testing checklist for all patients), physician reassurance, and a perceived medicolegal necessity "not to miss anything." This pattern of practice has led to a plethora of preoperative testing practices that are costly, highly variable across hospitals, and largely unrelated to patients' perioperative risk profiles.<sup>421-423</sup> For example, in 2011, almost half of Medicare beneficiaries (aged  $\geq 65$  years) in the United States underwent preoperative laboratory testing before cataract surgery, which is considered a very low-risk procedure.<sup>423</sup>

Preoperative diagnostic tests should be selectively ordered based on the patient's medical history, planned surgery, and expected degree of intraoperative blood loss. Testing should be for the detection of specific clinical indications that may increase perioperative risk. Randomized trials have demonstrated that such a shift in strategy from nonselective to selective preoperative testing in low-risk surgical procedures can reduce costs while preserving patients' safety.<sup>418,419</sup> As experts in perioperative medicine, anesthesiologists are in a unique position to appropriately select the preoperative laboratory tests needed to guide perioperative care. Indeed, anesthesiologist-led preoperative evaluation has been shown to result in more selective ordering of laboratory tests than evaluation led by surgeons or primary care physicians.<sup>14-17</sup> Thus, by educating and providing specific guidance to surgeons and other physician specialists on the appropriate ordering of preoperative tests, anesthesiologists can expedite patient care, reduce healthcare costs, and improve the delivery of perioperative medicine.

A framework for ordering preoperative diagnostic tests based on patients' medical history is presented in Table 31.18. These disease-specific recommendations are not intended as absolute, especially since many hospitals and regional jurisdictions (e.g., Ontario Pre-Operative Testing Grid)<sup>424</sup> have developed their own preoperative testing recommendations. In addition, the NICE in the United Kingdom published updated 2016 guidelines for preoperative testing following an extensive systematic review of the literature.<sup>274</sup> The NICE guidelines consider both patients' preoperative medical status and the extensiveness of the planned surgery to determine when preoperative testing is warranted. In these guidelines, surgical procedures are graded as minor (e.g., skin lesion excision), intermediate (e.g., inguinal hernia repair, varicose vein excision, tonsillectomy, knee arthroscopy), and major (e.g., total abdominal hysterectomy, transurethral prostate resection, lumbar spine discectomy, thyroidectomy, total joint replacement, lung operations, colon resection, radical neck dissection). Although the most recent 2012 ASA "Practice Advisory for Preadmission Evaluation" does recommend against routine preoperative testing,<sup>5</sup> it does

**TABLE 31.18** Framework for Preoperative Diagnostic Testing Based on Patients' Medical History

Preoperative Diagnosis	ECG	CXR	CBC	Electrolytes	Creatinine	Glucose	Coagulation	LFTs	Drug Levels	Ca
<b>Cardiac disease</b>										
IHD	X		X	±						
HF	X	±								
HTN	X	±		X*		X				
Chronic atrial fibrillation	X								X†	
PAD	X									
Valvular heart disease	X	±								
<b>Pulmonary disease</b>										
COPD	X	±	X						X‡	
Asthma§										
Diabetes mellitus	X			±		X	X			
<b>Liver disease</b>										
Infectious hepatitis							X	X		
Alcohol/drug induced							X	X		
Tumor infiltration							X	X		
<b>Renal disease</b>										
	X		X		X					
<b>Hematologic disorders</b>										
	X									
<b>Coagulopathies</b>										
	X						X			
<b>CNS Disorders</b>										
Stroke	X		X	X		X			X	
Seizures	X		X	X		X			X	
Tumor	X		X							
Vascular/aneurysms	X		X							
<b>Malignancy</b>										
	X									
<b>Hyperthyroidism</b>										
	X		X	X						X
<b>Hypothyroidism</b>										
	X		X	X						
<b>Cushing disease</b>										
	X		X	X		X				
<b>Addison disease</b>										
	X		X	X		X				
<b>Hyperparathyroidism</b>										
	X		X	X						X
<b>Hypoparathyroidism</b>										
	X			X						X
<b>Morbid obesity</b>										
	X	±				X				
<b>Malabsorption/poor nutrition</b>										
	X		X	X		X	X			
<b>Select Drug Therapies</b>										
Digoxin	X			±					X	
Anticoagulants		X					X			
Phenytoin										X
Phenobarbital										X
Diuretics		X		X		X				
Corticosteroids		X				X				
Chemotherapy		X			±					
Aspirin/NSAID										
Theophylline								X		

\*If the patient is taking diuretics.

†If the patient is taking digoxin.

‡If the patient is taking theophylline.

§Only test for consideration is pulmonary function testing if clinically indicated.

X, obtain; ±, consider.

Ca, Calcium; CBC, complete blood count; HF, heart failure; CXR, chest x-ray; ECG, electrocardiogram; HTN, hypertension; IHD, ischemic heart disease; LFTs, liver function tests; NSAID, nonsteroidal antiinflammatory drug; PAD, peripheral artery disease.

not make explicit recommendations about which tests should be ordered for specific clinical conditions. The practice advisory states that the indications for testing should be “*based on information obtained from medical records, patient interview, physical examination, and type and invasiveness of the planned procedure.*” In addition, it describes patient-related and surgery-related factors that anesthesiologists should consider when deciding whether to order a specific laboratory test.<sup>5</sup> Conversely, the updated 2018 ASA guidelines on preoperative evaluation do make some specific recommendations for when preoperative laboratory testing should be performed.<sup>6</sup>

The following subsections discuss specific preoperative laboratory tests. In general, testing does not have to be repeated during the preoperative evaluation of healthy patients (i.e., ASA-PS class 1 or 2) if similar testing has already been performed within the 2 months preceding surgery and there has been no major interval change in the patient’s medical status (e.g., recent chemotherapy).<sup>425</sup>

### COMPLETE BLOOD COUNT, HEMOGLOBIN, AND HEMATOCRIT

The proposed surgery, associated potential blood loss, and individualized patient-level clinical indications should determine the requirement for a preoperative CBC. Typical clinical indications include a history of increased bleeding, hematologic disorders, CKD, chronic liver disease, recent chemotherapy or radiation treatment, corticosteroid therapy, anticoagulant therapy, and poor nutritional status. The NICE guidelines recommend routine CBC testing only in ASA-PS class 3 or 4 patients undergoing intermediate grade procedures, and all patients undergoing major procedures.<sup>274</sup>

### RENAL FUNCTION TESTING

Renal function tests assess renal tubular function and glomerular filtration. Primary clinical indications include diabetes mellitus, hypertension, cardiac disease, potential dehydration (e.g., vomiting, diarrhea), anorexia, bulimia, fluid overload states (e.g., heart rate, ascites), known renal disease, liver disease, relevant recent chemotherapy (e.g., cisplatin, carboplatin), and renal transplantation. The NICE guidelines recommend routine renal function testing in ASA-PS class 3 or 4 patients undergoing intermediate procedures, and ASA-PS class 2, 3, or 4 patients undergoing major procedures.<sup>274</sup> If patients are deemed to be at risk for perioperative AKI, testing may also be considered in ASA-PS class 3 or 4 patients undergoing minor procedures, and ASA-PS class 2 patients undergoing intermediate procedures.<sup>274</sup>

### LIVER FUNCTION TESTING

The ordering of liver function tests should be based on a history of liver injury and physical examination findings. Primary clinical indications include a history of hepatitis (viral, alcohol, drug-induced, autoimmune), jaundice,

cirrhosis, portal hypertension, biliary disease, gallbladder disease, hepatotoxic drug exposure, tumor involvement of the liver, and bleeding disorders.

### COAGULATION TESTING

Routine preoperative coagulation testing is not indicated (even in patients undergoing regional procedures) unless a known or suspected coagulopathy is identified on preoperative evaluation. Primary clinical indications for testing include a known bleeding disorder, hepatic disease, and anticoagulant use.<sup>5</sup> The 2016 NICE guidelines state that coagulation testing should only be considered in patients who are (1) ASA-PS class 3 or 4; (2) undergoing intermediate, major, or complex surgical procedures; and (3) known to take anticoagulant medications or have chronic liver disease.<sup>274</sup>

### URINALYSIS

There is no indication for routine preoperative urinalysis.<sup>274</sup> Primary clinical indications include a suspected urinary tract infection and unexplained fever or chills.

### PREGNANCY TEST

Pregnancy testing is often determined by hospital-specific protocols. It can also be based on clinical indications such as sexual activity, birth control use, and date of the last menstrual period. Another important factor that should be considered is the potential for the planned surgical procedure harming a fetus, based on direct injury (e.g., uterine surgery), reduction in blood flow (e.g., major cardiac or vascular surgery), and exposure to teratogenic agents (e.g., x-rays). The 2012 ASA “Practice Advisory for Pre-anesthesia Evaluation” suggests offering pregnancy testing to female patients of childbearing age when the result would alter the patient’s management. It also recommends that informed consent be obtained for such testing, or that there be a full discussion of the risks, benefits, and alternatives related to preoperative pregnancy testing. The NICE guidelines recommend that all women of childbearing potential be asked whether there is any possibility they could be pregnant, and that any women who could possibly be pregnant be made aware of the risks of anesthesia and surgery to a fetus. The guidelines also recommend documenting all discussions about whether or not to carry out pregnancy testing, and to conduct pregnancy testing with patient consent if there is any doubt about pregnancy status.<sup>274</sup>

### SICKLE CELL TEST

Individuals at risk for sickle cell disease include those of African, Caribbean, Eastern Mediterranean, and Middle Eastern origin. Even in at-risk populations, routine preoperative screening for sickle cell disease has a very low yield,<sup>426</sup> especially in regions with newborn screening programs for sickle cell disease.<sup>427</sup> Consistent with this evidence, 2016 NICE guidelines recommend against routine preoperative testing for sickle cell disease or sickle cell trait.<sup>274</sup>

A reasonable approach is to consider testing in *previously untested* patients who have at-risk ethnic backgrounds and clinical indicators. These indicators include patient-related (e.g., family history of sickle cell disease, sickle cell symptoms) and surgery-related (e.g., deliberate hypothermia, cardiopulmonary bypass, intrathoracic procedures, intraabdominal procedures, orthopedic procedures with tourniquet use) factors.

## ELECTROCARDIOGRAM

The ECG can help detect a prior myocardial infarction, cardiac rhythm disturbances, ischemia, chamber hypertrophy, and electrolyte disorders. Nonetheless, when combined with usual clinical examination, the preoperative ECG may not provide additional prognostic information to identify individuals at risk for postoperative cardiac complications.<sup>100</sup> Primary clinical indications for preoperative ECGs include a history of IHD, hypertension, diabetes mellitus, heart failure, chest pain, palpitations, abnormal valvular murmurs, peripheral edema, syncope, dizziness, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and CVD. The 2014 ESC/ESA guidelines suggest preoperative ECGs in patients with risk factors for IHD or suspicious symptoms, especially if they are undergoing intermediate-risk or high-risk surgery.<sup>9</sup> The 2014 ACC/AHA guidelines are fairly consistent in that they support preoperative ECGs for patients who are undergoing intermediate-risk or high-risk surgery, and who have known IHD, significant arrhythmia, PAD, CVD, or other significant structural heart disease.<sup>7</sup> The guidelines also recommend against routine preoperative ECGs (see Box 31.2), especially in asymptomatic patients without known cardiovascular disease or risk factors.<sup>7</sup> The NICE guidelines recommend routine preoperative ECGs in ASA-PS class 3 or 4 patients undergoing intermediate grade procedures, and ASA-PS class 2, 3, or 4 patients undergoing major procedures.<sup>274</sup> If patients have cardiovascular disease, CKD, or diabetes mellitus, testing may also be considered in ASA-PS class 2 patients undergoing intermediate procedures.<sup>274</sup>

## CHEST RADIOGRAPH

Routine preoperative chest radiographs do not provide prognostically important information for assessing perioperative risk.<sup>428</sup> Preoperative chest radiographs should therefore not be ordered routinely,<sup>274</sup> but rather selectively based on abnormalities identified by preoperative evaluation. These indications include advanced COPD, bullous lung disease, suspected pulmonary edema, suspected pneumonia, suspected mediastinal masses, and suspicious findings on physical examination (e.g., rales, tracheal deviation).

## Preoperative Risk Assessment

A critical component of the preanesthesia evaluation is assessment of a patient's risk for undergoing anesthesia and surgery. This assessment improves patients' understanding of the inherent perioperative risks and better informs healthcare providers' clinical decision making.

**TABLE 31.19** American Society of Anesthesiologists Physical Status Classification

Category*	Definition
ASA-PS 1	A normal, healthy patient
ASA-PS 2	A patient with mild systemic disease
ASA-PS 3	A patient with severe systemic disease
ASA-PS 4	A patient with severe systemic disease that is a constant threat to life
ASA-PS 5	A moribund patient who is not expected to survive without the operation
ASA-PS 6	A declared brain-dead patient whose organs are being removed for donor purposes

\*The addition of "E" to the classification category indicates emergency surgery.

ASA-PS, American Society of Anesthesiologists physical status.

For example, these risk assessments might help identify individuals who warrant enhanced levels of postoperative monitoring, consideration for alternative nonoperative or less invasive treatment options for their underlying condition, or initiation of interventions intended to decrease perioperative risk. An anesthesiologist's designation of a surgical patient as being high-risk is clinically important. Specifically, when the initial preanesthesia evaluation deems that a patient is at unacceptably high risk for anesthesia and surgery, adherence to the anesthesiologist's recommendations for further perioperative management is associated with lower postoperative complication rates.<sup>429</sup> In addition, accurate risk assessments facilitate fairer comparisons of perioperative outcomes; specifically, estimates of patients' risks are required by statistical methods that adjust for case-mix differences across providers and hospitals.

The most commonly used method by anesthesiologists to assess overall perioperative risk is the ASA-PS classification system (Table 31.19). This classification system, which was developed in 1941, was originally intended to facilitate collection and comparison of statistical data in anesthesia.<sup>430</sup> The ASA-PS classification system seeks to describe a patient's preoperative medical status, but it does not consider risks inherent to the planned surgical procedure. Although *not* intended to guide estimation of patients' risks for anesthesia and surgery, the ASA-PS is often used for this purpose, especially given its simplicity of use. Indeed, several studies have shown a correlation of ASA-PS scores with postoperative mortality and major complications.<sup>9,218,431-433</sup> An important limitation to the classification system is its inherent subjectivity; consequently, previous research has shown only fair to modest interrater agreement when different individuals attempt to assign an ASA-PS category to the same patient.<sup>432,434-436</sup>

In addition to patients' preoperative medical status, which is described by the ASA-PS system, the operative procedure is an important determinant of perioperative risk.<sup>437-439</sup> Overall perioperative risk is necessarily a function of both the risk associated with the specific operative procedure and the risk associated with a patient's underlying medical status. For example, ambulatory surgical procedures are very

**TABLE 31.20** Johns Hopkins Surgery Risk Classification System

Category	Description
1	Minimal risk to the patient independent of anesthesia. Minimally invasive procedure with little or no blood loss. Procedures are often done in an office setting, with the operating room used principally for anesthesia and monitoring.
2	Minimal to moderately invasive procedure, with expected blood loss not exceeding 500 mL. Mild risk to patient independent of anesthesia.
3	Moderately to significantly invasive procedure, with expected blood loss of 500-1500 mL. Moderate risk to patient independent of anesthesia.
4	Highly invasive procedure, with expected blood loss exceeding 1500 mL. Major risk to patient independent of anesthesia.
5	Highly invasive procedure, with expected blood loss exceeding 1500 mL. Critical risk to patient independent of anesthesia. Usually requires postoperative critical care unit stay with invasive monitoring.

From Paternak LR, Johns A. Ambulatory gynaecological surgery: risk and assessment. *Best Pract Res Clin Obstet Gynaecol*. 2005;19:663-679.

safe with respect to risks of postoperative mortality and major adverse events,<sup>440-442</sup> as evidenced by a 7-day postoperative mortality rate of only 41 per 100,000 procedures in a large cohort of Medicare beneficiaries 65 years old or older.<sup>440</sup> Thus, although older patients with an increased burden of comorbidity do have increased relative risks of mortality and morbidity following ambulatory surgery, their *absolute* risks remain very low. Classification schemes have been proposed for assessing operative risk, such as the Johns Hopkins risk classification system (Table 31.20), elevated surgical risk category in the RCRI (see Table 31.5), and the strata employed by the ESA/ESC cardiovascular evaluation guidelines.<sup>9,439</sup> Importantly, individual operative procedures within broad categories (e.g., intraabdominal surgery) vary with respect to their perioperative risk.<sup>107</sup> As a consequence, there is a need to balance the desire to ensure that clinical prediction tools sufficiently capture the variability in operative risk across different procedures, against the need to ensure that these tools are sufficiently simple for straightforward clinical use.

Several commonly used and methodologically sound clinical indices can predict mortality and major morbidity after cardiac surgery with reasonable accuracy, such as the EuroSCORE,<sup>443</sup> Society of Thoracic Surgeons risk models,<sup>444</sup> and Cleveland Clinic AKI risk score.<sup>269</sup> A variety of prediction tools have also been developed for use in noncardiac surgery.<sup>445</sup> For example, the ACS NSQIP risk calculator is available on the Internet (<http://riskcalculator.acs.org>) and provides an estimate of risk based on patients' comorbidities and proposed surgical procedures.<sup>32</sup> High-quality validated indices have been developed for predicting specific major complications of noncardiac surgery, such as cardiovascular events (e.g., RCRI)<sup>97,106</sup> and respiratory complications (e.g., ARISCAT).<sup>257,261</sup> Other examples including the Surgical Risk Scale,<sup>446</sup> the Preoperative Score to Predict Postoperative Mortality (POSPOM),<sup>99</sup> and large

multinational prospective epidemiologic studies of surgical patients (which included accurate capture of perioperative characteristics and outcomes),<sup>77,78</sup> will likely help lead to the development of other high-quality predictive indices.

## ROLE OF SPECIALIZED TESTING IN PREOPERATIVE RISK ASSESSMENT

Based on an initial preoperative clinical evaluation, anesthesiologists may order subsequent specialized tests to help address diagnostic questions (e.g., “*Does this patient have aortic stenosis?*”) or determine perioperative risk more accurately. Examples of such tests include noninvasive cardiac stress tests (see section on “Ischemic Heart Disease”), coronary angiography (see section on “Ischemic Heart Disease”), echocardiography, CPET, and PFTs (see section on “Pulmonary Disorders”).

Resting echocardiography can provide information related to valvular lesions, pulmonary hypertension, fixed wall motion abnormalities, and ventricular function. Especially in cases of a suspicious murmur or other clinical indication, a preoperative echocardiogram can help diagnose prognostically important valvular or other cardiac lesions, such as aortic stenosis or pulmonary hypertension.<sup>447,448</sup> An echocardiogram can also identify fixed wall motion abnormalities consistent with a previous myocardial infarction. Although these findings can help support a diagnosis of IHD, fixed wall motion abnormalities are not themselves indicative of increased perioperative cardiac risk.<sup>122</sup> Similarly, while systolic ventricular dysfunction identified on echocardiography is associated with increased cardiac risk<sup>161,162</sup> this finding may not provide additional prognostic information when it is combined with routine preoperative clinical evaluation.<sup>161</sup> Thus, the overall role of echocardiography is to address focused *diagnostic* questions identified in usual clinical preoperative evaluation (e.g., suspicious systolic murmurs), not to provide important prognostic information pertaining to perioperative risk. Current guidelines therefore largely recommend preoperative echocardiography to assess dyspnea of unknown origin or recent altered clinical status in an individual with known heart failure (see Box 31.3).<sup>7</sup> In addition, repeat echocardiography is reasonable in clinically stable patients with known ventricular dysfunction who have not been tested in the previous year.<sup>7</sup> Conversely, routine preoperative echocardiography is discouraged.<sup>7,8</sup>

CPET is a noninvasive global assessment of exercise capacity; it involves a patient exercising on a bicycle or treadmill for 8 to 12 minutes while undergoing continuous measurement of respiratory gas exchange (i.e., oxygen uptake and carbon dioxide production).<sup>449</sup> Poor exercise capacity during CPET, based on either a low peak oxygen consumption or a low anaerobic threshold, is associated with increased risks of postoperative morbidity.<sup>29,36,450</sup> Thus, the test can help improve the accuracy of preoperative risk stratification. In some geographic settings,<sup>451</sup> CPET is a commonly used preoperative test. In these settings, it is used to aid preoperative risk assessment for major surgery, and to inform decisions on the appropriateness of planned major surgical procedures.

The role of PFTs for guiding preoperative assessment in the setting of specific comorbidities was discussed earlier in this chapter. These tests have an established and important role for assessing perioperative risk in lung resection surgery

(see section on “Patients Scheduled for Lung Resection” and **Chapter 53**).<sup>219</sup> PFTs also play an important diagnostic role. For example, they help differentiate between pulmonary and cardiac causes of dyspnea of unknown origin. Aside from these specific circumstances, the *prognostic* value of preoperative PFTs is limited. Practice guidelines from the American College of Physicians recommend against routine preoperative spirometry for estimating risks for pulmonary complications after noncardiothoracic surgery.<sup>10</sup> Research has not found a consistent link between poor PFT results and increased risks for perioperative pulmonary complications, with older studies being generally limited by important methodologic flaws.<sup>218</sup> Furthermore, there does not seem to be a critical PFT threshold below which patients should not be offered surgery. For example, in a previous cohort study, individuals with severe obstructive findings (i.e.,  $FEV_1 < 50\%$  of predicted and  $FEV_1/FVC$  ratio  $< 0.7$ ) had reasonably acceptable risks of postoperative death (5.6%) and respiratory failure (5.6%).<sup>452</sup>

## Preoperative Medication Management

The patient’s comorbidities and planned procedure must inform medication management during the perioperative

period. Some medications have beneficial effects during surgical procedures, whereas others may be detrimental. In some cases, abrupt *withdrawal* of medications can have a negative effect. Management of specific preoperative medications has been discussed in the previous sections of this chapter. These recommendations are outlined again in **Box 31.15**. Although issues pertaining to many drugs are covered in other sections of this chapter, several issues merit special mention.

NSAIDs have *reversible* antiplatelet effects; hence, once the drugs have been eliminated, platelet function returns to normal. Concomitant NSAID use does not appear to increase the risk of spinal hematoma with neuraxial anesthesia.<sup>196</sup> Preoperative discontinuation of NSAIDs may be of value in patients at risk for perioperative AKI. Typically, NSAIDs are discontinued 24 to 72 hours preoperatively. Earlier discontinuation does not increase safety, and it may be burdensome to many patients with significant arthritis or chronic pain. COX-2 inhibitors (e.g., celecoxib) have minimal effect on platelet function and can usually be continued in the perioperative period. However, the long-term COX-2 inhibitor use in the nonoperative setting does increase the risk of cardiac events, in comparison with placebo or naproxen.<sup>453</sup> Conversely, COX-2 inhibitors have a cardiac risk profile similar to that of ibuprofen or diclofenac.<sup>453</sup> In general, no clear evidence indicates increased

### BOX 31.15 Preoperative Management of Medications

Instruct patients to take these medications with a small sip of water, even if fasting.

**1. Antihypertensive medications**

Continue on the day of surgery, except for ACEIs and ARBs

**2. Cardiac medications (e.g.,  $\beta$ -blockers, digoxin)**

Continue on the day of surgery.

**3. Antidepressants, anxiolytics, and other psychiatric medications**

Continue on the day of surgery.

**4. Thyroid medications**

Continue on the day of surgery.

**5. Oral contraceptive pills**

Continue on the day of surgery.

**6. Eye drops**

Continue on the day of surgery.

**7. Heartburn or reflux medications**

Continue on the day of surgery.

**8. Opioid medications**

Continue on the day of surgery.

**9. Anticonvulsant medications**

Continue on the day of surgery.

**10. Asthma medications**

Continue on the day of surgery.

**11. Corticosteroids (oral and inhaled)**

Continue on the day of surgery.

**12. Statins**

Continue on the day of surgery.

**13. Aspirin**

Continue aspirin in patients with prior percutaneous coronary intervention, high-grade IHD, and significant CVD. Otherwise, discontinue aspirin 3 days before surgery.

**14. P2Y<sub>12</sub> inhibitors (e.g., clopidogrel, ticagrelor, prasugrel, ticlopidine)**

Patients having cataract surgery with topical or general anesthesia do not need to stop taking thienopyridines. If reversal of platelet inhibition is necessary, the time interval for discontinuing these medications before surgery is 5–7 days for clopidogrel, 5–7 days for ticagrelor, 7–10 days for prasugrel, and 10

days for ticlopidine. Do not discontinue P2Y<sub>12</sub> inhibitors in patients who have drug-eluting stents until they have completed 6 mo of dual antiplatelet therapy, unless patients, surgeons, and cardiologists have discussed the risks of discontinuation. The same applies to patients with bare metal stents until they have completed 1 month of dual antiplatelet therapy.

**15. Insulin**

For all patients, discontinue all short-acting (e.g., regular) insulin on the day of surgery (unless insulin is administered by continuous pump). Patients with type 2 diabetes should take none, or up to one half of their dose of long-acting or combination (e.g., 70/30 preparations) insulin, on the day of surgery. Patients with type 1 diabetes should take a small amount (usually one third) of their usual morning long-acting insulin dose on the day of surgery. Patients with an insulin pump should continue their basal rate only.

**16. Topical medications (e.g., creams and ointments)**

Discontinue on the day of surgery.

**17. Non-insulin antidiabetic medications**

Discontinue on the day of surgery (exception: SGLT2 inhibitors should be discontinued 24 hours before elective surgery)

**18. Diuretics**

Discontinue on the day of surgery (exception: thiazide diuretics taken for hypertension, which should be continued on the day of surgery).

**19. Sildenafil (Viagra) or similar drugs**

Discontinue 24 h before surgery.

**20. COX-2 inhibitors**

Continue on the day of surgery unless the surgeon is concerned about bone healing.

**21. Nonsteroidal antiinflammatory drugs**

Discontinue 48 hours before the day of surgery.

**22. Warfarin (Coumadin)**

Discontinue 5 days before surgery, except for patients having cataract surgery without a bulbar block.

**23. Monoamine oxidase inhibitors**

Continue these medications and adjust the anesthesia plan accordingly.

cardiac risk from *short-term* perioperative administration of COX-2 inhibitors. The exception is valdecoxib (now withdrawn from the market), which caused an excess of cardiac events in patients undergoing cardiac surgery.<sup>454</sup>

Postmenopausal hormone replacement therapies that contain estrogen increase the risk of thromboembolic events.<sup>455</sup> It may therefore be reasonable to discontinue these medications before operations. Estrogens must be stopped approximately 4 weeks preoperatively for coagulation function to return to baseline. Most modern oral contraceptives contain low doses of estrogen. Nonetheless, these medications are still associated with some elevation in thrombotic risk.<sup>456</sup> Since the risk of unanticipated pregnancy may outweigh the benefits of discontinuing oral contraceptives preoperatively, it is reasonable to continue oral contraceptives in most patients during the perioperative period. In patients who are deemed to be a high risk for postoperative VTE (see section on “Venous Thromboembolic Disorders”), consideration may be given to stopping oral contraceptives 4 weeks before surgery (and temporarily switching to other forms of contraception). This decision should be made collaboratively with the patient and must balance the risk of VTE versus the risk of unwanted pregnancy.

Most medications for psychiatric and psychological problems should be continued into the preoperative period. Thus, most antidepressants, antipsychotics, and benzodiazepines are best maintained to avoid exacerbations of symptoms. Historically, monoamine oxidase inhibitor (MAOI) antidepressants were discontinued preoperatively; however, elimination of the risks associated with many of these drugs required drug discontinuation at least 3 weeks before surgery. This long withdrawal period is specifically applied to MAOIs that cause irreversible inhibition of MAO. Some newer agents, such as moclobemide, cause reversible enzyme inhibition and have effects lasting less than 24 hours. Preoperative withdrawal of these drugs has potential risks. Specifically, case reports of suicides or severe depression following discontinuation of MAOIs have been reported. Thus, the safest approach may be to continue these drugs and adjust the anesthetic plan accordingly (e.g., avoid meperidine and indirect-acting vasopressors such as ephedrine). If this approach is taken, it is critical that details of a patient’s MAOI use must be clearly communicated to healthcare providers on the day of surgery. Patients receiving tricyclic antidepressants require a preoperative ECG, given the potential for a prolonged QT interval. Because tricyclic antidepressants block the reuptake of norepinephrine and serotonin, high doses may also result in augmented responses to vasopressor drugs, with the potential for exaggerated hemodynamic changes. Patients taking lithium require evaluation of electrolyte and creatinine concentrations. Discontinuation of lithium has also been associated with suicide. Continued perioperative use of selective serotonin reuptake inhibitors (SSRIs) are associated with increased surgical bleeding,<sup>457,458</sup> whereas abrupt discontinuation of SSRIs can also cause dizziness, chills, muscle aches, and anxiety. Overall, it is still reasonable to continue SSRI perioperatively in most patients, aside from those undergoing procedures where bleeding could have significant postoperative sequelae (e.g., intracranial surgery).

Complementary and alternative medications may interact with anesthetic drugs, alter effects of prescription

medications, and increase bleeding. In addition, many patients do not consider these drugs “medications,” and may not list them among their medications unless specifically asked. The perioperative management of complementary and alternative medications is discussed in further detail in Chapter 33.

## Planning for Anesthesia

### PREOPERATIVE FASTING STATUS

The overarching goal of preoperative fasting recommendations has been to reduce the risk of pulmonary aspiration. The ASA published practice guidelines pertaining to preoperative fasting in nonlaboring individuals undergoing elective procedures.<sup>459</sup> The recommended fasting period following clear fluids for all patients is 2 hours. In general, the volume of liquid ingested is less important than the type of liquid ingested. For neonates and infants, the recommended fasting period is 4 hours following breast milk, and 6 hours following formula, non-human milk, and solids. For patients other than infants, a fasting period of 6 hours after a light meal is recommended; this period may have to be increased to 8 or more hours if the meal includes fried or fatty foods. In addition to implementing these fasting intervals, the guidelines recommend that the preoperative evaluation include assessment of the potential for difficult airway management, as well as factors that may increase the risk for aspiration (e.g., gastrointestinal motility disorders, diabetes).

### PLANNING FOR POSTOPERATIVE PAIN MANAGEMENT

A preoperative evaluation should always include baseline pain assessment. Standardization of pain measurement is difficult because of the subjective nature of the variable. It is therefore helpful to incorporate standardized pain measurement scales into the preoperative evaluation process. The scales may either be single-dimension scales, such as visual analog and numeric rating scales, or multidimensional scales such as the McGill pain questionnaire,<sup>460</sup> and Modified Brief Pain Inventory—Short Form.<sup>461</sup> Although multidimensional scales are longer, they capture a broader range of important details. For example, the 9-item Modified Brief Pain Inventory—Short Form captures details on the pain intensity, pain location, adequacy of analgesic treatment, and pain-related interference in activities. Consistent use of the same scale during the perioperative episode of care allows comparison when reassessments are performed after surgery.

The preoperative evaluation provides an important opportunity to discuss and plan for the management of acute postoperative pain, for several reasons. First, adequacy of perioperative pain control is a frequent concern for patients during preoperative evaluation.<sup>462,463</sup> Second, intensive preoperative pain instructions may help improve postoperative pain control in surgical patients.<sup>464</sup> Third, preoperative anesthesia consultation is associated with improved patient acceptance of perioperative regional techniques,<sup>19</sup> which can help improve the quality of postoperative analgesia.<sup>465</sup> Fourth, preoperative evaluation

facilitates planning the perioperative care of patients with chronic pain conditions, who often present significant challenges with respect to managing postoperative analgesia. Specific issues include their tolerance to usual doses of opioid analgesics and the potential for acute withdrawal reactions if they receive insufficient doses of opioids postoperatively. The preoperative consultation should therefore be used to carefully document their usual baseline opioid requirements (to ensure adequate postoperative dosing), facilitate early involvement of an acute pain service or transitional pain specialist,<sup>466</sup> encourage regional analgesic techniques, and plan adjunct analgesic medications (e.g., NSAIDs, gabapentin, pregabalin, clonidine). Patients with preexisting chronic pain should be encouraged to develop reasonable goals for adequacy of postoperative pain control. They should be informed that although care providers will do everything possible to maintain comfort postoperatively, patients should not expect to have no pain at all.

In general, patients should not be weaned from pain medications before surgery. If instructed by their surgeons to temporarily discontinue NSAIDs or COX-2 analgesics, they may have to be transitioned to alternative analgesics before surgery. Patients should be instructed to take their usual morning dose of pain medication, including continued use of any transdermal medications.

## Regulatory Issues

Providers must be aware of various governmental regulatory requirements, which often differ by individual municipalities and countries. These requirements may be driven by quality regulations, such as those developed by The Joint Commission or by payment requirements as set by the Centers for Medicare and Medicaid Services (CMS) in the United States. For example, the CMS has determined that a comprehensive anesthesia evaluation can be done within 30 days, and a focused update is required within 48 hours of a procedure requiring anesthesia services. The evaluation should be performed by a practitioner qualified to provide anesthesia. At a minimum, the preanesthesia evaluation must include the following:

- Notation of anesthesia risk (e.g., ASA-PS classification)
- Review of the medical, anesthesia, drug, and allergy history
- Interview and examination of the patient
- Potential anesthesia problems (e.g., difficult airway, limited intravascular access)
- Additional evaluation, if deemed necessary (e.g., stress tests, specialist consultation)
- Development of a plan for anesthesia, including the type of medications for induction, maintenance, and postoperative care
- Discussion of the risks and benefits of anesthesia with the patient or the patient's representative

## Preoperative Evaluation Clinic

Many anesthesiology groups and medical centers have developed preoperative evaluation programs and outpatient

clinics, with the objectives of improving patient care and operating room efficiency.<sup>14,22,467</sup> Although these programs may differ with respect to staffing, structure, financial support, and daily operations, they all share a common goal of preventing delays, last-minute cancellations, and adverse patient outcomes that could have been addressed before the day of surgery.

The decision to develop a preoperative evaluation clinic depends on several key factors. They include the anticipated daily volume of surgical patients, the predominant level of medical acuity among these patients, the availability of clinic facilities, relevant patient demographics (e.g., average travel distances from patients' homes to the clinic), and requisite support from the anesthesia department, perioperative staff, and hospital administration. If the decision to implement a preoperative evaluation program is made, anesthesiologists must play a key role in its leadership and management. When this role is instead undertaken by other specialties, such as internal medicine, anesthesiologists' expertise in perioperative patient management often becomes secondary. This shift to a secondary role can result in interdepartmental conflicts concerning patients' preoperative evaluation, risk stratification, and fitness to proceed with anesthesia and surgery. These conflicts can, in turn, result in unplanned delays or cancellations of planned surgical procedures, despite the completion of an assessment in an outpatient preoperative evaluation clinic.

Such conflicts often relate to surgeons' interpretation of a nonanesthesia specialist's judgment that a patient is "cleared for surgery" as evidence that the patient is fit for anesthesia. Unfortunately, this "clearance" is frequently made with limited knowledge of factors critical to the responsible anesthesiologist in the operating room, such as current anesthesia practice and intraoperative patient management. Indeed, previous research has shown that preoperative histories, physical examinations, and assessments performed by medical specialists often fail to address specific anesthesia-related concerns.<sup>468</sup> As the specialist who makes the final determination of whether a patient is fit to proceed with anesthesia and surgery, the responsible anesthesiologist is a critical "end-user" of any assessment performed in a preoperative evaluation clinic. Consequently, a reliance on nonanesthesia specialists can result in preoperative assessments that are deemed inadequate by the responsible anesthesia providers and that lead to potential last-minute surgical delays and cancellations, with associated significant frustration among both patients and surgeons. Conversely, preoperative-to-intraoperative communication is likely significantly improved when anesthesiologists are responsible for most outpatient preanesthesia evaluations, as confirmed by previous studies showing fewer last-minute case cancellations,<sup>14,20,22,469</sup> shorter durations of hospitalization,<sup>22,469,470</sup> lower hospital costs,<sup>469</sup> and possibly reduced postoperative mortality,<sup>471</sup> with institution of anesthesia-led preoperative evaluation programs.

Awareness of the local hospital context is critical if a preoperative evaluation program is to have good outcomes. In a hospital with limited resources that has mostly healthy outpatient and same-day-admission surgical patients, the anesthesia group may be unable to evaluate all patients preoperatively in a clinic before the day of surgery. In this situation, the preoperative program must develop a means

for accurate screening and triage of patients based on their current health status. An accurate triage process helps target the use of preoperative clinic visits only among selected higher-risk patients without compromising patients' quality of care and outcomes.<sup>24</sup> An example of such a triage process may involve having patients initially complete an anesthesia screening questionnaire in their surgeons' office. This questionnaire can be a Web-based online document or even a paper version that would then be faxed to the anesthesia group before the date of surgery. The anesthesia group can develop local context-specific screening questionnaires, or adopt published instruments developed for this purpose.<sup>472,473</sup> In the case of a patient with a questionable medical history, a telephone call by the anesthesiologist could clarify any issues of concern. This opportunity to review a patient's medical history before the day of surgery helps reduce unresolved or unexpected medical concerns on the day of surgery. It also helps determine whether a patient requires formal preoperative consultation in advance of the surgical procedure, as opposed to evaluation on the day of surgery itself.

Conversely, anesthesia departments at hospitals with many medically complex surgical patients may benefit from the establishment of a formal preoperative evaluation facility with multiple examination rooms, dedicated staffing, and a full-time operational system. The establishment of a successful preoperative evaluation clinic requires commitment, collaboration, and support from several hospital disciplines.<sup>14</sup> At a minimum, the departments of anesthesia, surgery, nursing, and hospital administration must agree that such a clinic has value for the hospital, and they must commit to support its operational goals.

## COLLABORATION, COMMITMENT, AND TEAMWORK

The preoperative evaluation clinic is a partnership among the departments of anesthesia, surgery, nursing, and hospital administration to achieve common goals. This collaboration conveys the important theme that the new clinical program is an integrated enterprise that requires shared obligation, endeavor, and financial responsibility. Although these clinics are best led by anesthesiologists,<sup>14,20,22,469</sup> collaborative engagement with medical specialists (e.g., cardiologists, geriatricians) and hospitalists remains important to the success of any preoperative program. These nonanesthesia specialties provide unique expertise in the preoperative management of selected medically complex patients; furthermore, they can facilitate enhanced postoperative monitoring of high-risk patients through, for example, the comanagement model of postoperative care (see section on "Role of the Medical Consultant in Preoperative Evaluation").

Surgeons may be initially reluctant to send their patients to a newly established anesthesia-led preoperative evaluation clinic. This reluctance often stems from an unclear understanding of the benefits of outpatient preoperative anesthesia evaluation. Consequently, the surgeons' hesitation can be reduced by clearly identifying the specific advantages of an integrated anesthesia-led preoperative evaluation program. First, the proven benefits of anesthesiology-led preoperative evaluation should be highlighted.<sup>14,20,22,469-471</sup>

Second, anesthesiologists should emphasize the important practical advantages of an integrated assessment of medically complex surgical patients. Specifically, when relevant medical concerns are identified before the surgical procedure, the preoperative program can acquire all relevant prior medical data, coordinate any additional workup or consultation, prearrange any required specialized postoperative monitoring, and discuss the case beforehand with the surgeon and responsible anesthesiologist. This approach ensures that when such a patient presents for the operation, the responsible anesthesia provider is satisfied to proceed with the surgical procedure, and the perioperative team has all required medical information to manage the patient optimally during the hospitalization. This integration of the preoperative evaluation with the entire perioperative episode of care is an integral component of the Perioperative Surgical Home model.<sup>1</sup>

Third, informal assurances should be made to the surgical services that, if a patient is managed by the preoperative evaluation program, surgery will proceed without cancellation or delay by the assigned anesthesiologist unless an intervening illness or adverse medical event occurs between the outpatient evaluation and the scheduled operation. Because cancellations and delays on the day of surgery can be a prominent source of aggravation for surgeons and patients, these informal assurances would be viewed as a key strength of the newly developed preoperative program. Such assurances depend heavily on the anesthesia department's addressing relevant clinical practice variations. Specifically, issues that are subject to important interpractitioner differences, such as what fasting blood glucose level or degree of preoperative hypertension would merit cancelling a surgical case, must be discussed to achieve a departmental consensus standard. The absence of consensus standards can lead to situations in which half the anesthesia providers may proceed with a higher-risk surgical case, whereas the other half would cancel it instead. Wide inconsistency in practice will foster a lack of support among surgeons and will lead to reluctance to have their patients evaluated. Such a preoperative evaluation program is unlikely to be successful.

## ROLE OF THE MEDICAL CONSULTANT IN PREOPERATIVE EVALUATION

Use of preoperative medical consultation varies across hospitals, likely depending on the expertise in perioperative medicine among the clinicians performing preanesthesia assessments. Since exposure to preoperative evaluation is inadequate at many anesthesia residency programs,<sup>474</sup> some anesthesia departments may prefer that medical specialists take primary responsibility for preoperative evaluations at their centers. Conversely, when anesthesiologists involved with preoperative evaluation develop improved comfort with interpreting ECGs, cardiac stress tests, or other specialized tests, rates of medical consultations can be substantially reduced.<sup>17</sup>

Medical consultants have a clear role in the preoperative care of selected surgical patients. For example, these consultations can help manage unstable medical conditions (e.g., unstable angina), optimize poorly controlled medical diseases (e.g., asthma exacerbation), or facilitate clinically

indicated diagnostic workups (e.g., coronary angiography following high-risk cardiac stress test results).

Preoperative consultation by medical specialists or hospitalists can also help facilitate postoperative comanagement by these same individuals.<sup>475</sup> The comanagement model for postoperative care of surgical patients is increasingly common,<sup>476</sup> although its benefits with respect to clinical outcomes and healthcare costs remain uncertain.<sup>477-482</sup> Multidisciplinary collaboration with medical consultants can be especially helpful for perioperative management of complex or uncommon medical disorders. Indeed, some clinical practice guidelines recommend such multidisciplinary team management for patients with known cardiac disease undergoing high-risk noncardiac surgery,<sup>9</sup> as well as patients with significant pulmonary hypertension or adult congenital heart disease undergoing noncardiac surgery.<sup>7</sup>

Despite these theoretical benefits, preoperative medical consultation has shown a variable effect on postoperative outcomes. A randomized trial of outpatient preoperative evaluation demonstrated fewer last-minute surgical cancellations but no difference in hospital length of stay, as well as an increase in consultations.<sup>483</sup> In other nonrandomized studies, medical consultation was associated with increases in specialized testing, costs, hospital length of stay, and mortality.<sup>484,485</sup> Conversely, a transition from an anesthesiologist-led to a hospitalist-led preoperative assessment clinic was associated with reduced hospital length of stay in high-risk patients,<sup>486</sup> while preoperative geriatric consultation was associated with improved postoperative 90-day outcomes (i.e., survival, hospital length of stay, need for supported discharge, hospital readmission) in elderly patients (≥65 years) undergoing major elective noncardiac surgery.<sup>487</sup> Potential reasons for this variable effect may be the absence of recommendations or new interventions resulting from many medical consultations,<sup>488,489</sup> as well as disagreements among medical specialists, anesthesiologists, and surgeons on the intended purpose of these consultations.<sup>468</sup> In addition, increased burden of comorbidity is a very small determinant of whether patients are referred for preoperative medical consultations,<sup>490-492</sup> a finding suggesting poor patient selection during referral to medical specialists. Thus, during preoperative evaluation, the anesthesiologist should ensure that any referrals to medical specialists before surgery involve appropriate matching of patient profiles to specialist expertise. For example, patients with high-risk IHD should be referred to a cardiologist, while frail elderly patients should be referred to a geriatrician.

## STRUCTURES AND ACTIVITIES OF THE PREOPERATIVE EVALUATION CLINIC

The daily operations of a preoperative evaluation clinic vary based on the patient volume, the general level of medical complexity among surgical patients, the type of available clinic facilities, and staffing resources. Nonetheless, a general operational structure can be proposed based on examination of several preoperative clinic models currently in practice.

Centers with large surgical case volumes should have their patients formally scheduled in the clinic before the day of evaluation, to allow for medical records and relevant

outside information to be acquired and collated. The surgeon's office should schedule this clinic appointment at the same time that it books the operating room case. To ensure timely patient access and flow through the facility, these appointments should be booked using an efficient clinic scheduling system. Ideally, appointments should be scheduled to allow sufficient time between the clinic visit and the scheduled surgical procedure, to facilitate any additional preoperative testing, consultations, or interventions. Some degree of flexibility in the clinic schedule is also needed, especially to accommodate patients who have urgent indications for surgery. One approach for incorporating some flexibility is to include a few open appointment slots in the daily clinic schedule that can be used as needed for last-minute patient referrals. Such flexibility is required for individuals residing in rural and remote areas, who have been reported to have reduced rates of access to preoperative evaluation clinic facilities.<sup>493</sup> Anesthesiologists at some centers have also adopted telemedicine technology (defined as healthcare delivery and sharing of medical knowledge over a distance using telecommunications systems)<sup>494</sup> so that patients residing at remote locations can undergo preanesthesia consultations without traveling long distances to the clinic.<sup>495</sup>

At the clinic, a clinician interviews and examines the patient, obtains historical medical information and outside records, and determines whether (and which) additional laboratory tests, ECGs, radiographs, or other diagnostic tests are required. Phlebotomy, ECG, and hospital admitting and insurance registration services are typically available in the preoperative clinic facility. The ECGs are assessed during the clinic visit itself, whereas laboratory test results are evaluated at the end of each clinic day, with follow-up of abnormal findings as needed. In this manner, significant abnormalities can be addressed immediately; thus, any required delays or cancellations of surgical cases can occur well in advance of the scheduled day of surgery. This centralization of multiple services is also a significant convenience for patients, who no longer have to visit multiple hospital locations to complete their preoperative requirements. This arrangement should also centralize all medical data relevant to the scheduled hospital admission into a single chart, which remains in the preoperative evaluation clinic area until the date of surgery. In addition to addressing medical aspects relevant to the scheduled surgery, the preoperative evaluation program plays an important role in educating surgical patients. Typically, both the clinician performing the preoperative assessment and a specifically trained nurse educator discuss the forthcoming perioperative process with each patient and family members. By increasing patients' awareness of important components pertaining to their scheduled hospital admission (e.g., analgesic options, risks of anesthesia), this education process can decrease patients' anxiety,<sup>18</sup> as well as increase their willingness to receive regional analgesia.<sup>19</sup> The types of clinicians who perform the preanesthesia assessment include anesthesiologists and specially trained nurse practitioners. Some authors have questioned whether the responsible anesthesiologist in the operating room would be satisfied with preanesthesia assessments performed by another individual.<sup>496</sup> Patients themselves often report a preference for having the same anesthesiologist in both the preoperative

clinic and the operating room.<sup>497</sup> Nonetheless, it is simply not feasible for all patients in the preoperative clinic to be evaluated by their eventual anesthesia providers. Furthermore, a large Dutch cohort study of about 21,000 surgical patients demonstrated that responsible anesthesia providers were satisfied with 95% of outpatient preanesthesia assessments performed by other anesthesiologists or trained nurses.<sup>498</sup>

Preoperative programs must adopt several strategies to ensure that anesthesia providers in the operating room will be satisfied with the quality of outpatient preoperative assessments. First, the anesthesia department must develop consensus standards for determining when patients should have scheduled surgery cancelled for medical reasons. Second, the documentation required for all preanesthesia assessments in the clinic should be standardized. This standardization helps prevent situations in which an assessment does not contain information needed by the anesthesia provider in the operating room to determine a patient's fitness for surgery or to develop an anesthetic management plan. Some national anesthesiology groups have initiated work on consensus-based documentation standards for all preanesthesia assessments.<sup>23</sup> Strategies for improving the consistency of documentation across preanesthesia assessments include the use of checklists, as well as structured electronic or paper-based forms for documenting preanesthesia assessments. Third, all nurse practitioners or other nonanesthesia clinicians assessing patients in the clinic should undergo an intensive and ongoing education in preoperative assessment. Anesthesiologists with strong interest and expertise in preoperative evaluation should lead this education program. Previous research has shown that well-trained nurses do perform effectively in both screening and evaluating patients in preoperative clinics.<sup>499-501</sup>

## IMPACT ON OPERATING ROOM EFFICIENCY AND OUTCOMES

Anesthesia-led preoperative assessment clinics have had positive impact on operating room efficiency and outcomes (see the earlier section "Goals and Benefits of Preanesthesia Evaluation"). The demonstrated benefits of these clinics include fewer case cancellations on the day of surgery,<sup>14,20,22,469</sup> shorter duration of hospitalization,<sup>22,469,470</sup> and a possible reduction in postoperative mortality.<sup>471</sup> Other mechanisms whereby preoperative evaluation clinics reduce healthcare costs include more selective ordering of preoperative laboratory tests and specialist referrals.<sup>14,16,17</sup> Thus, although preoperative evaluation programs do incur costs (e.g., facility development costs, staff salaries), they can still lead to an overall reduction in hospital costs as a result of these associated cost savings.<sup>469</sup>

## PATIENT SATISFACTION WITH PREOPERATIVE EVALUATION CLINICS

In addition to addressing perioperative efficiencies and clinical outcomes, preoperative programs should also consider the experience and satisfaction of patients attending their clinics. During development of strategies to improve patient satisfaction, the underlying determinants of improved satisfaction

should be considered. They include being assessed by the same anesthesiologist who will administer anesthesia in the operating room, shorter wait times in the clinic, and good quality of communication from the clinic staff.<sup>497,502,503</sup> Because it is simply not feasible to have all patients in the clinic seen by their eventual anesthesia providers, the major focus should be on improving wait times and the quality of communication. Changes in appointment booking systems,<sup>504</sup> process flows, and clinic operations can decrease wait times,<sup>499</sup> which in turn can substantially improve patients' satisfaction.<sup>499</sup> In addition, preoperative programs can ensure that patients receive an accurate estimate of average waiting times before their scheduled clinic visit, and use any encountered wait times to conduct other clinic-related activities (e.g., physical therapy instructions, video-based preoperative education).

## Conclusion

The practice of anesthesiology has changed. The expanding role of the anesthesiologist outside the operating room will redefine the specialty's contribution to high-quality patient care in the healthcare system. Within the context of preoperative evaluation, anesthesiologists must be knowledgeable and adept at assessing patients of highly varying medical complexity, whether in an outpatient preoperative evaluation clinic before the day of the surgical procedure or at the bedside immediately before induction of anesthesia. Anesthesiologists must be familiar with the impact of a broad range of chronic and acute medical conditions on patients' risks for anesthesia and surgery. In addition, this role entails awareness of multiple practice guidelines, regulatory requirements, and approaches for efficient management of outpatient clinics. Despite this evolving and expanding role of anesthesiologists in preoperative care, the primary purpose of preoperative evaluation will never change. It is the clinical foundation for guiding perioperative patient management, and it has the potential to reduce perioperative morbidity and enhance patient outcome.

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## KEY POINTS

- The history and physical examination most accurately predict the risks of anesthesia and the likelihood of required changes in monitoring or therapy.
- For diabetic patients, end-organ dysfunction and the degree of glucose control in the perioperative and periprocedural periods are the critical issues with regard to risk.
- The keys to managing blood glucose levels in diabetic patients perioperatively are to set clear goals and then monitor blood glucose levels frequently enough to adjust therapy to achieve these goals.
- Obesity is associated with multiple comorbid conditions, including diabetes, hyperlipidemia, and cholelithiasis, but the primary concern is derangements of the cardiopulmonary system.
- Obstructive sleep apnea is important to recognize because of the increased sensitivity to and the consequence of the depressing effects of hypnotics and opioids on airway muscle tone and respiration, as well as the difficulty with laryngoscopy and mask ventilation.
- Although no controlled, randomized prospective clinical studies have been performed to evaluate the use of adrenergic receptor blocking drugs in patients undergoing resection of pheochromocytoma, the preoperative use of such drugs is generally recommended.
- For patients with hypertension, the routine administration of all drugs preoperatively is recommended, except angiotensin-converting enzyme inhibitors and angiotensin II antagonists.
- Evaluation of a patient with cardiovascular disease depends on clinical risk factors, the extent of surgery, and exercise tolerance.
- In patients with pulmonary disease, the following should be assessed: dyspnea, coughing and the production of sputum, recent respiratory infection, hemoptysis, wheezing, previous pulmonary complications, smoking history, and physical findings.
- In patients with pulmonary disease, several strategies have been suggested, including cessation of smoking 8 weeks or more preoperatively.
- Risk factors for perioperative renal dysfunction include advanced age, congestive heart failure, previous myocardial revascularization, diabetes, and increased baseline blood creatinine concentration.
- One of the primary objectives for a patient with renal disease is ensuring that the renal dysfunction is not augmented and thereby increasing the chance for renal failure, coma, and death.
- Mild perioperative anemia may be clinically significant only in patients with ischemic heart disease.
- Careful management of long-term drug administration should include questions about the effects and side effects of alternative as well as prescription drugs.

This chapter reviews many conditions requiring special preoperative and preprocedure evaluation, intraoperative or intraprocedure management, or postprocedure care. Patients undergoing surgical procedures move through a continuum of medical care to which a primary care physician, an internist or pediatrician, an anesthesiologist, and a surgeon, gastroenterologist, radiologist, or obstetrician-gynecologist contribute to ensure the best outcome possible. It may also involve comanagement with a hospitalist. No aspect of medical care requires greater cooperation among physicians than does performance of a surgical operation or a complex procedure involving multiple specialists and the perioperative care of a patient. Moreover, nowhere else can counseling make so huge a difference

in so many lives. The preoperative evaluation also represents a time when education on tobacco cessation, physical inactivity, brain health, and poor food choices can be discussed. The importance of integrating physicians' expertise is even greater within the context of the increasing life-span of our population. As the number of older adults and very old adults (those  $>85$  years old) grows, so does the need of surgical patients for preoperative consultation to help plan for comorbidity, frailty, and multiple drug regimens, the knowledge of which is crucial to successful patient management. At a time when medical information is encyclopedic, it is difficult, if not impossible, for even the most conscientious anesthesiologist to keep abreast of the medical issues relevant to every aspect of perioperative

or periprocedure patient management. This chapter reviews such issues with primary emphasis on the anesthesiologist providing preoperative evaluation and care, rather than transferring these responsibilities to other providers.

As with “healthy” patients, the history and physical examination most accurately predict not only the associated risks but also the likelihood of whether a monitoring technique, change in therapy, or “prehabilitation” will be beneficial or necessary for survival. This chapter emphasizes instances in which specific information should be sought in history taking, physical examination, or laboratory evaluation. Although controlled studies designed to confirm that optimizing a patient’s preoperative or preprocedure physical condition would result in a less frequent rate of morbidity have not been performed for most diseases, it is logical to assume that such is the case. That such preventive measures would cost less than treating the morbidity that would otherwise occur is an important consideration in a cost-conscious environment.

Minimally invasive procedures such as cataract extraction, magnetic resonance imaging (MRI), or diagnostic arthroscopy, performed in conjunction with the best current anesthetic practices, may pose no greater risk than daily living and thus may not be considered an opportunity for special evaluation. Nevertheless, the preoperative evaluation may identify conditions that could change perioperative management and that may improve both throughput of surgery and the speed of recovery. Examples include the following: ensuring the administration of long-term medications such as a  $\beta$ -adrenergic blocking drug, aspirin for patients with coronary stents, or a statin (or any combination); administering a histamine type 2 ( $H_2$ ) antagonist 1 to 2 hours before entry into the operating room; ensuring the availability of equipment to measure blood glucose levels; obtaining a history of the patient’s diabetic course and treatment from the primary care physician, as well as from the patient; and performing a fiberoptic laryngoscopic examination or procuring additional skilled attention.

The following conditions are discussed in this chapter:

1. Diseases involving the endocrine system and disorders of nutrition (discussed first because of its increasing importance to care)
2. Diseases involving the cardiovascular system
3. Disorders of the respiratory and immune system
4. Diseases of the central nervous system (CNS), neuromuscular diseases, and mental disorders
5. Diseases involving the kidney, infectious diseases, and disorders of electrolytes
6. Diseases involving the gastrointestinal (GI) tract or the liver
7. Diseases involving hematopoiesis and various forms of cancer
8. Diseases of aging or those that occur more commonly in older adults, as well as chronic and acute medical conditions requiring drug therapy

## Role of the Primary Care Physician or Consultant

The roles of the primary care physician or consultant are not to select and suggest anesthetic or surgical methods but

### BOX 32.1 Guidelines for Consultation Practice

- Complete a prompt, thorough, generalist-oriented evaluation.
- Respond specifically to the question or questions posed.
- Indicate clearly the perioperative importance of any observations and recommendations outside the area of initial concern.
- Provide focused, detailed, and precise diagnostic and therapeutic guidance.
- Emphasize verbal communication with the anesthesiologist and surgeon, particularly to resolve complex issues.
- Avoid chart notations that unnecessarily create or exacerbate regulatory or medicolegal risk.
- Use frequent follow-up visits in difficult cases to monitor clinical status and compliance with recommendations.

From American College of Physicians. Medical consultation. *Medical Knowledge Self-Assessment Program IX*. Part C. Book 4. Philadelphia: American College of Physicians; 1992: 939.

rather to optimize the patient’s preoperative and preprocedure status regarding conditions that increase the morbidity and mortality associated with surgery and to alert the anesthesia care team about these conditions. Within the context of shared decision making, the primary care physician may also be involved in the decision to proceed with surgery.

Quotations and a box in a Medical Knowledge Self-Assessment Program published by the leading organization representing internists, the American College of Physicians, highlight this role for the consultant<sup>1</sup>:

*Effective interaction with colleagues in other specialties requires a thorough grounding in the language and science of these other disciplines as well as an awareness of basic guidelines for consultation [Box 32.1]. The consulting internists’ role in perioperative care is focused on the elucidation of medical factors that may increase the risks of anesthesia and surgery. Selecting the anesthetic technique for a given patient, procedure, surgeon, and anesthetist is highly individualized and remains the responsibility of the anesthesiologist rather than the internist.*

Optimizing a patient’s preoperative and preprocedure condition and, in settings with a preoperative clinic, counseling a patient about needed future lifestyle changes such as exercise, food choices, and tobacco cessation are cooperative ventures between the anesthesiologist and the internist, pediatrician, surgeon, or family physician. If available, the primary care physician should affirm that the patient is in the very best physical state attainable (for that patient), or the anesthesiologist and primary care physician should do what is necessary to optimize that condition. Although not yet definitively proven, prehabilitation prior to surgery has been advocated by many groups.

Primary care physicians can prepare and treat a patient to provide optimal conditions for daily life. The preoperative clinic should collaborate with the primary care physician to start the process of preparing the patient for the needs of surgery or complex procedures. Although such education is more readily available and of better quality than in previous decades, and although cardiologic organizations have provided considerable data on the importance of this aspect of care,<sup>2-4</sup> the primary care physician’s training, knowledge,

and ability may not include an in-depth understanding of the perioperative evaluation. Without understanding the physiologic changes that occur perioperatively, appropriate therapy is difficult to prescribe. It is therefore part of the anesthesiologist's job to guide the patient's consultants about the type of information needed from the preoperative and preprocedure consultation.

## Diseases Involving the Endocrine System and Disorders of Nutrition

### PANCREATIC DISORDERS

#### Preoperative and Preprocedure Diabetes Mellitus

Diabetes mellitus is a heterogeneous group of disorders that have the common feature of a relative or absolute insulin deficiency. The disease is characterized by a multitude of hormone-induced metabolic abnormalities, diffuse microvascular lesions, and long-term end organ complications. The diagnosis of diabetes is made with a fasting blood glucose level greater than 110 mg/dL (6.1 mmol/L), and impaired glucose tolerance is diagnosed if the fasting glucose level is less than 110 mg/dL (6.1 mmol/L) but greater than 100 mg/dL (5.5 mmol/L). Diabetes can be divided into two very different diseases that share the same long-term end-organ complications. Type 1 diabetes is associated with autoimmune diseases and has a concordance rate of 40% to 50% (i.e., if one of a pair of monozygotic twins had diabetes, the likelihood that the other twin would have diabetes is 40%-50%). In type 1 diabetes, the patient is insulin deficient, principally from autoimmune destruction of the pancreatic  $\beta$  cells, and susceptible to ketoacidosis if insulin is withheld. Type 2 diabetes has a concordance rate approaching 80% (i.e., genetic material is both necessary and sufficient for the development of type 2 diabetes).<sup>4a</sup> How markedly the aging and end-organ effects of these genes are expressed is based on lifestyle choices of food and physical activity. These patients are not susceptible to the development of ketoacidosis in the absence of insulin, and they have peripheral insulin resistance through multiple defects with insulin action and secretion. Patients with non-insulin-dependent (type 2) diabetes account for the majority (>90%) of the diabetic patients in Europe and North America. These individuals tend to be overweight, relatively resistant to ketoacidosis, and susceptible to the development of a hyperglycemic-hyperosmolar nonketotic state. Plasma insulin levels are normal or increased in type 2 diabetes but are relatively low for the level of blood glucose. This hyperinsulinemia by itself is postulated to cause accelerated cardiovascular disease. Gestational diabetes develops in more than 3% of all pregnancies and increases the risk of developing type 2 diabetes by 17% to 63% within 15 years.

Type 1 and type 2 diabetes differ in other ways as well. Contrary to long-standing belief, a patient's age does not allow a firm distinction between type 1 and type 2 diabetes; type 1 diabetes can develop in an older person, and clearly, type 2 diabetes can develop in overweight children. Type 1 diabetes is associated with a 15% prevalence of other autoimmune diseases, including Graves disease, Hashimoto thyroiditis, Addison disease, and myasthenia gravis.

Over the next decade, the prevalence of diabetes is expected to increase by 50%. This growth is primarily the

result of the increase in type 2 diabetes caused by excessive weight gain in adults and now also in the pediatric population. Large clinical studies show that long-term, strict control of blood glucose levels and arterial blood pressure, along with regular physical activity, results in a major delay in microvascular complications and perhaps indefinite postponement of type 2 diabetes in patients.<sup>5,6</sup>

The common administered drugs can be classified into eight major groups: acarbose, biguanides (e.g., metformin), dipeptidyl peptidase-4 inhibitors (e.g., sitagliptin, saxagliptin, vildagliptin), glucagon-like peptide-1 receptor agonists (e.g., albiglutide, dulaglutide, or exenatide), meglitinide (e.g., repaglinide or nateglinide), sodium-glucose transport protein 2 inhibitors (e.g., canagliflozin or empagliflozin), sulfonylureas (e.g., glibenclamide, glipizide, glimepiride, gliquidone), and thiazolidinediones (e.g., pioglitazone or rosiglitazone).<sup>6a</sup>

Patients with insulin-dependent diabetes tend to be younger, nonobese, and susceptible to the development of ketoacidosis. Plasma insulin levels are low or un-measurable, and therapy requires insulin replacement. Patients with insulin-dependent diabetes experience an increase in their insulin requirements in the post-midnight hours, which may result in early morning hyperglycemia (dawn phenomenon). This accelerated glucose production and impaired glucose use reflect nocturnal surges in secretion of growth hormone (GH). Physiologically normal patients and diabetic patients taking insulin have steady-state levels of insulin in their blood. Absorption of insulin is highly variable and depends on the type and species of insulin, the site of administration, and subcutaneous blood flow. Nevertheless, attainment of a steady state depends on periodic administration of the preparations received by the patient. Thus it seems logical to continue the insulin combination perioperatively that the patient had been receiving after assessing previous blood glucose control.<sup>6b</sup>

The major risk factors for diabetic patients undergoing surgery are the end-organ diseases associated with diabetes: cardiovascular dysfunction, renal insufficiency, joint collagen tissue abnormalities (limitation in neck extension, poor wound healing), inadequate granulocyte production, neuropathies, and infectious complications.<sup>7-15</sup> Thus a major focus of the anesthesiologist should be the preoperative and preprocedure evaluation and treatment of these diseases to ensure optimal preoperative and preprocedure conditions. Poor preoperative glucose control, as measured by the hemoglobin A<sub>1C</sub> (glycosylated hemoglobin) level, is an independent predictor of worse perioperative outcome.<sup>16-18</sup>

#### Glucotoxicity

Long-term tight control of blood glucose has been motivated by concern for three potential glucotoxicities, in addition to the results from major randomized outcome studies involving diabetic patients.<sup>5,13</sup>

1. Glucose itself may be toxic because high levels can promote nonenzymatic glycation reactions that lead to the formation of abnormal proteins. These proteins may weaken endothelial junctions and decrease elastance, which is responsible for the stiff joint syndrome (and difficult intubation secondary to fixation of the atlanto-occipital joint), as well as decrease wound-healing tensile strength.

2. Glycemia also disrupts autoregulation. Glucose-induced vasodilation prevents target organs from protecting against increases in systemic blood pressure. A glycosylated hemoglobin level of 8.1% is the threshold at which the risk for microalbuminuria increases logarithmically. A person with type 1 diabetes who has microalbuminuria of greater than 29 mg/day has an 80% chance of experiencing renal insufficiency. The threshold for glycemic toxicity differs for various vascular beds. For example, the threshold for retinopathy is a glycosylated hemoglobin value of 8.5% to 9.0% (12.5 mmol/L or 225 mg/dL), and that for cardiovascular disease is an average blood glucose value of 5.4 mmol/L (96 mg/dL). Thus different degrees of hyperglycemia may be required before different vascular beds are damaged. Another view is that perhaps severe hyperglycemia and microalbuminuria are simply concomitant effects of a common underlying cause. For instance, diabetic patients in whom microalbuminuria develops are more resistant to insulin, insulin resistance is associated with microalbuminuria in first-degree relatives of patients with type 2 diabetes, and persons who are normoglycemic but subsequently have clinical diabetes are at risk for atherosclerosis before the onset of disease.

Diabetes itself may not be as important to perioperative outcome as are its end-organ effects. Epidemiologic studies segregated the effects of diabetes itself on the organ system from the effects of the complications of diabetes (e.g., cardiac, nervous system, renal, and vascular disease) and the effects of old age and the accelerated aging that diabetes causes. Even in patients requiring intensive care unit (ICU) management, long-standing diabetes does not appear to be as important an issue as the end-organ dysfunction that exists and the degree of glucose control in the perioperative or periprocedure and ICU periods.<sup>6b,8-13</sup>

The World Health Organization's surgical safety checklist bundle suggests control with a target perioperative blood glucose concentration of 6 to 10 mmol/L (acceptable range, 4-12 mmol/L) or 100 to 180 mg/dL.<sup>19</sup> Poor perioperative glycemic control has a significant impact on the risk of postoperative infection across a variety of surgical specialities.<sup>20</sup> Different regimens permit almost any degree of perioperative control of blood glucose levels, but the tighter the control desired, the greater the risk of hypoglycemia. Therefore, debate regarding optimal control during the perioperative period has been extensive. Tight control retards all these glucotoxicities and may have other benefits in retarding the severity of diabetes itself.<sup>5-13,21</sup> Management of intraoperative glucose may be influenced by specific situations, such as the following: the type of operation, pregnancy,<sup>22</sup> expected global CNS insult, the bias of the patient's primary care physician, or the type of diabetes.

Much of the research on perioperative control is derived from studies in the ICU, as opposed to the operating room. The first major trial demonstrating the benefit of tight glucose control was in medical ICU patients in Leuven, Belgium.<sup>23</sup> The most recent trial was from the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) group.<sup>24</sup> In this randomized controlled trial, the investigators examined the associations between moderate and severe hypoglycemia

(blood glucose, 41-70 mg/dL [2.3-3.9 mmol/L] and  $\leq$ 40 mg/dL [2.2 mmol/L], respectively) and death among 6026 critically ill patients in ICUs. Intensive glucose control leads to moderate and severe hypoglycemia, both of which are associated with an increased risk of death. The association exhibits a dose-response relationship and is strongest for death from distributive shock. The optimal perioperative management has been reviewed elsewhere.<sup>25</sup> Guidelines have been developed on the use of insulin infusions in the critical care unit to achieve these goals (Table 32.1).<sup>26</sup>

### Diabetes and Accelerated Physiologic Aging

Adverse perioperative outcomes have repeatedly and substantially correlated with the age of the patient,<sup>2,3,27-30</sup> and diabetes does cause physiologic aging. When one translates the results of the Diabetes Control and Complications Trials into age-induced physiologic changes, a patient with type 1 diabetes who has poor control of blood glucose ages approximately 1.75 years physiologically for every chronologic year of the disease and 1.25 years if blood glucose has been controlled tightly.<sup>27-29</sup> A patient with type 2 diabetes ages approximately 1.5 years for every chronologic year of the disease and approximately 1.06 years with tight control of blood glucose and blood pressure.<sup>6,27-29,31</sup> Thus when providing care for a diabetic patient, one must consider the associated risks to be those of a person who is much older physiologically; the physiologic age of a diabetic patient is considerably older than that person's calendar age just by virtue of having the disease.<sup>1</sup>

Obesity and lack of physical exercise seem to be major contributors to the increasing prevalence of type 2 diabetes. As with type 1 diabetes, tight control of blood glucose, increased physical activity, and reduction in weight appear to reduce the accelerated aging associated with type 2 diabetes, and possibly delay the appearance of the disease and aging from it substantially.<sup>27-29,31</sup> Although such a reduction in aging should reduce the perioperative risk for diabetic patients, no controlled trials have confirmed this theory.

The key to managing blood glucose levels perioperatively in diabetic patients is to set clear goals and then monitor blood glucose levels frequently enough to adjust therapy to achieve these goals.<sup>31a</sup>

### Other Conditions Associated With Diabetes

Diabetes is associated with microangiopathy (in retinal and renal vessels), peripheral neuropathy, autonomic dysfunction, and infection. Diabetic patients are often treated with angiotensin-converting enzyme (ACE) inhibitors, even in the absence of gross hypertension, in an effort to prevent the effects of disordered autoregulation, including renal failure.<sup>5,6,32</sup>

Preoperatively, assessment and optimization of treatment of the potential and potent end-organ effects of diabetes are at least as important as assessment of the diabetic patient's current overall metabolic status. The preoperative evaluation of diabetic patients is also discussed in Chapter 31.

The presence of autonomic neuropathy likely makes the operative period more hazardous and the postoperative period crucial to survival. Evidence of autonomic neuropathy may be routinely sought before the surgical procedure. Patients with diabetic autonomic neuropathy are at increased risk for gastroparesis (and consequent aspiration

**TABLE 32.1** Recommended Glucose Target Ranges for Intensive Care Patients and Related Subgroups

Society, Guideline	Patient Group	Trigger Blood Glucose Value to Start Insulin Infusion (mM [mg/dL])	Target range, (mM [mg/dL])	Rationale
Society of Critical Care Medicine's clinical practice guideline <sup>26</sup>	General recommendation	8.3 (150)	5.6-8.3 (100-150)	
	Cardiac surgical patients		<8.3 (150)	Decreased risk for deep sternal wound infection and death <sup>73,118-121</sup>
	Critically ill trauma patients	8.3 (150)	<10 (180)	
	Patients with traumatic brain injury	8.3 (150)	<10 (180)	
	Neurologic ICU patients	8.3 (150)	<10 (180)	
	Ischemic stroke			
	Intraparenchymal hemorrhage			
	Aneurysmal subarachnoid hemorrhage			
American Diabetes Association guidelines <sup>446</sup>	General recommendation	10 (180)	7.8-10 (140-180)	
	Adaptation		6.1-7.8 (110-140)	Adjust to lower target range in documented low rate of severe hypoglycemia
American Association of Clinical Endocrinologists <sup>447</sup>	General recommendation		7.8-10 (140-180)	
	Surgical patients		Lower range	Only in units showing low rates of hypoglycemia
Surviving Sepsis Campaign <sup>448</sup>	General recommendation	10 (180)	<10 (180)	Based on the NICE-SUGAR study
Clinical Practical Guideline from the American College of Physicians <sup>449</sup>	General recommendation		7.8-11.1 (140-200)	If insulin infusion is applied; however, guideline does not recommend intensive insulin therapy
Spanish Society of Intensive Care Medicine and Coronary Units <sup>450</sup>	General recommendation		<8.3 (150)	
French Society of Anesthesia and Intensive Care <sup>451</sup>	General recommendation		10 (180)	
	Surgical patients		<6.1 (110)	
	Cardiac patients		<6.1 (110)	
Society of Thoracic Surgeons <sup>452</sup>	Cardiac surgical patients		<10 (180) except <8.3 (150) for those with devices in place	

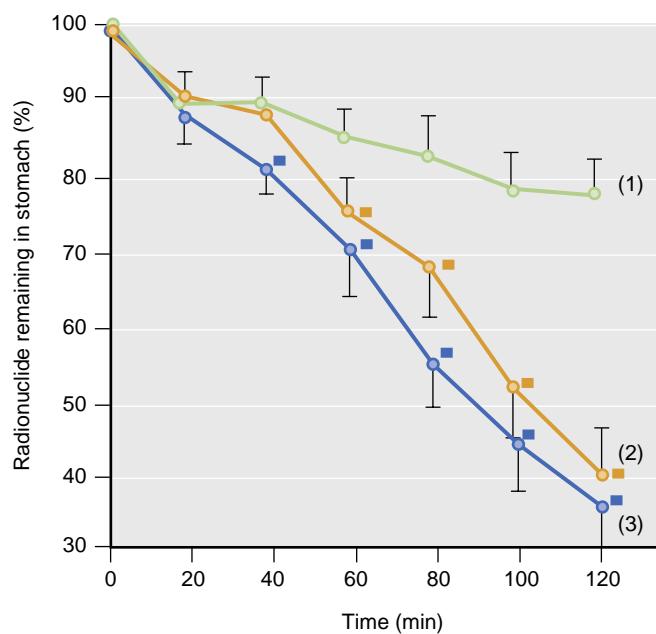
ICU, Intensive care unit; NICE-SUGAR, normoglycemia in intensive care evaluation and survival using glucose algorithm regulation.

Data from Sebranek JJ, Lugli AK, Coursin DB. Glycaemic control in the perioperative period. *Br J Anaesth.* 2013;111(suppl 1):i18-i34; and Jacobi J, Bircher N, Krinsley J, et al. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. *Crit Care Med.* 2012;40:3251-3276.

of gastric contents) and for perioperative cardiorespiratory arrest. Diabetic patients who exhibit signs of autonomic neuropathy, such as early satiety, lack of sweating, lack of pulse rate change with inspiration or orthostatic maneuvers, and impotence, have a very frequent incidence of painless myocardial ischemia.<sup>15,33</sup> Administration of metoclopramide, 10 mg preoperatively to facilitate gastric emptying of solids, may be helpful (Fig. 32.1). Interference with respiration or sinus automaticity by pneumonia or by anesthetic agents, pain medications, or sedative drugs is likely the precipitating cause in most cases of sudden cardiorespiratory arrest. Measuring the degree of sinus arrhythmia or

beat-to-beat variability provides a simple, accurate test for significant autonomic neuropathy. The difference between the maximum and minimum heart rate on deep inspiration is normally 15 beats/min, but it is 5 beats/min or less in all patients who subsequently sustain cardiorespiratory arrest.<sup>15,33</sup>

Other characteristics of patients with autonomic neuropathy include postural hypotension with a decrease in arterial blood pressure of more than 30 mm Hg, resting tachycardia, nocturnal diarrhea, and dense peripheral neuropathy. Diabetic patients with significant autonomic neuropathy may have impaired respiratory responses to



**Fig. 32.1** Gastric emptying time (mean  $\pm$  standard deviation) of a solid test meal in three groups of patients: diabetic patients (line 1), diabetic patients given metoclopramide (10 mg intravenously) 1.5 hours before the test meal (line 2), and nondiabetic patients (line 3). (From Wright RA, Clemente R, Wathen R. Diabetic gastroparesis: an abnormality of gastric emptying of solids. *Am J Med Sci*. 1985;289:240–242.)

hypoxia and are particularly sensitive to the action of drugs that have depressant effects. These patients may warrant continuous cardiac and respiratory monitoring for 24 to 72 hours postoperatively, although this has not been tested in a rigorous, controlled trial.<sup>15</sup> In the absence of autonomic neuropathy, outpatient surgery is preferred for a diabetic patient if possible (see Table 32.1).<sup>31a</sup>

### Emergency Surgery

Many diabetic patients requiring emergency surgery for trauma or infection have significant metabolic decompensation, including ketoacidosis. Frequently, little time is available to stabilize the patient, but even a few hours may be sufficient for correction of any fluid and electrolyte disturbances that are potentially life-threatening. It is futile to delay surgery in an attempt to eliminate ketoacidosis completely if the underlying surgical condition will lead to further metabolic deterioration. The likelihood of intraoperative cardiac arrhythmias and hypotension resulting from ketoacidosis will be reduced if intravascular volume depletion and hypokalemia are at least partially treated. During the initial resuscitation phase of ketoacidosis bicarbonate should initially be avoided with crystalloid fluids, potassium repletion, and intravenous insulin therapy favored.<sup>33a</sup>

Insulin therapy is initiated with a 10-unit intravenous bolus of regular insulin, followed by continuous insulin infusion. The rate of infusion is determined most easily by dividing the last serum glucose value by 150 (or 100 if the patient is receiving steroids, has an infection, or is considerably overweight [body mass index  $\geq 35$ ]). The actual amount of insulin administered is less important than is regular monitoring of glucose, potassium, and arterial pH. The maximum rate of glucose decline is fairly constant, averaging 75 to 100 mg/dL/h, regardless of the dose of

insulin because the number of insulin binding sites is limited.<sup>34</sup> During the first 1 to 2 hours of fluid resuscitation, the glucose level may decrease more precipitously. When serum glucose reaches 250 mg/dL, the intravenous fluid should include 5% dextrose.

The volume of intravenously administered fluid required varies with the overall deficit; it ranges from 3 to 5 L and may be as large as 10 L. Despite losses of water in excess of losses of solute, sodium levels are generally normal or reduced. Furtitious hyponatremia caused by hyperglycemia or hypertriglyceridemia may result in this seeming contradiction. The plasma sodium concentration decreases by approximately 1.6 mEq/L for every 100 mg/dL increase in plasma glucose greater than normal. Initially, balanced crystalloid solution is infused at a rate of 250 to 1000 mL/h, depending on the degree of intravascular volume depletion and cardiac status. Some measure of left ventricular volume should be monitored in diabetic patients who have a history of myocardial dysfunction. Approximately one third of the estimated fluid deficit is corrected during the first 6 to 8 hours and the remaining two thirds over the next 24 hours.<sup>34a</sup>

The degree of acidosis is determined by analysis of arterial blood gases and detection of an increased anion gap (see also Chapter 48). Acidosis with an increased anion gap ( $\geq 16$  mEq/L) in an acutely ill diabetic patient may be caused by ketones in ketoacidosis, lactic acid in lactic acidosis, increased organic acids from renal insufficiency, or all three disorders. In ketoacidosis, plasma levels of acetoacetate,  $\beta$ -hydroxybutyrate, and acetone are increased. Plasma and urinary ketones can be measured semiquantitatively with Ketostix and Acetest tablets. The role of bicarbonate therapy in diabetic ketoacidosis is controversial, but could be considered in severe acidemia and hemodynamic instability as myocardial function and respiration are known to be depressed at a blood pH lower than 7.00 to 7.10.<sup>34b</sup> This careful consideration is because rapid correction of acidosis with bicarbonate therapy may result in alterations in CNS function and structure. These alterations may be caused by (1) paradoxical development of cerebrospinal fluid and CNS acidosis from rapid conversion of bicarbonate to carbon dioxide and diffusion of the acid across the blood-brain barrier, (2) altered CNS oxygenation with decreased cerebral blood flow, and (3) the development of unfavorable osmotic gradients. After treatment with fluids and insulin,  $\beta$ -hydroxybutyrate levels decrease rapidly, whereas acetoacetate levels may remain stable or even increase before declining. Plasma acetone levels remain elevated for 24 to 42 hours, long after blood glucose,  $\beta$ -hydroxybutyrate, and acetoacetate levels have returned to normal; the result is continuing ketonuria.<sup>34</sup> Persistent ketosis with a serum bicarbonate level less than 20 mEq/L in the presence of a normal glucose concentration is an indication of the continued need for intracellular glucose and insulin for reversal of lipolysis.

The most important electrolyte disturbance in diabetic ketoacidosis is depletion of total-body potassium. Deficits range from 3 to 10 mEq/kg body weight. Serum potassium levels decline rapidly and reach a nadir within 2 to 4 hours after the start of intravenous insulin administration. Aggressive replacement therapy is required. The potassium administered moves into the intracellular

space with insulin as the acidosis is corrected. Potassium is also excreted in urine because of the increased delivery of sodium to the distal renal tubules that accompanies volume expansion. Phosphorus deficiency in ketoacidosis as a result of tissue catabolism, impaired cellular uptake, and increased urinary losses may give rise to significant muscular weakness and organ dysfunction. The average phosphorus deficit is approximately 1 mmol/kg body weight; no clear guidance for replacement exists, but replacement is appropriate in patients with cardiac dysfunction, anemia, respiratory depression, or if the plasma phosphate concentration is less than 1.0 mg/dL.<sup>34</sup>

### Anticipated Newer Treatments of Diabetes

At least three major changes in the care of diabetic patients have made it to the clinical trial stage:

- Implanted (like a pacemaker) glucose analyzer with electronic transmission to a surface (watch) monitor
- New islet transplantation medication that makes islet cell transplants much more successful and rejection medication less hazardous
- Medications such as INGAP (islet neogenesis-associated protein) peptide, which may cause regrowth of normally functioning islet cells (without the need for transplantation)

Some of these treatments may radically change the therapies used in the perioperative period. If regrowth of islet cells becomes common, type 1 diabetes could all but disappear; if implanted minute-to-minute glucose reading is possible, tight control may be much easier and more expected.

### Insulinoma and Other Causes of Hypoglycemia

Hypoglycemia in persons not treated for diabetes is rare. Hypoglycemia in nondiabetic patients can be caused by such diverse entities as pancreatic islet cell adenoma or carcinoma, large hepatoma, large sarcoma, alcohol ingestion, use of  $\beta$ -adrenergic receptor blocking drugs, haloperidol therapy, hypopituitarism, adrenal insufficiency, altered physiology after gastric or gastric bypass surgery, hereditary fructose intolerance, ingestion of antidiabetic drugs, galactosemia, or autoimmune hypoglycemia.<sup>35</sup> The last four entities cause postprandial reactive hypoglycemia. Because restriction of oral intake prevents severe hypoglycemia, the practice of keeping the patient NPO (nothing by mouth) and infusing small amounts of a solution containing 5% dextrose greatly lessens the possibility of perioperative postprandial reactive hypoglycemia. The other causes of hypoglycemia can cause serious problems during the perioperative period.<sup>35</sup>

Symptoms of hypoglycemia fall into one of two groups: adrenergic excess (tachycardia, palpitations, tremulousness, or diaphoresis) or neuroglycopenia (headache, confusion, mental sluggishness, seizures, or coma). All these symptoms may be masked by anesthesia, so blood glucose levels should be determined frequently in at-risk patients to ensure that hypoglycemia is not present. Because manipulation of an insulinoma can result in massive insulin release, this tumor should probably be operated on only at centers equipped with a mechanical pancreas. Perioperative use of the somatostatin analogue octreotide, which suppresses insulin release from such tumors, makes the perioperative period safer in anecdotal experience.

## DISORDERS OF NUTRITION, INCLUDING OBESITY

### Hyperlipoproteinemia, Hyperlipidemia, and Hypolipidemia

Hyperlipidemia may result from obesity, estrogen or corticoid therapy, uremia, diabetes, hypothyroidism, acromegaly, alcohol ingestion, liver disease, inborn errors of metabolism, or pregnancy. Hyperlipidemia may cause premature coronary, peripheral vascular disease, or pancreatitis.

Coronary events can be decreased by treating individuals with even normal levels of low-density lipoprotein (LDL) cholesterol with statins (3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors)—through an increase in high-density lipoprotein (HDL) and a decrease in LDL cholesterol levels. This approach has markedly decreased the rate of myocardial reinfarction in high-risk patients.<sup>36-38</sup> Secondary prevention efforts were successful when these high-risk patients stopped smoking, reduced their arterial blood pressure, controlled stress, increased physical activity, and used aspirin, folate,  $\beta$ -blocking drugs, angiotensin inhibitors, diet, and other drugs to reduce their levels of LDL and increase their levels of HDL.

Although controlling the diet remains a major treatment modality for all types of hyperlipidemia, the drugs fenofibrate and gemfibrozil, which are used to treat hypertriglyceridemia, can cause myopathy, especially in patients with hepatic or renal disease; clofibrate is also associated with an increased incidence of gallstones. Cholestyramine binds bile acids, as well as oral anticoagulants, digitalis drugs, and thyroid hormones. Nicotinic acid causes peripheral vasodilation and should probably not be continued through the morning of the surgical procedure. Probucol (Lorelco) decreases the synthesis of apoprotein A-1; its use is associated on rare occasion with fetid perspiration or prolongation of the QT interval, or both, and sudden death in animals.

The West of Scotland Coronary Prevention Study and its congeners produced convincing evidence that drugs in the statin class prevent the morbidity and mortality related to arterial aging and vascular disease, as well as their consequences, such as coronary artery disease (CAD), stroke, and peripheral vascular insufficiency.<sup>37</sup> Thus, the statins—lovastatin (Mevacor), pravastatin (Pravachol), simvastatin, fluvastatin, atorvastatin (Lipitor), and rosuvastatin (Crestor)—are mainstays of therapy, limited by patient tolerance most commonly secondary to musculoskeletal complaints.<sup>38a</sup>

However, the report of Downs and coworkers from the Air Force/Texas Coronary Atherosclerosis Prevention Study went further.<sup>37</sup> This report showed a 37% reduction in the risk for first acute major coronary events in patients who had no risk factors and normal (average) LDL cholesterol levels. In this study lovastatin did not alter mortality rates, but that had been true for many early short-term trials with the statins. Although much of the effect of the statins has been attributed to their lipid-lowering effects, statins also influence endothelial function, inflammatory responses, plaque stability, and thrombogenicity. In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) released a new clinical practice guideline for the treatment of blood cholesterol in

people at high risk for cardiovascular diseases.<sup>39</sup> They now advocate statin therapy for the following:

- Patients who have cardiovascular disease (coronary syndromes, previous myocardial infarction [MI], stable or unstable angina, previous stroke or transient ischemic attack, or peripheral artery disease)
- Patients with an LDL cholesterol level of 190 mg/dL or higher
- Patients with diabetes (type 1 or 2) who are between 40 and 75 years old
- Patients with an estimated 10-year risk of cardiovascular disease greater than 7.5% (the report provided formulas for calculating 10-year risk)

The 2014 National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia further emphasize the use of statins as a first-line therapy for dyslipidemia, but emphasize the inclusion of non-high density lipoprotein in addition to LDL as markers for risk. They further advocated for management of other atherosclerotic cardiovascular disease risk factors including high blood pressure, tobacco use, and diabetes mellitus.<sup>39a</sup>

Statins are drugs that block HMG-CoA reductase, the rate-limiting enzyme of cholesterol synthesis. Their use is occasionally accompanied by liver dysfunction, CNS dysfunction, and severe depression not related to the high cost of each drug and its congeners. Based on the available evidence, statin therapy should be continued in patients already taking these drugs.<sup>40</sup> Other drugs that reduce LDL and increase HDL cholesterol and decrease triglycerides are docosahexaenoic acid (an  $\omega$ -3 fatty acid) and niacin. Statins also provide the substantial benefit of reversing inflammation in arteries, as evidenced by their ability to decrease highly specific C-reactive protein and pull cholesterol from plaque.<sup>41</sup>

Hypolipidemic conditions are rare diseases often associated with neuropathy, anemia, and renal failure. Although anesthetic experience with hypolipidemic conditions has been limited, some specific recommendations can be made: continuation of caloric intake and intravenous administration of protein hydrolysates and glucose should be continued throughout the perioperative period.

## Obesity

Obesity is a risk factor for perioperative morbidity. In the study of Medicare claims in which obese patients were matched to non-obese patients undergoing surgery, the obese patients displayed increased odds of wound infection, renal dysfunction, urinary tract infection, hypotension, respiratory events, 30-day readmission, and a 12% longer length of stay.<sup>41a</sup> Although many conditions associated with obesity (diabetes, hyperlipidemia, cholelithiasis, gastroesophageal reflux disease, cirrhosis, degenerative joint and disk disease, venous stasis with thrombotic or embolic disease, sleep disorders, and emotional and altered body image disorders) contribute to chronic morbidity in these patients, the main concerns for the anesthesiologist have been the same since the 1970s—derangements of the cardiopulmonary system.

Morbid obesity with minimal or no coexisting pulmonary conditions (e.g., no obesity-hypoventilation syndrome or chronic obstructive pulmonary disease [COPD]) is referred to here as “simple” obesity. In simple obesity,

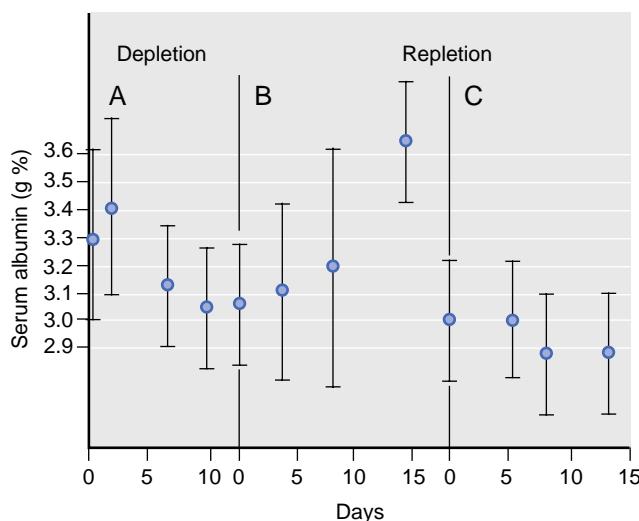
the pathophysiology of mild alterations in daytime gas exchange and pulmonary function may also result from compression and restriction of the chest wall and diaphragm by excess adipose tissue.<sup>42</sup> Typically, in obese patients, the expiratory reserve volume and functional residual capacity are most affected and are reduced to 60% and 80% of normal, respectively. Care must be taken with medication choice and dosing, as simple obese patients may be more sensitive to sedative and narcotic agents leading to hypoventilation.<sup>42a</sup>

## Other Eating Disorders: Anorexia Nervosa, Bulimia, and Starvation

Many endocrine and metabolic abnormalities occur in patients with anorexia nervosa, a condition characterized by starvation to the point of 40% loss of normal weight, hyperactivity, and a psychiatrically distorted body image. Many anorectic patients exhibit impulsive behavior, including suicide attempts, and intravenous drug use is much more common than in the general population. Acidosis, hypokalemia, hypocalcemia, hypomagnesemia, hypothermia, diabetes insipidus, and severe endocrine abnormalities mimicking panhypopituitarism may need attention before patients undergo anesthesia. Similar problems occur in bulimia (bulimorexia), a condition that may affect as many as 50% of female college students and is even unintentionally present in many older adults. As in severe protein deficiency, anorexia nervosa and bulimia may be accompanied by the following: alterations on the electrocardiogram (ECG), including a prolonged QT interval, atrioventricular (AV) block, and other arrhythmias; sensitivity to epinephrine; and cardiomyopathy.<sup>43</sup> Total depletion of body potassium makes the addition of potassium to glucose solutions useful; although, fluid administration can precipitate pulmonary edema in these patients and should be monitored judiciously. Esophagitis, pancreatitis, and aspiration pneumonia are more frequent in these patients, as is delayed gastric emptying. One review reported that in patients with severe anorexia, a body mass index less than 13 kg/m<sup>2</sup>, marked hypoglycemia or leukocytopenia lower than  $3.0 \times 10^9/L$ , or both, potentially fatal complications frequently occur.<sup>44</sup> Intraoperatively, glucose or catecholamine administration may lead to disturbance of electrolytes or fatal arrhythmia. Intensive care and early nutritional support as soon as possible postoperatively are important to prevent surgical site infection with close monitoring for refeeding syndrome.

## HYPERALIMENTATION (TOTAL PARENTERAL OR ENTERAL NUTRITION)

Hyperalimentation (i.e., total parenteral nutrition [TPN]) consists of concentrating hypertonic glucose calories in the normal daily fluid requirements. The solutions contain protein hydrolysates, soybean emulsions (i.e., Intralipid), or synthetic amino acids (or any combination of these ingredients). The major benefits of TPN or enteral nutrition have been fewer complications postoperatively and shorter hospital stays for patients scheduled to have no oral feeding for 7 days or who were malnourished preoperatively.<sup>45,46</sup> Starker and colleagues found that the response to TPN, as monitored by serum albumin levels, predicted the postoperative outcome.<sup>47</sup> The group of patients demonstrating



**Fig. 32.2** The response to hyperalimentation (A, repletion), as measured by variation in serum albumin levels, predicted the outcome of surgery. Patients who responded (B) to nutritional support with increased albumin levels had a significantly better outcome than did those whose albumin level did not increase (C). See the text for a more complete explanation. (Modified from Starker PM, Group FE, Askanazi J, et al. Serum albumin levels as an index of nutritional support. *Surgery*. 1982;91:194–199.)

an increase in serum albumin concentrations from TPN had diuresis, weight loss, and fewer complications (1 of 15 patients) than did the group that gained weight and had a decrease in serum albumin (8 of 16 patients had 15 complications; **Fig. 32.2**). The Veterans Administration (former name for Veterans Affairs [VA used for both]) studies also found that the serum albumin level was one of the most powerful predictors of perioperative outcome.<sup>45</sup>

The major complications of TPN are infection, metabolic abnormalities, and longer duration of ICU stay.<sup>47a</sup> The central lines used for TPN require an absolutely aseptic technique and should not be used as an intravenous access or as a route for drug administration during anesthesia and surgery. Major metabolic complications of TPN relate to electrolyte deficiencies, and the development of hyperosmolar states. Complications of hypertonic dextrose can develop if the patient has insufficient insulin (diabetes mellitus) to metabolize the sugar or if insulin resistance occurs (e.g., because of uremia, burns, or sepsis).

A gradual decrease in the infusion rate of TPN prevents the hypoglycemia that can occur on abrupt discontinuance. Thus the infusion rate of TPN should be decreased the night before anesthesia and surgery, or should be continued throughout the operation at its current rate. The main reason for slowing or discontinuing TPN before anesthesia is to avoid intraoperative hyperosmolarity secondary to accidental rapid infusion of the solution or hypoglycemia if the infusion is discontinued because of high levels of endogenous insulin and lower levels of glucose present in the usual crystalloid solutions.<sup>45</sup> Hypophosphatemia is a particularly serious complication that results from the administration of phosphate-free or phosphate-depleted solutions for hyperalimentation. The low serum phosphate level causes a shift of the oxygen dissociation curve to the left. The resulting low 2,3-diphosphoglycerate and adenosine triphosphatase levels mean that cardiac output must increase for oxygen

delivery to remain the same. Hypophosphatemia of less than 1.0 mg/dL of blood may cause hemolytic anemia, cardiac failure, tachypnea, neurologic symptoms, seizures, and death. In addition, long-term TPN is associated with deficiencies in trace metals such as copper (refractory anemia), zinc (impaired wound healing), and magnesium.

## ADRENOCORTICAL MALFUNCTION

Three major classes of hormones—androgens, glucocorticoids, and mineralocorticoids—are secreted by the adrenal cortex. For each class, an excess or a deficiency of hormone produces a characteristic clinical syndrome. The widespread use of steroids can also make the adrenal cortex unable to respond normally to the demands placed on it by surgical trauma and subsequent healing. The increase in computed tomography (CT) abdominal imaging procedures has meant that many adrenal masses have unfortunately been discovered incidentally. These adrenal “incidentalomas,” as they are termed because they were initially thought a nuisance discovered by body scans, have proved more serious. As many as 30% are hormonally active; in one review of 2000 such masses, 82% were not hormonally active, 5.3% proved to be cortisone-secreting adenomas, 5.1% were pheochromocytomas, 4.7% were adrenal carcinomas, 2.5% were unsuspected metastatic disease, and 1% were aldosterone-secreting adenomas. “Incidentalomas” may therefore require serious pursuit; however, well accepted and utilized guidelines are absent, but caution should be taken during anesthesia.

Controlled comparisons of the perioperative management of patients who have disorders of adrenal function are lacking, although steroids are used more and more commonly, with the results of some controlled trials available for specific uses. However, a review of the possible pathophysiologic changes in the adrenal cortex and techniques for their management should enable physicians to improve the perioperative care of patients with adrenal abnormalities.

### Physiologic Properties of Adrenocortical Hormones

**Androgens.** Androstenedione and dehydroepiandrosterone, weak androgens arising from the adrenal cortex, constitute major sources of androgen in women (and have gained prominence for their abuse among athletes). Excess secretion of androgen causes masculinization, pseudopuberty, or female pseudohermaphroditism. With some tumors, androgen is converted to an estrogenic substance, in which case feminization results. No special anesthetic evaluation is needed for such patients. Some congenital enzyme defects that cause androgen abnormalities also result in glucocorticoid and mineralocorticoid abnormalities that should be evaluated preoperatively. Most of these patients are treated with exogenous glucocorticoids and mineralocorticoids and may require supplementation of these hormones perioperatively.

**Glucocorticoids.** The principal glucocorticoid, cortisol, is an essential regulator of carbohydrate, protein, lipid, and nucleic acid metabolism. Cortisol exerts its biologic effects through a sequence of steps initiated by the binding of hormone to stereospecific intracellular cytoplasmic receptors.

This bound complex stimulates nuclear transcription of specific mRNA molecules. These molecules are then translated to give rise to proteins that mediate the ultimate effects of hormones.

Most cortisol is bound to corticosterone-binding globulin (CBG, transcortin). The relatively small amounts of unbound cortisol enter cells to induce actions or to be metabolized. Conditions that induce changes in the amount of CBG include liver disease and nephrotic syndrome, both of which result in decreased circulating levels of CBG, and estrogen administration and pregnancy, which result in increased CBG production. Total serum cortisol levels may become elevated or depressed under conditions that alter the amount of bound cortisol, and yet the unbound, active form of cortisol is present in normal amounts. The most accurate measure of cortisol activity is the level of urinary cortisol (i.e., the amount of unbound, active cortisol filtered by the kidney).

The serum half-life of cortisol is 80 to 110 minutes. However, because cortisol acts through intracellular receptors, pharmacokinetic data based on serum levels are not good indicators of cortisol activity. After a single dose of glucocorticoid, serum glucose is elevated for 12 to 24 hours; improvement in pulmonary function in patients with bronchial asthma can still be measured 24 hours after glucocorticoid administration. Treatment schedules for glucocorticoid replacement are therefore based not on the measured serum half-life but on the well-documented prolonged end-organ effect of these steroids. Hospitalized patients requiring long-term glucocorticoid replacement therapy are usually treated twice daily, with a slightly higher dose given in the morning than in the evening to simulate the normal diurnal variation in cortisol levels. For patients who require parenteral "steroid coverage" during and after surgery (see later paragraphs), administration of glucocorticoid every 6 to 12 hours is appropriate pending the type of surgery and expected stress response.<sup>47b</sup> The relative potencies of glucocorticoids are listed in Table 32.2. Cortisol is inactivated primarily in the liver and is excreted as 17-hydroxycorticosteroid. Cortisol is also filtered and excreted unchanged into urine.

The synthetic glucocorticoids vary in their binding specificity in a dose-related manner. When given in supraphysiologic doses (>30 mg/day), cortisol and cortisone bind to mineralocorticoid receptor sites, and cause salt and water retention and loss of potassium and hydrogen ions. When these steroids are administered in maintenance doses of 30 mg/day or less, patients require a specific mineralocorticoid for electrolyte and volume homeostasis. Many other steroids do not bind to mineralocorticoid receptors, even at high doses, and have no mineralocorticoid effect (see Table 32.2).<sup>47b</sup>

Secretion of glucocorticoids is regulated by pituitary adrenocorticotrophic hormone (ACTH). ACTH is synthesized from a precursor molecule (pro-opiomelanocortin) that is metabolized to form an endorphin ( $\beta$ -lipotropin) and ACTH. Episodic secretion of ACTH has a diurnal rhythm that is normally greatest during the early morning hours in men and later in women and is regulated at least in part by light-dark cycles. Its secretion is stimulated by release of corticotropin-releasing factor (CRF) from the hypothalamus. (An abnormality in the diurnal rhythm of corticoid

**TABLE 32.2** Relative Potencies and Equivalent Doses for Commonly Used Glucocorticoids

Steroids	Relative Glucocorticoid Potency	Equivalent Glucocorticoid Dose (mg)
<b>SHORT ACTING</b>		
Cortisol (hydrocortisone)	1.0	20.0
Cortisone	0.8	25.0
Prednisone	4.0	5.0
Prednisolone	4.0	5.0
Methylprednisolone	5.0	4.0
<b>INTERMEDIATE ACTING</b>		
Triamcinolone	5.0	4.0
<b>LONG ACTING</b>		
Betamethasone	25.0	0.60
Dexamethasone	30.0	0.75

Data from Axelrod L. Glucocorticoid therapy. *Medicine (Baltimore)*. 1976;55:39–65.

secretion has been implicated as a cause of so-called jet lag.) Cortisol and other glucocorticoids exert negative feedback at both the pituitary and hypothalamic levels to inhibit the secretion of ACTH and CRF. If the CRF- or ACTH-producing cells are destroyed, the adrenal gland takes more than 30 days to atrophy to the point at which short-term administration of exogenous ACTH will cause almost no adrenal responsiveness.<sup>48</sup>

**Mineralocorticoids.** Aldosterone, the major mineralocorticoid secreted in humans, comes from the zona glomerulosa of the adrenal cortex and causes reabsorption of sodium and secretion of potassium and hydrogen ions, thereby contributing to electrolyte and volume homeostasis. This action is most prominent in the distal renal tubule but also occurs in the salivary and sweat glands. The major regulator of aldosterone secretion is the renin-angiotensin system. Juxtaglomerular cells in the cuff of renal arterioles are sensitive to decreased renal perfusion pressure or volume and, consequently, secrete renin. Renin transforms the precursor angiotensinogen (from the liver) into angiotensin I, which is further converted by a converting enzyme, primarily in the lung, to angiotensin II. Angiotensin II binds to specific receptors to increase mineralocorticoid secretion, which is also stimulated by an increased potassium concentration and, to a lesser degree, by ACTH.

### Adrenocortical Hormone Excess

**Glucocorticoid Excess.** Glucocorticoid excess (Cushing syndrome) resulting from either endogenous oversecretion or long-term treatment with glucocorticoids at higher than physiologic doses produces a moon-faced plethoric individual with a centripetal distribution of fat (truncal obesity and skinny extremities), thin skin, easy bruising, and striae. Skeletal muscle wasting is common, but the heart and diaphragm are usually spared. A test for this syndrome is to ask the patient to get up from a chair without using the hands with the inability to do so indicating proximal

**TABLE 32.3** Clinical Features of Hyperadrenalinism (Cushing Syndrome) and Hypoadrenalinism

Cushing Syndrome	Hypoadrenalinism
Central obesity	Weight loss
Proximal muscle weakness	Weakness, fatigue, lethargy
Osteopenia at a young age	Muscle, joint, and back pain
Hypertension	Postural hypotension and dizziness
Headache	Headache
Psychiatric disorders	Anorexia, nausea, abdominal pain, constipation, diarrhea
Purple striae	
Spontaneous ecchymoses	
Plethoric facies	
Hyperpigmentation	Hyperpigmentation
Hirsutism	
Acne	
Hypokalemic alkalosis	Hyperkalemia, hyponatremia
Glucose intolerance	Occasional hypoglycemia
Kidney stones	Hypercalcemia
Polyuria	Prerenal azotemia
Menstrual disorders	
Increased leukocyte count	

muscle weakness consistent with Cushing syndrome. These patients often have osteopenia as a result of decreased formation of bone matrix and impaired absorption of calcium. Fluid retention and hypertension (because of increases in renin substrate and vascular reactivity caused by glucocorticoid activity) are common. Such patients may also have hyperglycemia and even diabetes mellitus from inhibition of peripheral use of glucose, as well as anti-insulin action and concomitant stimulation of gluconeogenesis (Table 32.3).

The most common cause of Cushing syndrome is the administration of glucocorticoids for such conditions as arthritis, asthma, and allergies. In these conditions, the adrenal glands atrophy and cannot respond to stressful situations (e.g., the perioperative period) by secreting more steroid; therefore, additional glucocorticoids may be required perioperatively (see the later section “Patients Taking Steroids for Other Reasons”). Spontaneous Cushing syndrome may be caused by pituitary production of ACTH (65% to 75% of all spontaneous cases), which is usually associated with pituitary microadenoma, or by nonendocrine ectopic ACTH production (principally by tumors of the lung, pancreas, or thymus).<sup>49</sup> Ten percent to 20% of cases of spontaneous Cushing syndrome are caused by an ACTH-independent process, either an adrenal adenoma or carcinoma.<sup>49</sup>

Special preoperative and preprocedure considerations for patients with Cushing syndrome include regulating blood glucose control, managing hypertension, and ensuring intravascular volume and electrolyte concentrations are

normal. Ectopic ACTH production may cause marked hypokalemic alkalosis. Treatment with the aldosterone antagonist spironolactone stops the potassium loss and helps mobilize excess fluid. Because of the incidence of severe osteopenia and the risk of fractures, meticulous attention must be paid to positioning of the patient. In addition, glucocorticoids are lympholytic and immunosuppressive, thus increasing the patient’s susceptibility to infection. The tensile strength of healing wounds decreases in the presence of glucocorticoids, an effect that is at least partially reversed by the topical administration of vitamin A.

Ten percent to 15% of patients with Cushing syndrome exhibit adrenal overproduction of glucocorticoids from an adrenal adenoma or carcinoma. If either unilateral or bilateral adrenal resection is planned, the physician should begin administering glucocorticoids at the start of resection of the tumor. Despite the absence of definitive studies, 100 mg of hydrocortisone every 24 hours intravenously is reasonable. This amount can be reduced over a period of 3 to 6 days until a maintenance dose is reached. Beginning on day 3, the surgeons may also give a mineralocorticoid, 9 $\alpha$ -fluorocortisol (0.05-0.1 mg/day). In certain patients, both steroids may require several adjustments. This therapy continues if the patient has undergone bilateral resection. For a patient who has undergone unilateral adrenal resection, therapy is individualized according to the status of the remaining adrenal gland. The incidence of pneumothorax in an open adrenal resection approach can be as high as 20%; the diagnosis of pneumothorax is sought and treatment is initiated before the wound is closed. The use of the laparoscopic technique has markedly decreased this complication.

Bilateral adrenalectomy (now performed laparoscopically) in patients with Cushing syndrome is associated with a perioperative morbidity rate up to 20% and a perioperative mortality rate up to 3%. This procedure often results in permanent mineralocorticoid and glucocorticoid deficiency.<sup>49a</sup> Ten percent of patients with Cushing syndrome who undergo adrenalectomy have an undiagnosed pituitary tumor. After cortisol concentrations are decreased by adrenalectomy, the pituitary tumor will likely enlarge. These pituitary tumors are potentially invasive and may produce large amounts of ACTH and melanocyte-stimulating hormone, thereby increasing pigmentation.

Approximately 85% of adrenal tumors are discovered incidentally during screening CT scans. Nonfunctioning adrenal adenomas are found in patients on autopsy, ranging from 1% to 32% in different series. Functioning adenomas are generally treated surgically; often, the contralateral gland resumes functioning after several months. Frequently, however, the effects of carcinomas are not cured surgically. In such cases, administration of inhibitors of steroid synthesis, such as metyrapone or mitotane (*o,p*-DDD[2,2-bis(2-chlorophenyl4-chlorophenyl)-1,1-dichloroethane]), may ameliorate some symptoms, as these drugs and specific aldosterone antagonists may aid in reducing symptoms of ectopic ACTH secretion if the primary tumor is unresectable. Patients given these adrenal suppressants are also prescribed long-term glucocorticoid replacement therapy with the goal of therapy being complete adrenal suppression. Therefore, these patients should be considered to have suppressed adrenal function, and glucocorticoid replacement should be increased perioperatively.

**Mineralocorticoid Excess.** Excess mineralocorticoid activity (common with glucocorticoid excess because most glucocorticoids have some mineralocorticoid properties) leads to potassium depletion, sodium retention, muscle weakness, hypertension, tetany, polyuria, inability to concentrate urine, and hypokalemic alkalosis. These symptoms constitute primary hyperaldosteronism, or Conn syndrome (a cause of low-renin hypertension because renin secretion is inhibited by the effects of the high levels of aldosterone).

Primary hyperaldosteronism is present in 0.5% to 1% of hypertensive patients who have no other known cause of hypertension. Primary hyperaldosteronism most often results from unilateral adrenal adenoma, although 25% to 40% of patients have been found to have bilateral adrenal hyperplasia. Intravascular fluid volume, electrolyte concentrations, and renal function should be restored to within normal limits preoperatively by administering the aldosterone antagonist spironolactone. The effects of spironolactone are slow in onset and increase for 1 to 2 weeks. Frequently, a period of at least 24 hours is required to restore potassium equilibrium as the deficit can be up to 400 mEq; however, normal serum potassium level does not necessarily imply correction of a total-body deficit of potassium. In addition, patients with Conn syndrome have a high incidence of hypertension and ischemic heart disease; hemodynamic monitoring should be tailored to the individual patient.

A retrospective anecdotal study indicated that intraoperative hemodynamic status was more stable when arterial blood pressure and electrolytes were controlled preoperatively with spironolactone than when other antihypertensive agents were used. However, the efficacy of optimizing the perioperative status of patients who have disorders of glucocorticoid or mineralocorticoid secretion has not been clearly defined. Therefore, we have assumed that gradual restoration of physiologic norms is good medicine and expect that it would decrease perioperative morbidity and mortality.

### Adrenocortical Hormone Deficiency

**Glucocorticoid Deficiency.** Withdrawal of steroids or suppression of synthesis by steroid therapy is the leading cause of underproduction of corticosteroids (its management is discussed in the later section “Patients Taking Steroids for Other Reasons”). Other causes of adrenocortical insufficiency include the following: defects in ACTH secretion and destruction of the adrenal gland by autoimmune disease, tuberculosis, hemorrhage (e.g., Sheehan syndrome), or cancer; some forms of congenital adrenal hyperplasia (see previous discussion); and administration of cytotoxic drugs.

Primary adrenal insufficiency (Addison disease) is associated with local destruction of all zones of the adrenal cortex and results in both glucocorticoid and mineralocorticoid deficiency if the insufficiency is bilateral; common symptoms and signs are listed in Table 32.3. Autoimmune disease is the most common cause of primary (nonexogenous) bilateral ACTH deficiency in the United States, whereas tuberculosis is the most common cause worldwide. Tuberculosis is associated not only with decreased adrenal function, but also large adrenal glands, which are a common finding in sarcoidosis, histoplasmosis, amyloidosis, metastatic malignant disease, heparin-induced thrombocytopenia, and adrenal hemorrhage. Further, destruction or

injury by trauma, human immunodeficiency virus (HIV), and other infections (e.g., cytomegalovirus, mycobacteria, and fungi) is being recognized more frequently.

Autoimmune destruction of the adrenal glands may be associated with other autoimmune disorders, such as some forms of type 1 diabetes and Hashimoto thyroiditis. Enzymatic defects in cortisol synthesis cause glucocorticoid insufficiency, compensatory elevations in ACTH, and congenital adrenal hyperplasia. Because adrenal insufficiency usually develops slowly, such patients are subject to marked pigmentation (from excess ACTH trying to stimulate an unproductive adrenal gland) and cardiopenia (secondary to chronic hypotension).

Secondary adrenal insufficiency occurs when ACTH secretion is deficient, often because of a pituitary or hypothalamic tumor. Treatment of pituitary tumors by surgery or radiation therapy may result in hypopituitarism and subsequent adrenal failure.

If unstressed, glucocorticoid-deficient patients usually have no perioperative problems. However, acute adrenal crisis (addisonian crisis) can occur when even a minor stress is present (e.g., upper respiratory infection). Preparation of such a patient for anesthesia and surgery should include treatment of hypovolemia, hyperkalemia, and hyponatremia. Because these patients cannot respond to stressful situations, it was traditionally recommended that they be given a stress dose of glucocorticoids ( $\approx 200$  mg hydrocortisone/day) perioperatively. However, Symreng and colleagues gave 25 mg of hydrocortisone phosphate intravenously to adults at the start of the operative procedure, followed by 100 mg intravenously over the next 24 hours.<sup>50</sup> Because using the minimum drug dose that would produce an appropriate effect is desirable, this latter regimen seems attractive. Such a regimen has proved to be as successful as a regimen using maximum doses ( $\approx 300$  mg hydrocortisone/day). Thus we now recommend giving the patient's usual daily dose plus 50 to 100 mg of hydrocortisone before surgical incision and 25 to 50 mg of hydrocortisone every 8 hours for 24 to 48 hours, depending on the type and duration of surgery.<sup>47b</sup>

**Mineralocorticoid Deficiency.** Hypoaldosteronism, a less common condition, can be congenital, can occur after unilateral adrenalectomy, or be a consequence of prolonged heparin administration, long-standing diabetes, or renal failure. Nonsteroidal inhibitors of prostaglandin synthesis may also inhibit renin release and exacerbate this condition in patients with renal insufficiency. Plasma renin activity is lower than normal and fails to increase appropriately in response to sodium restriction or diuretic drugs. Most symptoms are caused by hyperkalemic acidosis rather than hypovolemia; in fact, some patients are hypertensive. These patients can have severe hyperkalemia, hyponatremia, and myocardial conduction defects. These defects can be treated successfully by administering mineralocorticoids ( $9\alpha$ -fluorocortisol, 0.05–0.1 mg/day) preoperatively. Doses must be carefully titrated and monitored to avoid an increase in hypertension.

### Patients Taking Steroids for Other Reasons

**Perioperative Stress and the Need for Corticoid Supplementation.** The adrenal responses of normal patients

to the perioperative period, as well as the responses of patients taking steroids for other diseases, indicate the following:

1. Perioperative stress is related to the degree of trauma and the depth of anesthesia. Deep general or regional anesthesia delays the usual intraoperative glucocorticoid surge to the postoperative period.
2. A few patients with suppressed adrenal function will have perioperative cardiovascular problems if they do not receive supplemental steroids perioperatively.
3. Although a patient who takes steroids on a long-term basis may become hypotensive perioperatively; glucocorticoid or mineralocorticoid deficiency is seldom the cause. Longer duration and higher home steroid dose increase the likelihood of deficiency.<sup>47b</sup>
4. Acute adrenal insufficiency rarely occurs, but can be life-threatening.
5. Giving these patients steroid coverage equivalent to 100 mg of hydrocortisone perioperatively has little risk.<sup>47b</sup>

In a well-controlled study of glucocorticoid replacement in nonhuman primates, the investigators clearly defined the life-threatening events that can be associated with inadequate perioperative corticosteroid replacement.<sup>48</sup> In this study, adrenalectomized primates and sham-operated controls were given physiologic doses of steroids for 4 months. The animals were then randomly allocated to groups that received subphysiologic (one-tenth of the normal cortisol production), physiologic, or supraphysiologic (10 times the normal cortisol production) doses of cortisol for 4 days preceding abdominal surgery (cholecystectomy). The group given subphysiologic doses of steroid perioperatively had a significant increase in postoperative mortality. Death rates for the physiologic and supraphysiologic replacement groups were the same and did not differ from the rate for sham-operated controls. Death in the subphysiologic replacement group was related to severe hypotension associated with a significant decrease in systemic vascular resistance and a reduced left ventricular stroke work index. Filling pressures of the heart were unchanged when compared with those in control animals. No evidence of hypovolemia or severe congestive heart failure (CHF) was observed. Despite the low systemic vascular resistance, the animals did not become tachycardic. All these responses are compatible with the previously documented interaction of glucocorticoids and catecholamines, and thus suggest that glucocorticoids mediate catecholamine-induced increases in cardiac contractility and maintenance of vascular tone.

The investigators used a sensitive measure of wound healing involving accumulation of hydroxyproline. All treatment groups, including the group given supraphysiologic doses of glucocorticoids, had the same capacity for wound healing. Furthermore, perioperative administration of supraphysiologic doses of corticosteroids produced no adverse metabolic consequences.

This study confirmed long-standing intuitive impressions concerning patients who had inadequate adrenal function as a result of either underlying disease or administration of exogenous steroids—inadequate replacement of corticosteroids can lead to addisonian crisis and increased mortality, whereas the administration of supraphysiologic doses of steroids for a short time perioperatively can

be safe. It is clear that inadequate corticosteroid coverage can cause death, but what is not so clear is what dose of steroid should be recommended for replacement therapy. Yong and colleagues reviewed the randomized controlled trials for a Cochrane Systemic Review and reported only two trials involving 37 patients that met the inclusion criteria.<sup>51</sup> These studies reported that supplemental perioperative steroids were not required during surgery for patients with adrenal insufficiency, but neither study reported any adverse effects or complications in the intervention or control groups. The authors concluded that they were unable to support or refute the use of supplemental perioperative steroids for patients with adrenal insufficiency during surgery. Because the risk is low and the benefit is high, physicians should consider providing supplementation for any patient who has received steroids within a year.<sup>48,50</sup>

How can one determine when adrenal responsiveness has returned to normal? The morning plasma cortisol level does not reveal whether the adrenal cortex has recovered sufficiently to ensure that cortisol secretion will increase adequately to meet the demands of stress. Inducing hypoglycemia with insulin has been advocated as a sensitive test of pituitary-adrenal competence, but it is impractical and is probably a more dangerous practice than simply administering glucocorticoids. If the plasma cortisol concentration is measured during acute stress, a value of greater than 25 µg/dL assuredly (and a value >15 µg/dL probably) indicates normal pituitary-adrenal responsiveness. In another test of pituitary-adrenal sufficiency, the baseline plasma cortisol level is determined. Then, 250 µg of synthetic ACTH (cosyntropin) is given, and plasma cortisol is measured 30 to 60 minutes later. An increase in plasma cortisol of 6 to 20 µg/dL or more is normal.<sup>52,53</sup> A normal response indicates recovery of pituitary-adrenal axis function. A lesser response usually indicates pituitary-adrenal insufficiency, possibly requiring perioperative supplementation with steroids.<sup>53a</sup>

Under perioperative conditions, the adrenal glands secrete 116 to 185 mg of cortisol daily. Under maximum stress, they may secrete 200 to 500 mg/day. Good correlation exists between the severity and duration of the operation and the response of the adrenal gland. “Major surgery” would be represented by procedures such as laparoscopic colectomy and “minor surgery” by procedures such as herniorrhaphy. In a study of 20 patients during major surgery, the mean maximal concentration of cortisol in plasma was 47 µg/dL (range, 22–75 µg/dL). Values remained higher than 26 µg/dL for a maximum of 72 hours postoperatively. During minor surgery, the mean maximal concentration of cortisol in plasma was 28 µg/dL (range, 10–44 µg/dL).

Although the precise amount required has not been established, we usually intravenously administer the maximum amount of glucocorticoid that the body manufactures in response to maximal stress (i.e., approximately 200 mg/day of hydrocortisone).<sup>53b</sup> For minor surgical procedures, we usually give hydrocortisone intravenously, 50 to 100 mg/day. Unless infection or some other perioperative complication develops, we decrease this dose by approximately 50%/day until the standard home dose is resumed. For major surgical procedures, we usually give 50 mg every 6 hours to 100 mg every 8 hours. Again unless a complication develops, this is decreased 50%/day until the standard home dose is resumed.<sup>53b</sup>

**Risks of Supplementation.** Rare complications of perioperative steroid supplementation include aggravation of hypertension, fluid retention, inducement of stress ulcers, and psychiatric disturbances. Two possible complications of short-term perioperative supplementation with glucocorticoids are abnormal wound healing and an increased rate of infections. This evidence is inconclusive, however, because it relates to short-term glucocorticoid administration and not to long-term administration of glucocorticoids with increased doses at times of stress. In contrast to a deleterious effect of perioperative glucocorticoid administration on wound healing in rats, a study involving primates suggested that large doses of glucocorticoids, administered perioperatively, do not impair sensitive measures of wound healing.<sup>48</sup> An overall assessment of these results suggests that short-term perioperative supplementation with steroids has a small but definite deleterious effect on wound healing that is perhaps partially reversed by topical administration of vitamin A.

Information on the risk of infection from perioperative glucocorticoid supplementation is also unclear as there are no controlled trials addressing these effects. In many studies of long-term use by patients and supplementation, no increased risk of serious infections was reported with long-term use of steroids alone. Data indicate that the risk of infection in a patient taking steroids on a long-term basis is real, but whether perioperative supplementation with steroids increases that risk is not clear.

### Adrenal Cortex Function in Older Adults

Production of androgens by the adrenal gland progressively decreases with age; this change has no known implications for anesthesia. Plasma levels of cortisol are unaffected by increasing age. Levels of CBG are also unaffected by age, a finding suggesting that a normal fraction of free cortisol (1%-5%) is present in older patients. Older patients have a progressively impaired ability to metabolize and excrete glucocorticoids. In normal individuals, the quantity of 17-hydroxycorticosteroids excreted is reduced by half by the seventh decade. This decreased excretion undoubtedly reflects the reduced renal function that occurs with aging. When excretion of cortisol metabolites is expressed as a function of creatinine clearance, the age difference disappears. Further reductions in cortisol clearance may reflect impaired hepatic metabolism of circulating cortisol.

The rate of secretion of cortisol is 30% slower in older adults. This reduced secretion may be an appropriate compensatory mechanism for maintaining a normal cortisol level in the presence of decreased hepatic and renal clearance of cortisol. The reduced cortisol production can be overcome during periods of stress, and even extremely old patients (>100 years old) display an entirely normal adrenal response to the administration of ACTH and to stresses such as hypoglycemia.

Both underproduction and overproduction of glucocorticoids are generally considered diseases of younger individuals. The highest incidence of Cushing disease of either pituitary or adrenal origin occurs during the third decade of life. The most common cause of spontaneous Cushing disease is benign pituitary adenoma. However, in patients older than 60 years in whom Cushing disease develops, the most likely cause is adrenal carcinoma or ectopic ACTH

production from tumors usually located in the lung, pancreas, or thymus.

### ADRENAL MEDULLARY SYMPATHETIC HORMONE EXCESS: PHEOCHROMOCYTOMA

Less than 0.1% of all cases of hypertension are caused by pheochromocytomas, or catecholamine-producing tumors derived from chromaffin tissue.<sup>54</sup> Nevertheless, these tumors are clearly important to the anesthesiologist as previously 25% to 50% of hospital deaths in patients with pheochromocytoma occurred during induction of anesthesia or during operative procedures for other causes.<sup>55</sup> This high mortality has been reduced with the improvements in anesthesia management during our current era.<sup>55a</sup> Although usually found in the adrenal medulla, these vascular tumors can occur anywhere (referred to as paragangliomas), with a proportion of up to 20%.<sup>55b</sup> Malignant spread, which occurs in less than 15% of pheochromocytomas, usually proceeds to venous and lymphatic channels with a predisposition for the liver. This tumor is occasionally familial or part of the multiglandular-neoplastic syndrome known as multiple endocrine adenoma type IIa or type IIb, and is manifested as an autosomal dominant trait. Type IIa consists of medullary carcinoma of the thyroid, parathyroid adenoma or hyperplasia, and pheochromocytoma. What used to be called type IIb is now often called pheochromocytoma in association with phakomatoses such as von Recklinghausen neurofibromatosis and von Hippel-Lindau disease with cerebellar hemangioblastoma. Frequently, bilateral tumors are found in the familial form. Localization of tumors can be achieved by MRI or CT, metaiodobenzylguanidine nuclear scanning, ultrasonography, or intravenous pyelography (in decreasing order of combined sensitivity and specificity).

Symptoms and signs that may be solicited before surgery or procedures and are suggestive of pheochromocytoma are as follows: excessive sweating; headache; hypertension; orthostatic hypotension; previous hypertensive or arrhythmic response to induction of anesthesia or to abdominal examination; paroxysmal attacks of sweating, headache, tachycardia, and hypertension; glucose intolerance; polycythemia; weight loss; and psychological abnormalities. In fact, the occurrence of combined symptoms of paroxysmal headache, sweating, and hypertension is probably a more sensitive and specific indicator than any one biochemical test for pheochromocytoma (Table 32.4).

The value of preoperative and preprocedure adrenergic receptor blocking drugs probably justifies their use as these drugs may reduce the perioperative complications of hypertensive crisis, the wide arterial blood pressure fluctuations during tumor manipulation (especially until venous drainage is obliterated), and the myocardial dysfunction. Mortality is decreased with resection of pheochromocytoma (from 40% to 60% to the current 0% to 6%) when adrenergic receptor blockade is introduced as preoperative and preprocedure preparatory therapy for such patients.<sup>56-60</sup>

$\alpha$ -Adrenergic receptor blockade with prazosin or phenoxybenzamine restores intravascular plasma volume by counteracting the vasoconstrictive effects of high levels of catecholamines. This reexpansion of intravascular fluid volume is often followed by a decrease in hematocrit. Because some patients may be very sensitive to the effects of phenoxybenzamine, this drug should initially be

**TABLE 32.4** Characteristics of Tests for Pheochromocytoma

Test/Symptoms	Sensitivity (%)	Specificity (%)	LIKELIHOOD RATIO	
			Positive Result*	Negative Result†
Vanillylmandelic acid excretion	81	97	27.0	0.20
Catecholamine excretion	82	95	16.4	0.19
Metanephrine excretion	83	95	16.6	0.18
Abdominal computed tomography	92	80	4.6	0.10
Concurrent paroxysmal hypertension, headache, sweating, and tachycardia‡	90	95	18.0	0.10

\*The ratio representing the likelihood of a positive result is obtained by dividing the sensitivity by 1 and then subtracting the specificity.

†The ratio representing the likelihood of a negative result is obtained by subtracting the sensitivity from 1 and then dividing by the specificity.

‡Data for concurrent paroxysmal symptoms are best estimates from available data.

Modified from Pauker SG, Kopelman RI. Interpreting hoofbeats: can Bayes help clear the haze? *N Engl J Med*. 1992;327:1009–1013.

given in doses of 20 to 30 mg/70 kg orally once or twice a day. Most patients usually require 60 to 250 mg/day. The Endocrine Society Task Force guidelines from 2014 recommend  $\alpha$ -adrenergic receptor blockade for all patients with active tumors.<sup>60a</sup> The efficacy of therapy should be judged by the reduction in symptoms and stabilization of arterial blood pressure. For patients who have carbohydrate intolerance because of inhibition of insulin release mediated by  $\alpha$ -adrenergic receptor stimulation,  $\alpha$ -adrenergic receptor blockade may reduce fasting blood glucose levels. For patients who exhibit ST-T changes on the ECG, long-term preoperative and preprocedure  $\alpha$ -adrenergic receptor blockade (1–6 months) has produced ECG and clinical resolution of catecholamine-induced myocarditis.<sup>56,57,59–63</sup>

$\beta$ -Adrenergic receptor blockade with propranolol is suggested for patients who have persistent arrhythmias or tachycardia,<sup>56,57,59–63</sup> the reason being that these conditions can be precipitated or aggravated by  $\alpha$ -adrenergic receptor blockade. It is important to remember that  $\beta$ -adrenergic receptor blockade should not be used without concurrent  $\alpha$ -adrenergic receptor blockade lest the vasoconstrictive effects of the latter go unopposed and thereby increasing the risk of malignant hypertension.

The optimal duration of preoperative therapy with  $\alpha$ -adrenergic receptor blockade has not been well studied. The Endocrine Society Task Force guidelines from 2014 recommend  $\alpha$ -adrenergic receptor blockade at least 7 to 14 days prior to surgery; however, most centers report a preoperative treatment duration of 2 to 6 weeks.<sup>19</sup> Most patients will require 10 to 14 days, as judged by the time needed to stabilize arterial blood pressure and ameliorate symptoms. The Endocrine Society Task Force guidelines further recommended a high sodium diet and fluid intake to reverse the catecholamine-induced volume contraction.<sup>63a</sup> Because the tumor spreads slowly, little is lost by waiting until medical therapy has optimized the patient's preoperative condition. The following criteria are reasonable for assessing the adequacy of treatment:

1. No in-hospital arterial blood pressure reading higher than 165/90 mm Hg should be evident for 48 hours preoperatively.
2. Orthostatic hypotension is acceptable as long as arterial blood pressure when the patient is standing is not less than 80/45 mm Hg.

3. The ECG should be free of ST-T changes that are not permanent.
4. No more than one premature ventricular contraction (PVC) should occur every 5 minutes.

Other drugs, including prazosin, calcium channel blocking drugs, clonidine, dexmedetomidine, and magnesium, have also been used to achieve suitable degrees of  $\alpha$ -adrenergic blockade preoperatively. Multiple case series have confirmed the clinical utility of this approach in adults before tumor excision, including in a hemodynamic catecholamine crisis.<sup>64</sup> Magnesium therapy has shown efficacy for the resection of pheochromocytoma or paraganglioma during pregnancy. The dosing of magnesium for the management of pheochromocytoma has been reviewed elsewhere.<sup>65</sup>

The key clinical components of ideal patient care include optimal preoperative preparation, slow and controlled induction of anesthesia, and good communication among members of the perioperative team. Virtually all anesthetic drugs and techniques (including isoflurane, sevoflurane, sufentanil, remifentanil, fentanyl, and regional anesthesia) have been used with success, although all drugs studied were associated with a high rate of transient intraoperative arrhythmias.<sup>59</sup>

Because of ease of use, the preference is to give phenylephrine for hypotension and nitroprusside or nicardipine for hypertension. Phentolamine has too long an onset and duration of action. Painful or stressful events such as intubation often cause an exaggerated stress response in less than perfectly anesthetized patients who have pheochromocytoma. This response is caused by release of catecholamines from nerve endings that are “loaded” by the reuptake process. Such stresses may result in catecholamine levels of 200 to 2000 picograms (pg)/mL in normal patients. For a patient with pheochromocytoma, even simple stress can lead to blood catecholamine levels of ten times normal. However, infarction of a tumor, with release of products onto peritoneal surfaces, or surgical pressure causing release of products, can result in blood levels of 200,000 to 1,000,000 pg/mL—a situation that should be anticipated and avoided (if possible ask for a stay of surgery to increase vasodilator infusion). Once the venous supply is secured and if intravascular volume is normal, normal arterial blood pressure usually results. However,

some patients may become hypotensive and occasionally require catecholamine infusions. Vasopressin has also been used for hemodynamic rescue in catecholamine-resistant vasoplegic shock after resection of a massive pheochromocytoma.<sup>66</sup> On rare occasion, patients remain hypertensive intraoperatively. Postoperatively, approximately 50% of patients remain hypertensive for 1 to 3 days and initially have markedly increased but declining plasma catecholamine levels—at which time all but 25% will become normotensive. Other family members should be advised to inform their future anesthesiologist about the potential for such familial disease.

### **HYPOFUNCTION OR ABERRATION IN FUNCTION OF THE SYMPATHETIC NERVOUS SYSTEM (DYSAUTONOMIA)**

Disorders of the sympathetic nervous system include Shy-Drager syndrome, Riley-Day syndrome, Lesch-Nyhan syndrome, Gill familial dysautonomia, diabetic dysautonomia, and the dysautonomia of spinal cord transection.

Although individuals can function well without an adrenal medulla, a deficient peripheral sympathetic nervous system occurring late in life poses major problems; nevertheless, perioperative sympathectomy or its equivalent is often recommended.<sup>67-73</sup> A primary function of the sympathetic nervous system appears to be regulation of arterial blood pressure and intravascular fluid volume during changing of body position. Common features of all the syndromes with hypofunction of the sympathetic nervous system are orthostatic hypotension and decreased beat-to-beat variability in heart rate. These conditions can be caused by deficient intravascular volume, deficient baroreceptor function (as also occurs in carotid artery disease<sup>74</sup>), abnormalities in CNS function (as in Wernicke or Shy-Drager syndrome), deficient neuronal stores of norepinephrine (as in idiopathic orthostatic hypotension<sup>75</sup> and diabetes), or deficient release of norepinephrine (as in traumatic spinal cord injury<sup>76</sup>). These patients may have a compensatory upregulation of available adrenergic receptors causing an exaggerated response to sympathomimetic drugs. In addition to other abnormalities, such as retention of urine or feces and deficient heat exchange, hypofunction of the sympathetic nervous system is often accompanied by renal amyloidosis. Thus electrolyte and intravascular fluid volume status should be assessed preoperatively. Because many of these patients have cardiac abnormalities, cardiac function and intravascular volume status may require invasive assessment with echocardiography, central venous catheter, or a pulmonary artery catheter per the treating physician's discretion.

Because the functioning of the sympathetic nervous system is not predictable in these patients, slow and controlled induction of anesthesia and treatment of sympathetic excess or deficiency should be initiated through titratable direct-acting vasodilators (nicardipine/nitroprusside), vasoconstrictors (phenylephrine/norepinephrine), chronotropes (isoproterenol), or negative chronotropes (esmolol). A 20% perioperative mortality rate for 2600 patients after spinal cord transection has been reported, thus indicating that such patients are difficult to manage and deserve particularly close attention.

After reviewing 300 patients with spinal cord injuries, Kendrick and coworkers concluded that autonomic hyperreflexia syndrome does not develop if the lesion is below spinal dermatome T7.<sup>77</sup> If the lesion is above that level (splanchnic outflow), 60% to 70% of patients experience extreme vascular instability. The trigger to this instability, a mass reflex involving noradrenergic release and motor hypertonus, can be a cutaneous, proprioceptive, or visceral stimulus (a full bladder is a common initiator). The sensation enters the spinal cord and causes a spinal reflex, which in normal persons is inhibited from above. Sudden increases in arterial blood pressure are sensed in the pressure receptors of the aorta and carotid sinus. The resulting vagal hyperactivity produces bradycardia, ventricular ectopia, or various degrees of heart block. Reflex vasodilation may occur above the level of the lesion and result in flushing of the head and neck. In the acute injury period, modest therapeutic hypothermia may provide benefit but many note that further large randomized trials are needed; the anesthesiologist must be vigilant to avoid hyperthermia and maintain normothermia—hypothermia during procedures.<sup>77a</sup>

Depending on the length of time since spinal cord transection, other abnormalities may occur. In the short term (i.e., <3 weeks from the time of spinal injury), retention of urine and feces is common and, through elevation of the diaphragm, may affect respiration. Hyperesthesia is present above the lesion; reflexes and flaccid paralysis are present below the lesion. The intermediate period (3 days to 6 months) is marked by a hyperkalemic response to depolarizing drugs.<sup>78</sup> The chronic phase is characterized by return of muscle tone, Babinski sign, and, frequently, the occurrence of hyperreflexia syndromes (e.g., mass reflex [see earlier]).

Thus in addition to meticulous attention to perioperative intravascular volume and electrolyte status, the anesthesiologist should know—by history taking, physical examination, and laboratory data—the status of the patient's myocardial conduction (as revealed by the ECG), the status of renal functioning (by noting the ratio of creatinine to blood urea nitrogen [BUN]), and the condition of the respiratory muscles (by determining the ratio of forced expiratory volume in 1 second to forced vital capacity). The anesthesiologist may also obtain a chest radiograph if atelectasis or pneumonia is suspected on the basis of history taking or the physical examination. Temperature control, the presence of bone fractures or decubitus ulcers, and normal functioning of the urination and defecation systems must be assessed.

### **THYROID DYSFUNCTION**

The major thyroid hormones are thyroxine (T<sub>4</sub>), a prohormone product of the thyroid gland, and the more potent 3,5,3'-triiodothyronine (T<sub>3</sub>), a product of both the thyroid and extrathyroidal enzymatic deiodination of T<sub>4</sub>. Under normal circumstances, approximately 85% of T<sub>3</sub> is produced outside the thyroid gland. Production of thyroid secretions is maintained by secretion of thyroid-stimulating hormone (TSH) in the pituitary, which in turn is regulated by secretion of thyrotropin-releasing hormone (TRH) in the hypothalamus. Secretion of TSH and TRH appears to be negatively regulated by T<sub>4</sub> and T<sub>3</sub>. Many investigators believe that all effects of thyroid hormones are mediated by T<sub>3</sub> and that T<sub>4</sub> functions only as a prohormone.

**TABLE 32.5** Biochemical Measurements of Thyroid Function That Account for Variation in Production of Thyroxine-Binding Globulin

EXAMPLES OF NORMAL THYROID STATUS*					
	FT <sub>4</sub> E	=	T <sub>4</sub>	× THBR	TSH
Normal	0.19 (0.12-0.25)	=	0.6 (0.4-0.9)	× 31% (25%-35%)	0.2 (0.2-0.8)
During use of oral contraceptives	0.19	=	1.3	× 15%	0.3
During use of corticosteroids	0.18	=	0.3	× 60%	0.3

\*FT<sub>4</sub>E is the free T<sub>4</sub> (thyroxine) estimate. It is usually obtained by multiplying the total T<sub>4</sub> concentration (the free amount and the amount bound to protein) by the thyroid hormone-binding ratio (THBR, formerly called the resin T<sub>3</sub> uptake). THBR is a measure of the bound thyroid hormone-binding protein. TSH is the thyroid-stimulating hormone secreted by the pituitary in the negative feedback loop. (TSH increases when FT<sub>4</sub>E is low in hypothyroidism.)

Because T<sub>3</sub> has greater biologic effect than does T<sub>4</sub>, one would expect the diagnosis of thyroid disorders to be based on levels of T<sub>3</sub>. However, this is not usually the case. The diagnosis of thyroid disease is confirmed by one of several biochemical measurements: levels of free T<sub>4</sub> or total serum concentrations of T<sub>4</sub> and the “free T<sub>4</sub> estimate.” This estimate is obtained by multiplying total T<sub>4</sub> (free and bound) by the thyroid-binding ratio (formerly called resin T<sub>3</sub> uptake) (Table 32.5). Free T<sub>4</sub> can be accurately measured by many laboratories, this direct measurement of free T<sub>4</sub> obviates the need to account for changes in binding protein synthesis and affinity caused by other conditions. The T<sub>3</sub>-binding ratio measures the extra quantity of serum protein-binding sites. This measurement is necessary because thyroxine-binding globulin (TBG) levels are abnormally high during pregnancy, hepatic disease, and estrogen therapy (all of which would elevate the total T<sub>4</sub> level; Box 32.2). Reliable interpretation of measurements of the total hormone concentration in serum necessitates data on the percentage of bound hormone. The thyroid hormone-binding ratio test provides this information. In this test, iodine-labeled T<sub>3</sub> is added to a patient’s serum and is allowed to reach an equilibrium binding state. A resin is then added that binds the remaining radioactive T<sub>3</sub>. Resin uptake is greater if the patient has fewer TBG-binding sites. In normal patients, resin T<sub>3</sub> uptake (the thyroid hormone-binding ratio) is 25% to 35%. When serum TBG is elevated, the thyroid hormone-binding ratio is diminished (see Table 32.5). When serum TBG is diminished, as in nephrotic syndrome, in conditions in which glucocorticoids are increased, or in chronic liver disease, the thyroid hormone-binding ratio is increased.

The free T<sub>4</sub> estimate and the free T<sub>3</sub> estimate are frequently used as measures of a patient’s serum T<sub>4</sub> and T<sub>3</sub> hormone concentrations, respectively. To obtain these estimates, the concentration of total serum T<sub>4</sub> or total serum T<sub>3</sub> is multiplied by the measured thyroid hormone-binding ratio. Values of these two indices are normal in the event of a primary alteration in binding but not with an alteration in secretion of thyroid hormone.

Hyperthyroidism can be diagnosed by measuring levels of TSH after the administration of TRH. Although

## BOX 32.2 Factors Influencing Serum Levels of Thyroxine-Binding Globulin

### Conditions Increasing Serum Levels

- Use of oral contraceptives
- Pregnancy
- Use of estrogen
- Infectious hepatitis
- Chronic active hepatitis
- Neonatal state
- Acute intermittent porphyria
- Inherited conditions

### Conditions Decreasing Serum Levels

- Testosterone
- Use of corticosteroids
- Severe illness
- Cirrhosis
- Nephrotic syndrome
- Inherited conditions

administering TRH normally increases TSH levels in blood, even a small increase in the T<sub>4</sub> or T<sub>3</sub> level in blood abolishes this response. Thus a subnormal or absent serum TSH response to TRH is a very sensitive indicator of hyperthyroidism. In one group of disorders involving hyperthyroidism, serum TSH levels are elevated in the presence of elevated levels of free thyroid hormone.

Measurement of the  $\alpha$ -subunit of TSH has been helpful in identifying the rare patients who have a pituitary neoplasm and who usually have increased  $\alpha$ -subunit concentrations. Some patients are clinically euthyroid in the presence of elevated levels of total T<sub>4</sub> in serum. Certain drugs, notably propranolol, glucocorticoids, and amiodarone, block the conversion of T<sub>4</sub> to T<sub>3</sub> and thereby elevate T<sub>4</sub> levels. Severe illness also slows this conversion, termed “sick thyroid” in a critical-illness setting. Levels of TSH are often high in situations in which the rate of conversion is decreased. In hyperthyroidism, cardiac function and responses to stress are abnormal; return of normal cardiac function parallels the return of TSH levels to normal.

### Hyperthyroidism

Although hyperthyroidism is usually caused by the multinodular diffuse enlargement in Graves disease (also associated with disorders of the skin or eyes, or both), it can also occur with pregnancy, thyroiditis, thyroid adenoma, choriocarcinoma, or TSH-secreting pituitary adenoma. Five percent of women have thyrotoxic effects 3 to 6 months postpartum and tend to have recurrences with subsequent pregnancies. Major manifestations of hyperthyroidism are weight loss, diarrhea, warm and moist skin, weakness of large muscle groups, menstrual abnormalities, osteopenia, nervousness, jitteriness, intolerance to heat, tachycardia, cardiac arrhythmias, mitral valve prolapse, and heart failure. When the thyroid is functioning abnormally, the cardiovascular system is most at risk. When diarrhea is severe, the associated dehydration and electrolyte abnormalities should be corrected preoperatively. Mild anemia, thrombocytopenia, increased serum alkaline phosphatase, hypercalcemia, muscle wasting, and bone loss frequently occur in

hyperthyroidism. Muscle disease usually involves the proximal large muscle groups; it has not been reported to cause respiratory muscle paralysis. In the apathetic form of hyperthyroidism (seen most commonly in persons  $>60$  years old), cardiac effects predominate and include tachycardia, irregular heart rhythm, atrial fibrillation (in 10%), heart failure, and occasionally, papillary muscle dysfunction.

Although  $\beta$ -adrenergic receptor blockade can control the heart rate, its use is challenging in the setting of heart failure. However, a decreasing heart rate may improve heart-pumping function. Thus hyperthyroid patients who have fast ventricular rates and in heart failure, requiring emergency surgery, can be safely given short-acting  $\beta$ -blockers guided by clinical response. If slowing the heart rate with a small dose of esmolol (50  $\mu\text{g}/\text{kg}$ ) does not aggravate the heart failure, the physician should administer more esmolol, and titrate to effect. Antithyroid medications include propylthiouracil and methimazole, both of which decrease the synthesis of  $\text{T}_4$  and may enhance remission by reducing TSH receptor antibody levels (the primary pathologic mechanism in Graves disease). Propylthiouracil also decreases the conversion of  $\text{T}_4$  to the more potent  $\text{T}_3$ . However, the literature indicates a trend toward preoperative preparation with propranolol and iodides alone.<sup>79</sup> This approach is quicker (i.e., 7–14 days vs. 2–6 weeks); it shrinks the thyroid gland, as does the more traditional approach; it decreases conversion of the prohormone  $\text{T}_4$  into the more potent  $\text{T}_3$ ; and it treats symptoms but may not correct abnormalities in left ventricular function. Regardless of the approach, antithyroid drugs should be administered on a long-term basis and on the morning of the surgical procedure. If emergency surgery is necessary before the euthyroid state is achieved, if subclinical hyperthyroidism progresses without adequate treatment, or if hyperthyroidism is out of control intraoperatively, intravenous administration of esmolol, 50 to 500  $\mu\text{g}/\text{kg}$ , could be titrated to restore a normal heart rate (assuming the absence of heart failure). In addition, intravascular fluid volume and electrolyte balance should be restored. However, administering propranolol or esmolol does not always prevent “thyroid storm.” No specific anesthetic drug is preferred for surgical patients who have hyperthyroidism.

A patient with a large goiter and an obstructed airway can be managed in the same way as any other patient with a problematic airway. In this type of case, reviewing CT scans of the neck preoperatively may provide valuable information regarding the extent of compression. Maintenance of anesthesia usually presents little difficulty. Postoperatively, extubation of the trachea should be performed under optimal circumstances for reintubation in the event that tracheomalacia (the tracheal rings have been weakened and the trachea collapses) developed.

Of the many possible postoperative complications including: nerve injury, bleeding, metabolic abnormalities, and thyroid storm (discussed in the next section); bilateral recurrent laryngeal nerve trauma and hypocalcemic tetany are the most feared. Bilateral recurrent laryngeal nerve injury (secondary to trauma or edema) causes stridor and laryngeal obstruction as a result of unopposed adduction of the vocal cords and closure of the glottic aperture. Immediate endotracheal intubation is required, usually followed by tracheostomy to ensure an adequate airway. Fortunately,

Lahey Clinic records indicate that this rare complication occurred only once in more than 30,000 thyroid operations. Unilateral recurrent nerve injury often goes unnoticed because of compensatory overadduction of the uninvolved cord. However, we often test vocal cord function before and after this operation by asking the patient to say “e” or “moon.” Unilateral nerve injury is characterized by hoarseness, whereas aphonia characterizes bilateral nerve injury. Selective injury to the adductor fibers of both recurrent laryngeal nerves leaves the abductor muscles relatively unopposed, and pulmonary aspiration is a risk. Selective injury to the abductor fibers leaves the adductor muscles relatively unopposed, and airway obstruction can occur.

The intimate involvement of the parathyroid gland with the thyroid gland can result in inadvertent hypocalcemia during surgery for thyroid disease. Complications related to hypocalcemia are discussed in the later section on this disorder.

Because postoperative hematoma can compromise the airway, neck and wound dressings are placed in a crossing fashion (rather than vertically or horizontally) and should be examined for evidence of bleeding before a patient is discharged from the recovery room.

### Thyroid Storm

Thyroid storm is the name for the clinical diagnosis of a life-threatening illness in a patient whose hyperthyroidism has been severely exacerbated by illness or surgery. Thyroid storm is characterized by hyperthermia or pyrexia, tachycardia, and striking alterations in consciousness. Its clinical appearance is similar to malignant hyperthermia, pheochromocytoma, and neuroleptic malignant syndrome, further complicating the differential.<sup>79a</sup> No laboratory tests are diagnostic of thyroid storm, and the precipitating (non-thyroidal) cause is the major determinant of survival. Therapy can include blocking the synthesis of thyroid hormones by administering antithyroid drugs and the release of pre-formed hormone with iodine. Blocking the sympathetic nervous system symptoms with reserpine,  $\alpha$ - and  $\beta$ -receptor antagonists, or  $\alpha_2$  drugs may be exceedingly hazardous and requires skillful management with constant monitoring of the critically ill patient.

Thyroid dysfunction, either hyperthyroidism or hypothyroidism, develops in more than 10% of patients treated with the antiarrhythmic agent amiodarone.<sup>80</sup> Approximately 35% of the drug’s weight is iodine, and a 200-mg tablet releases approximately 20 times the optimal daily dose of iodine. This iodine can lead to reduced synthesis of  $\text{T}_4$  or increased synthesis. In addition, amiodarone inhibits the conversion of  $\text{T}_4$  to the more potent  $\text{T}_3$ . These patients receiving amiodarone are in need of special attention preoperatively and intraoperatively, not just because of the arrhythmia that led to such therapy, but to ensure that no perioperative dysfunction or surprises result from unsuspected thyroid hyperfunction or hypofunction.<sup>81</sup>

### Hypothyroidism

Hypothyroidism is a common disease that has been detected in 5% of a large population in Great Britain, in 3% to 6% of a healthy older population in Massachusetts, in 4.5% of a medical clinic population in Switzerland, and in 8.5% of a

large Turkish population presenting to an anesthesiology preoperative clinic.<sup>81a</sup> The apathy and lethargy that often accompany hypothyroidism frequently delay its diagnosis, thus the perioperative period may be the first opportunity to spot many such hypothyroid patients. However, hypothyroidism is usually subclinical, serum concentrations of thyroid hormones are in the normal range, and only serum TSH levels are elevated. The normal range of TSH is 0.3 to 4.5 milliunits/L, and TSH values of 5 to 15 milliunits/L are characteristic of this entity. In such cases, hypothyroidism may have little or no perioperative significance. However, a retrospective study of 59 mildly hypothyroid patients found that more hypothyroid patients than control subjects required prolonged postoperative intubation (9 of 59 vs. 4 of 59), had significant electrolyte imbalances (3 of 59 vs. 1 of 59), and bleeding complications (4 of 59 vs. 0 of 59).<sup>82</sup> Because only a few charts were examined, these differences did not reach statistical significance. In another study, overt hypothyroidism later developed in a high percentage of patients with a history of subclinical hypothyroidism.<sup>83,84</sup>

Overt hypothyroidism is associated with slow mental functioning, slow movement, slow reflexes, dry skin, arthralgias, carpal tunnel syndrome, periorbital edema, intolerance to cold, depression of the ventilatory responses to hypoxia and hypercapnia, impaired clearance of free water with or without hyponatremia, slow gastric emptying, sleep apnea,<sup>85</sup> and bradycardia. In extreme cases, cardiomegaly, heart failure, pericardial and pleural effusions can develop, often presenting as orthopnea, dyspnea, or general fatigue. Hypothyroidism is often associated with amyloidosis, which may produce an enlarged tongue, cardiac conduction abnormalities, and renal disease. Hypothyroidism decreases the anesthetic requirement slightly. The tongue may be enlarged in a hypothyroid patient even in the absence of amyloidosis, and such enlargement may hamper endotracheal intubation.

An increasing TSH level is the most sensitive indicator of failing thyroid function. Ideal preoperative and preprocedure management of hypothyroidism consists of restoring normal thyroid status: the physicians should consider administering the normal dose of levothyroxine the morning of the surgical procedure, even though these drugs have long half-lives (1.4-10 days). Reduced GI absorption of levothyroxine may occur with the coadministration of cholestyramine or aluminum hydroxide, iron, a high-fiber meal, or sucralfate or colestipol. For patients in myxedema coma who require emergency surgery, liothyronine (T3 hormone) can be given intravenously (with fear of precipitating myocardial ischemia, however) while supportive therapy is undertaken to restore normal intravascular fluid volume, body temperature, cardiac function, respiratory function, and electrolyte balance.<sup>85a</sup>

In hypothyroidism, respiratory control mechanisms and renal fluid balance do not function normally, however, the response to hypoxia and hypercapnia, and clearance of free water normalize with thyroid replacement therapy. Drug metabolism is anecdotally reported to be slowed, and awakening times from sedatives are reported to be prolonged by hypothyroidism. However, few formal studies, and none in humans, of the pharmacokinetics and pharmacodynamics of sedatives or anesthetic drugs in this population have been published. These concerns disappear when thyroid function

is normalized preoperatively. Addison disease (with its relative steroid deficiency) is more common in hypothyroidism, and some endocrinologists routinely treat patients with noniatrogenic hypothyroidism with stress doses of steroids perioperatively because both conditions are commonly caused by autoimmune responses. The possibility that this steroid deficiency exists should be considered if the patient becomes hypotensive perioperatively. Body heat mechanisms are inadequate in hypothyroid patients, so temperature should be monitored and maintained, especially in patients requiring emergency surgery. Because of an increased incidence of myasthenia gravis in hypothyroid patients, a peripheral nerve stimulator is used to guide judicious administration of muscle relaxants.

### Thyroid Nodules and Carcinoma

More than 90% of thyroid nodules are benign, yet identifying malignancy in a solitary thyroid nodule is a difficult and important procedure. Male patients and patients with previous radiation therapy to the head and neck have an increased likelihood of malignant disease in their nodules. Often, needle biopsy and scanning are sufficient for the diagnosis, but occasionally excisional biopsy is needed. Papillary carcinoma accounts for more than 70% of all thyroid carcinomas. Simple excision of lymph node metastases appears to be as efficacious as radical neck procedures for the patient's survival. Follicular carcinoma, which accounts for approximately 15% of thyroid carcinomas, is more aggressive, and has a less favorable prognosis.

Medullary carcinoma, the most aggressive form of thyroid carcinoma, is associated with a familial occurrence of pheochromocytoma, as are parathyroid adenomas. For this reason, a history should be obtained from patients with a surgical scar in the thyroid region so that the possibility of occult pheochromocytoma can be assessed and excluded.

### DISORDERS OF CALCIUM METABOLISM

The three substances that regulate serum concentrations of calcium, phosphorus, and magnesium are parathyroid hormone (parathyroidin, PTH), calcitonin, and vitamin D, which act on bone, kidney, gut, and their own receptors. Calcium excess in blood is caused by either malignant disease or hyperparathyroidism in more than 90% of patients.<sup>86</sup> PTH stimulates bone resorption, inhibits renal excretion of calcium, and increases conversion to active vitamin D, three conditions that lead to hypercalcemia. Calcitonin can be considered an antagonist to PTH. Through its metabolites, vitamin D aids in the absorption of calcium, phosphate, and magnesium from the gut and facilitates the bone resorptive effects of PTH. Secretion of PTH is modulated through the calcium-sensing receptor on the cell surface of parathyroid cells. An increase in ionized calcium stimulates this receptor and thus causes a decrease in PTH secretion. Recognition of this effect has led to reevaluation of the therapy for hyperparathyroidism inasmuch as a drug upregulating this receptor's sensitivity reduces PTH levels.<sup>87</sup>

### Hyperparathyroidism and Hypercalcemia

Primary hyperparathyroidism occurs in approximately 0.1% of the population, most commonly begins in the third to fifth decades of life, and occurs two to three times more

frequently in women than in men. Primary hyperparathyroidism usually results from enlargement of a single gland, commonly an adenoma and very rarely a carcinoma. Hypercalcemia almost always develops.

Calcium is the chief mineral component of the body; it provides structure to the skeleton and performs key roles in neural transmission, intracellular signaling, blood coagulation, and neuromuscular functioning. Ninety-nine percent of the 1000 g of calcium present in the average human body is stored in the bone mineral reservoir. Fifty percent to 60% is bound to plasma proteins or is complexed with phosphate or citrate. The normal total serum calcium level is 8.6 to 10.4 mg/dL, as measured in most laboratories; though this value depends on the albumin level, noting a decline of 0.8 mg/dL for each 1 g/dL drop in albumin. Binding of calcium to albumin depends on pH: binding decreases with acidic pH and increases with alkaline pH. Serum calcium, not ionized calcium, decreases with reductions in albumin levels. Although ionized calcium is the clinically significant fraction, the cost and technical difficulties of stabilizing the electrodes used for measurement have limited the available assays. Nevertheless, PTH and vitamin D<sub>3</sub> work to keep the level stable within 0.1 mg/dL in any individual.

Many of the prominent symptoms of hyperparathyroidism are a result of the hypercalcemia that accompanies it. Regardless of the cause, hypercalcemia can produce any of a number of symptoms, the most prominent of which involve the renal, skeletal, neuromuscular, and GI system, including anorexia, vomiting, constipation, polyuria, polydipsia, lethargy, confusion, renal calculi, pancreatitis, bone pain, and psychiatric abnormalities. Free intracellular calcium initiates or regulates muscle contraction, release of neurotransmitters, secretion of hormones, enzyme action, and energy metabolism.

Nephrolithiasis occurs in 60% to 70% of patients with hyperparathyroidism. Sustained hypercalcemia can result in tubular and glomerular disorders, including proximal (type II) renal tubular acidosis. Polyuria and polydipsia are common complaints.

Skeletal disorders related to hyperparathyroidism are osteitis fibrosa cystica, simple diffuse osteopenia, and osteoporosis. The rate of bone turnover is five times higher in patients with hyperparathyroidism than in normal controls. Patients may have a history of frequent fractures or may complain of bone pain, especially in the anterior margin of the tibia.

Because free intracellular calcium initiates or regulates muscle contraction, neurotransmitter signaling, hormone secretion, enzyme action, and energy metabolism, abnormalities in these end organs are often symptoms of hyperparathyroidism. Patients may experience profound muscle weakness, especially in proximal muscle groups, as well as muscle atrophy. Depression, psychomotor retardation, and memory impairment may occur. Lethargy and confusion are frequent complaints.

Peptic ulcer disease is more common in these patients than in the rest of the population. Production of gastrin and gastric acid is increased. Anorexia, vomiting, and constipation may also be present.

Approximately one third of all hypercalcemic patients are hypertensive, but the hypertension usually resolves with successful treatment of the primary disease. Neither

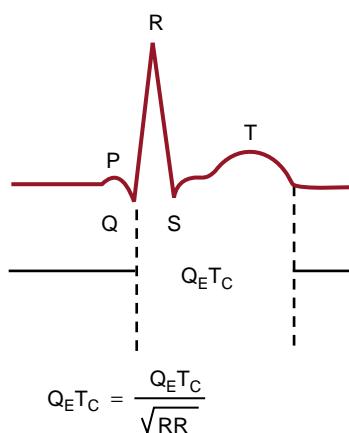
hypertension nor minimally invasive surgery seems to alter the perioperative risk associated with surgery in such patients in comparison with the usual hypertensive patients.<sup>88,89</sup> Even octogenarians with asymptomatic hyperparathyroidism can be operated on without mortality and with morbidity no different from that in younger individuals, thus encouraging the use of parathyroidectomy as preventive therapy.<sup>90</sup> Long-standing hypercalcemia can lead to calcifications in the myocardium, blood vessels, brain, and kidneys. Cerebral calcifications may cause seizures, whereas renal calcifications lead to polyuria that is unresponsive to vasopressin.<sup>90</sup>

The most useful confirmatory test for hyperparathyroidism is radioimmunoassay for PTH. In fact, two changes have radically reduced anesthesia involvement in the care of patients with primary hyperparathyroidism. One change, the use of the calcimimetic drug class which modulates the calcium-sensitive PTH cell receptor and thereby decreases calcium levels, has been emphasized in older individuals. The other change is use of minimally invasive approaches after imaging procedures with just local anesthesia or a cervical plexus block—as with thyroidectomy.<sup>91,92</sup> Most surgeons now performing minimally invasive parathyroid removal monitor PTH levels intraoperatively to determine whether the causative adenoma has been resected. The baseline PTH level should be determined before induction of anesthesia because even monitored anesthesia care increases PTH levels.<sup>93</sup> In hyperparathyroid patients, hormone levels are abnormal for a given level of calcium. The level of inorganic phosphorus in serum is usually low, but it may be within normal limits. Alkaline phosphatase levels are elevated if considerable skeletal involvement is present.

Glucocorticoid administration reduces the level of calcium in blood in many other conditions that cause hypercalcemia, but not usually in primary hyperparathyroidism. In sarcoidosis, multiple myeloma, vitamin D intoxication, and some malignant diseases, all of which can cause hypercalcemia, administration of glucocorticoids may lower serum calcium levels through an effect on GI absorption. This effect occurs to a lesser degree in primary hyperparathyroidism.

Hypercalcemia may also occur as a consequence of secondary hyperparathyroidism in patients who have chronic renal disease. When phosphate excretion decreases as a result of decreased nephron mass, serum calcium levels fall because of deposition of calcium and phosphate in bone. Secretion of PTH subsequently increases, and this causes the fraction of phosphate excreted by each nephron to increase. Eventually, the chronic intermittent hypocalcemia of chronic renal failure leads to chronically high levels of serum PTH and hyperplasia of the parathyroid glands—one of the entities termed secondary hyperparathyroidism.

Symptomatic primary hyperparathyroidism in patients younger than 50 years or with serum calcium levels more than 1 mg/dL higher than the upper limit of normal, a 30% or greater reduction in the glomerular filtration rate (GFR), or severe bone demineralization is usually treated surgically. If the patient refuses surgery or if other illnesses render surgery inadvisable, medical management with the calcimimetic, cinacalcet, makes management much more feasible. The difficulty with such management is that the hyperfunctioning parathyroid glands secrete more hormone as the serum calcium concentration is lowered—as



**Fig. 32.3** Measurement of the QTc interval (properly termed  $Q_E T_C$  to indicate that it begins with the start of the Q wave, lasts throughout the QT interval, ends with the end of the T wave, and is corrected for heart rate). RR is the RR interval in seconds. (From Hensel P, Roizen MF. Patients with disorders of parathyroid function. *Anesthesiol Clin North Am*. 1987;5:287–291.)

though the calcium set point for feedback regulation of PTH secretion had been raised. Blanchard and colleagues demonstrated that patients with “asymptomatic” primary hyperparathyroidism have clinical improvement of their symptoms postoperatively even after 1 year, noting younger patients and those with higher preoperative calcium levels show the best improvement.<sup>94</sup>

Patients with moderate hypercalcemia who have normal renal and cardiovascular function present no special preoperative and preprocedure problems. The ECG can be examined preoperatively and intraoperatively for shortened PR or QT intervals (Fig. 32.3). Because severe hypercalcemia can result in substantial hypovolemia, normal intravascular volume and electrolyte status should be evaluated and then restored before anesthesia and surgery.

Management of hypercalcemia preoperatively should include (even in urgent or emergency situations) treatment of the underlying cause, a frequent strategy in surgical patients with malignancy-associated hypercalcemia. Therapy preoperatively for both malignant and nonmalignant causes of hypercalcemia include aggressive volume repletion, with the addition of diuresis only if volume overload develops. Intravenous fluid infusion rates of 250 to 500 mL/h preoperatively are commonly used to maintain urine output greater than 200 mL/h.<sup>94a</sup> Careful monitoring during this time is needed to avoid administration of an excessive amount of intravenous fluids, as many patients may have compromised cardiac function. In the setting of fluid overload, diuresis with furosemide can be warranted; however, evidence for benefit is limited and mainly theoretical.<sup>94a</sup> Other complications of these interventions include hypomagnesemia and hypokalemia.

In emergency situations, vigorous expansion of intravascular volume usually reduces serum calcium to a safe level (<14 mg/dL). Phosphate should be given to correct hypophosphatemia because it decreases calcium uptake into bone, increases calcium excretion, and stimulates breakdown of bone. Hydration, accompanied by electrolyte repletion mainly phosphate, suffices in the management of most hypercalcemic patients. Other measures to decrease

reabsorption of bone include the bisphosphonates pamidronate sodium (90 mg intravenously) and zoledronate (4 mg intravenously). Case reports note success in the setting of extreme hypercalcemia (>20 mg/dL) correction with a low calcium bath dialysate.<sup>94b</sup>

Calcitonin lowers serum calcium levels through direct inhibition of bone resorption. It can decrease serum calcium levels within minutes after intravenous administration. Side effects include urticaria and nausea. It is so rapid acting that it can be used to reduce calcium levels while waiting for hydration and a bisphosphonate to take effect.

It is especially important to know whether the hypercalcemia has been chronic because serious cardiac, renal, or CNS abnormalities may have resulted.

### Hypocalcemia

Hypocalcemia (caused by hypoalbuminemia, hypoparathyroidism, hypomagnesemia, hypovitaminosis D, hungry bone syndrome after correction of hyperparathyroidism, anticonvulsant therapy, citrate infusion, or chronic renal disease) is not usually accompanied by a clinically evident cardiovascular disorder. The most common cause of hypocalcemia is hypoalbuminemia. In true hypocalcemia (i.e., when the free calcium concentration is low), myocardial contractility is affected, noting myocardial contractility varies directly with levels of blood ionized calcium. The clinical signs of hypocalcemia include clumsiness; convulsions; laryngeal stridor; depression; muscle stiffness; paresthesias; parkinsonism; tetany; Chvostek sign; dry and scaly skin, brittle nails, and coarse hair; low serum concentrations of calcium; prolonged QT intervals; soft tissue calcifications; and Trouseau sign.

Hypocalcemia delays ventricular repolarization, hence increasing the QTc interval (normal, 0.35–0.44 second). With electrical systole prolonged, the ventricles may fail to respond to the next electrical impulse from the sinoatrial node, with second-degree heart block resulting. Prolongation of the QT interval is a moderately reliable ECG sign of hypocalcemia, not for the population as a whole, but for the individual patient.<sup>95</sup> Thus monitoring the QT interval as corrected for the heart rate is a useful, but not always accurate means of monitoring hypocalcemia in any individual patient (see Fig. 32.3). Heart failure may also occur with hypocalcemia, but is rare. Because heart failure in patients with coexisting heart disease is reduced in severity when calcium and magnesium ion levels are restored to normal, these levels may be normalized preoperatively in a patient with impaired exercise tolerance or signs of cardiovascular dysfunction; normalization can be achieved intravenously over a 15-minute period if absolutely necessary. Sudden decreases in blood levels of ionized calcium (as with chelation therapy) can result in severe hypotension.

Patients with hypocalcemia may have seizures. They may be focal, petit mal, or grand mal in appearance, often indistinguishable from such seizures in the absence of hypocalcemia. Patients may also have a type of seizure called cerebral tetany, which consists of generalized tetany followed by tonic spasms. Therapy with standard anticonvulsants is ineffective and may even exacerbate these seizures (by an anti–vitamin D effect), calcium must be repleted for treatment. In long-standing hypoparathyroidism, calcifications may appear above the sella; these calcifications

represent deposits of calcium in and around small blood vessels of the basal ganglia. They may be associated with a variety of extrapyramidal syndromes.

The most common cause of acquired hypoparathyroidism is surgery of the thyroid or parathyroid glands. Other causes include autoimmune disorders, therapy with iodine-131, hemosiderosis or hemochromatosis, neoplasia, and granulomatous disease. Idiopathic hypoparathyroidism has been divided into three categories: an isolated persistent neonatal form, branchial dysembryogenesis, and autoimmune candidiasis related to multiple endocrine deficiency.

Pseudohypoparathyroidism and pseudopseudohypoparathyroidism are rare hereditary disorders characterized by short stature, obesity, rounded face, and shortened metacarpals. Patients with pseudohypoparathyroidism have hypocalcemia and hyperphosphatemia despite high serum levels of PTH. These patients have a deficient end-organ response to PTH as a result of abnormalities in G-protein function.

Because treatment of hypoparathyroidism is not surgical, hypoparathyroid patients who come to the operating room are those who require surgery for unrelated conditions. Their calcium, phosphate, and magnesium levels should be measured both preoperatively and postoperatively. Patients with symptomatic hypocalcemia may be treated with intravenous calcium gluconate preoperatively. Initially, 10 to 20 mL of 10% calcium gluconate may be given at a rate of 5 mL/min. The effect on serum calcium levels is of short duration, but a continuous infusion with 10 mL/min of 10% calcium gluconate in 500 mL of solution over a period of 6 hours helps keep serum calcium at adequate levels. For severe symptoms in emergent settings, 10 mL of 10% calcium chloride may be given over 10 minutes, followed by a 10% calcium gluconate infusion. Magnesium and phosphate levels may also require normalization to normalize cardiovascular and nervous system function.

The objective of therapy is to bring the symptoms under control before the surgical procedure and anesthesia. For patients with chronic hypoparathyroidism, the objective is to keep the serum calcium level in the lower half of the normal range. A preoperative and preprocedure ECG is useful for maintaining the QTc interval. The preoperative and preprocedure QTc value may be used as a guide to the serum calcium level if rapid laboratory assessment is not possible. Changes in the calcium level may alter the duration of muscle relaxation; thus careful monitoring and titration of muscle relaxation with a twitch monitor is necessary.

The intimate involvement of the parathyroid gland with the thyroid gland can result in unintentional hypocalcemia during surgery for diseases of either organ. Because of the affinity of their bones for calcium, this relationship is crucial in patients with advanced osteitis. Internal redistribution of magnesium, calcium, or both ions may occur (into "hungry bones") after parathyroidectomy and may cause hypomagnesemia, hypocalcemia, or both. Because the tendency to tetany increases with alkalosis, hyperventilation should be avoided. The most prominent manifestations of acute hypocalcemia are distal paresthesias and muscle spasm (tetany). Potentially fatal complications of severe hypocalcemia include laryngeal spasm and hypocalcemic seizures. The clinical sequelae of magnesium deficiency include cardiac

arrhythmias (principally ventricular tachyarrhythmias), hypocalcemic tetany, and neuromuscular irritability independent of hypocalcemia (tremors, twitching, asterixis, and seizures).

In addition to monitoring total serum calcium or ionized calcium postoperatively, one can test for the Chvostek and Troussseau signs. The Chvostek sign is a contracture of the facial muscles produced by tapping the ipsilateral facial nerve at the angle of the jaw, of note this sign can be elicited in up to 15% of patients who are not hypocalcemic, an attempt should be made to elicit this sign preoperatively to ensure that its appearance is meaningful. The Troussseau sign is elicited by applying a blood pressure cuff at a level slightly above the systolic level for a few minutes. The resulting carpopedal spasm, with contraction of the fingers and inability to open the hand, stems from the increased muscle irritability in hypocalcemic states, aggravated by ischemia produced by the blood pressure cuff.

### Osteoporosis

Fifty percent of women who are older than 65 years sustain an osteoporotic fracture. (Because men are living longer, osteoporosis has become an increasing problem for them, too, and reports indicate a 15% per decade hip fracture rate for men >65 years old.)<sup>95</sup> Men with COPD (even without steroid treatment) are at high risk for vertebral fractures. Furthermore, in either gender, each vertebral fracture is associated with up to a 10% decrease in lung capacity. Diagnosis and treatment of these conditions have increased with routine use of dual-energy x-ray absorptiometry or quantitative ultrasonography. Because T-scores and Z-scores were developed to relate changes in white postmenopausal women to those at age 21 years, care must be used in interpreting the results. Known risk factors for osteoporosis include age, relative lifetime estrogen deficiency (late menarche, amenorrhea, early menopause, nulliparity), deficiency of dietary calcium, tobacco use, increased aerobic exercise in combination with decreased weight-bearing exercise, decreased weight-bearing exercise by itself, use of soft drinks, and Asian or white ancestry. Although therapy for osteoporosis (use of bisphosphates, bone mineral depositors, weight-bearing exercises, calcium, vitamin D, estrogen, and now designer estrogens that may be useful for men, such as raloxifene [Evista]) does not have major known implications for anesthesia care.<sup>96-98</sup> Bone fractures in such patients have occurred on movement to and from an operating table, therefore these patients should be allowed to move and position themselves when possible. Recombinant PTH and calcitonin are also used, but again, no reports of perioperative interactions have been prominent.

## PITUITARY ABNORMALITIES

### Anterior Pituitary Hypersecretion

The anterior pituitary gland (or master endocrine gland) consists of five identifiable types of secretory cells and hormones produced: somatotrophs (GH), corticotrophs (ACTH), lactotrophs (prolactin), gonadotrophs (luteinizing hormone and follicle-stimulating hormone), and thyrotrophs (TSH). Secretion of these pituitary hormones is largely regulated by a negative-feedback loop by hypothalamic regulatory hormones and by signals that originate from the target site

of pituitary action. Six hypothalamic hormones have been characterized: dopamine, the prolactin-inhibiting hormone; somatostatin, the GH release-inhibiting hormone; GH-releasing hormone; corticotropin-releasing hormone; gonadotropin-releasing hormone; and TRH. Most pituitary tumors (>60%) are hypersecretory and are classified according to the excess production of a specific anterior pituitary hormone.

The most common disorders of pituitary hypersecretion are those related to excesses of prolactin (amenorrhea, galactorrhea, and infertility), ACTH (Cushing syndrome), and GH (acromegaly). In addition to knowing the pathophysiological processes of the disease involved, the anesthesiologist must determine whether the patient recently underwent air pneumoencephalography (almost obsolete, but still used rarely). If so, nitrous oxide should not be used to lessen the risk of intracranial hypertension from gas collection. CT or MRI of the sella has largely replaced neuroencephalography.

More than 99% of cases of acromegaly are attributable to pituitary adenoma (or use of recombinant human GH). Thus the primary treatment of acromegaly is transsphenoidal surgery (or withdrawal of drug) and symptomatic treatment of the carpal tunnel or other syndromes provoked. If the pituitary tumor is not totally removed, patients are often offered external pituitary irradiation. In the case of suprasellar extension, conventional transfrontal hypophysectomy is often performed. The dopaminergic agonist bromocriptine can lower GH levels, but the long-term follow-up with this drug is not favorable. Octreotide, a long-acting analogue of somatostatin, now given in depot form approximately once a month, produces effective palliation in 50% of patients. Other medical therapies such as pegvisomant or somatostatin analogues are also medications that have been tried before surgical intervention. In 2011, new guidelines were published with few changes to the available recommendations.<sup>99</sup> However, the new guidelines reported some evidence that medication taken preoperatively may result in a better postoperative outcome.

Difficulty with endotracheal intubation should be anticipated in a patient with acromegaly; lateral neck radiographs or CT scans of the neck and direct or indirect visualization can identify patients with subglottic stenosis or an enlarged tongue, mandible, epiglottis, or vocal cords. If placement of an arterial line is necessary, a brachial or femoral site may be preferable to a radial site.<sup>100</sup>

### Anterior Pituitary Hypofunction

Anterior pituitary hypofunction results in deficiency of one or more of the following hormones: GH, TSH, ACTH, prolactin, or gonadotropin. No special preoperative and preprocedure preparation is required for a patient deficient in prolactin or gonadotropin; deficiency in GH, however, can result in atrophy of cardiac muscle, a condition that may necessitate preoperative and preprocedure cardiac evaluation. Nonetheless, anesthetic problems have not been documented in patients with isolated GH deficiency. Acute deficiencies are another matter.

Acute pituitary deficiency is often caused by bleeding into a pituitary tumor. In surgical specimens of resected adenomas, as many as 25% show evidence of hemorrhage. These patients often have acute headache, visual loss, nausea

or vomiting, ocular palsies, disturbances of consciousness, fever, vertigo, or hemiparesis. In such patients, rapid transsphenoidal decompression should be accompanied by consideration of replacement therapy, including glucocorticoids and the treatment of increased intracranial pressure.

Obstetric anesthesiologists are often aware of these pituitary failure problems; Sheehan syndrome is the clinical manifestation of pituitary infarction associated with hypotension during or after obstetric hemorrhage. Conditions that strongly suggest this diagnosis are failure to start postpartum lactation, increasing fatigue, cold intolerance, and especially hypotension unresponsive to volume replacement and pressors; treatment is prompt hormone therapy.<sup>100a</sup>

### Posterior Pituitary Hormone Excess and Deficiency

Secretion of vasopressin or antidiuretic hormone (ADH) is enhanced by increased serum osmolality or the presence of hypotension. Inappropriate secretion of vasopressin, without relation to serum osmolality, results in hyponatremia and fluid retention. This inappropriate secretion can result from the following: a variety of CNS lesions; drugs including nicotine, narcotics, tramadol, chlorpropamide, clofibrate, vincristine, vinblastine, and cyclophosphamide; and pulmonary infections, hypothyroidism, adrenal insufficiency, and ectopic production from tumors. Preoperative and preprocedure management of a surgical patient with inappropriate secretion of vasopressin includes appropriate treatment of the causative disorders and restriction of water. Occasionally, drugs that inhibit the renal response to ADH (e.g., lithium or demeclocycline) should be administered preoperatively to restore normal intravascular volume and electrolyte status.

Most of the clinical features associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) are related to hyponatremia and the resulting brain edema; such features include weight gain, weakness, lethargy, mental confusion, obtundation, and disordered reflexes and may culminate in convulsions and coma.

Investigators have recognized that up to 20% of long-distance runners have SIADH with increased vasopressin secretion. Because such people infrequently undergo surgical treatment of injuries, SIADH symptoms and laboratory evaluation may be routine for that group as well.

SIADH should be suspected in any patient with hyponatremia who excretes urine that is hypertonic relative to plasma. The following laboratory findings further support the diagnosis:

1. Urinary sodium greater than 20 mEq/L
2. Low serum levels of BUN, creatinine, uric acid, and albumin
3. Serum sodium lower than 130 mEq/L
4. Plasma osmolality lower than 270 mOsm/L
5. Urine hypertonic relative to plasma

Noting the response to water loading is a useful way of evaluating patients with hyponatremia. Patients with SIADH are unable to excrete dilute urine even after water loading. Assay of ADH in blood can confirm the diagnosis. Too vigorous treatment of chronic hyponatremia can result in disabling osmotic demyelination syndrome.<sup>101,102</sup> The increase in serum sodium should not be greater than 1 mEq/L/h.<sup>101,102</sup>

Patients with mild to moderate symptoms of water intoxication can be treated with restriction of fluid intake to approximately 500 to 1000 mL/day. Patients with severe water intoxication and CNS symptoms may need vigorous treatment consisting of intravenous administration of hypertonic saline solutions until symptoms resolve, followed by fluid restriction.

Treatment should be directed at the underlying problem. If SIADH is drug induced, use of the drug should be withdrawn. Inflammation should be treated with appropriate measures, and neoplasms should be managed by surgical resection, irradiation, or chemotherapy, whichever is indicated.

No drugs are available that can suppress release of ADH from the neurohypophysis or from a tumor. Phenytoin (Dilantin) and narcotic antagonists such as naloxone and butorphanol have some inhibiting effect on physiologic ADH release but are clinically ineffective in patients with SIADH. Drugs that block the effect of ADH on renal tubules include lithium, which is rarely used because its toxicity often outweighs its benefits, and demethylchlortetracycline in doses of 900 to 1200 mg/day. Demethylchlortetracycline interferes with the ability of the renal tubules to concentrate urine, thereby causing excretion of isotonic or hypotonic urine and lessening the hyponatremia. This drug can be used in ambulatory patients with SIADH when it is difficult to restrict fluids.

When a patient with SIADH comes to the operating room for any surgical procedure, fluids are managed by measuring volume status, when the clinical picture is unclear the use of arterial wave form analysis, central venous pressure, pulmonary artery pressure, or transthoracic and/or transesophageal echocardiography may be of value. Despite the common impression that SIADH is frequently seen in older patients in the postoperative period, studies have shown that the patient's age and the type of anesthetic used have no bearing on the postoperative development of SIADH. It is common to see several patients in the neurosurgical ICU suffering from this syndrome. The diagnosis is usually one of exclusion. Patients with SIADH generally require only restriction of intravenous fluids, very rarely is hypertonic saline needed.

Lack of ADH, which results in diabetes insipidus, is caused by pituitary disease, brain tumors, infiltrative diseases such as sarcoidosis, head trauma (including trauma after neurosurgery), or lack of a renal response to ADH. The last can result from such diverse conditions as hypokalemia, hypercalcemia, sickle cell anemia, obstructive uropathy, and renal insufficiency. Preoperative or preprocedure treatment of diabetes insipidus consists of restoring normal intravascular volume by replacing urinary losses, administering desmopressin acetate (DDAVP) nasally, and giving daily fluid requirements intravenously.

Perioperative management of patients with diabetes insipidus is based on the extent of the ADH deficiency. Management of a patient with complete diabetes insipidus and a total lack of ADH does not usually present any major problem as long as the side effects of the drug are avoided and the presence of the condition is known preoperatively. Just before the surgical procedure, the patient is given the usual dose of DDAVP intranasally or an intravenous bolus of 100 milliunits of aqueous vasopressin, followed by a

constant infusion of 100 to 200 milliunits/h.<sup>1</sup> The dose is usually adjusted to permit the daily breakthrough polyuria that prevents the iatrogenic syndrome of SIADH. All the intravenous fluids given intraoperatively should be isotonic to reduce the risk of water depletion and hypernatremia. Plasma osmolality should be frequently measured, both intraoperatively and immediately postoperatively. If plasma osmolality rises much higher than 300 mOsm/L, hypotonic fluids can be administered; the rate of the intraoperative vasopressin infusion can be increased to greater than 200 milliunits/h.

For patients who have a partial deficiency of ADH, it is not necessary to use aqueous vasopressin perioperatively unless plasma osmolality rises to more than 300 mOsm/L. Nonosmotic stimuli (e.g., volume depletion) and the stress of surgery usually cause the release of large quantities of ADH perioperatively. Consequently, these patients require only frequent monitoring of plasma osmolality during this period.

Because of side effects, the dose of vasopressin should be limited to that necessary for control of diuresis. The oxytocic and coronary artery-constricting properties of vasopressin make this limit especially applicable to patients who are pregnant or have CAD.

## Diseases Involving the Cardiovascular System

### HYPERTENSION

Analysis of the perioperative treatment of hypertension is important because of the prevalence of the condition (33.5% of adults aged 20 and over in the United States), the great risk in perioperative care of a hypertensive patient, and the high cost of unnecessary delays in surgical treatment. Numerous studies over the years have evaluated the impact of hypertension as one of the risk factors for cardiac morbidity. However, the need to delay surgery because of poorly controlled hypertension has been questioned. Wekster and colleagues studied 989 hypertensive patients who were treated on a long-term basis and who underwent noncardiac surgery with diastolic blood pressure between 110 and 130 mm Hg and no previous MI, unstable or severe angina pectoris, renal failure, pregnancy-induced hypertension, left ventricular hypertrophy, previous coronary revascularization, aortic stenosis, preoperative dysrhythmias, conduction defects, or stroke.<sup>103</sup> The control group had their surgical procedures postponed and remained in the hospital for control of blood pressure, and the study patients received 10 mg of nifedipine intranasally. No statistically significant differences in postoperative complications were observed, thus suggesting that this subset of patients without significant cardiovascular comorbid conditions can proceed with surgery despite elevated blood pressure on the day of the operation.

Several studies have assessed the relationship between cardiovascular disease and preoperative hypertension. In a multicenter study of patients undergoing coronary artery bypass graft (CABG), the presence of isolated systolic hypertension was associated with a 30% increased incidence of perioperative cardiovascular complications

when compared with normotensive individuals.<sup>104</sup> Khetpal and colleagues integrated data from their anesthesia information system (AIMS) and the American College of Surgeons National Surgical Quality Improvement Project (NSQIP) and found hypertension to be one of the independent predictors of events.<sup>105</sup> Wax and colleagues used AIMS to identify independent predictors of troponin elevation or death, and independent predictors of adverse outcome included increased baseline systolic blood pressure (SBP), intraoperative diastolic blood pressure lower than 85 mm Hg, increased intraoperative heart rate, blood transfusion, and anesthetic technique, controlling for standard risk factors.<sup>106</sup> A delay of surgery did not result in interval normalization of blood pressure.

Although preoperative blood pressure (both systolic and diastolic) is a significant predictor of postoperative morbidity, no data definitively establish whether preoperative treatment of hypertension reduces perioperative risk. Until a definitive study is performed, we recommend letting the weight of evidence guide preoperative treatment of a patient with hypertension. Such treatment would be based on three general beliefs: (1) the patient should be educated regarding the importance of lifelong treatment of hypertension, even isolated systolic hypertension; (2) perioperative hemodynamic fluctuations occur less frequently in treated than in untreated hypertensive patients (as demonstrated by Prys-Roberts and colleagues<sup>107</sup> and confirmed by Goldman and Caldera<sup>108</sup> and Mangano and associates<sup>109</sup>); and (3) hemodynamic fluctuations have some relation to morbidity. Khetpal and colleagues demonstrated that patients who sustained a cardiac adverse event were more likely to experience an episode of mean arterial pressure lower than 50 mm Hg, an episode of 40% decrease in mean arterial pressure, and an episode of heart rate higher than 100 beats/min.<sup>105</sup> The data of Pasternack and colleagues and Weksler and associates imply that rapid correction of blood pressure or prevention of increases in heart rate may be all that is needed.<sup>103,110</sup> Sessler and colleagues (2018) studied 9765 patients in the POISE-II trial to assess the relationship between perioperative hypotension and a composite of MI and death within 30-days of surgery.<sup>110aa</sup> Intraoperatively, the estimated average relative effect was 1.08 (98.3% confidence interval [CI], 1.03, 1.12;  $P < .001$ ) per 10-minute increase in hypotension duration. The average relative effect odds ratio was 2.83 (98.3% CI, 1.26, 6.35;  $P = .002$ ) in patients with hypotension during the subsequent 4 days of hospitalization. The Intraoperative Nor-epinephrine to Control Arterial Pressure (INPRESS) study was a multicenter, randomized, parallel-group clinical trial in adult patients ( $n = 298$ ) at increased risk of postoperative complications of individualized management strategy aimed at achieving a SBP within 10% of the reference value (i.e., patient's resting SBP) or standard management strategy of treating SBP less than 80 mm Hg or lower than 40% from the reference value during and for 4 hours following surgery.<sup>110a</sup> Management targeting an individualized SBP, compared with standard management, reduced the risk of postoperative organ dysfunction. Taken together, these data suggest that maintenance of normal blood pressure is critical in patients with hypertension.

The INPRESS study demonstrated that preoperative data should be used to determine the individualized range of

suitable arterial blood pressure values that are tolerable by a particular patient during and after a surgical procedure. Importantly, hypotension in patients at risk for a cerebrovascular event should be avoided. For example, the POISE (Perioperative Ischemic Evaluation) study demonstrated that short-term  $\beta$ -blocker administration resulted in an increased incidence of stroke and death that was associated with an increased rate of hypotension.<sup>111</sup>

### Preoperative Administration of All Antihypertensive Drugs

Continuation of all antihypertensive drugs preoperatively should be considered, except ACE inhibitors or angiotensin II antagonists, for which no clear consensus exists. Coriat and colleagues found that ACE inhibitors were associated with hypotension in 100% of patients during induction versus approximately 20% in whom ACE inhibitors were withheld on the morning of the surgical procedure.<sup>112</sup> Bertrand and coworkers performed a prospective randomized study that demonstrated that more severe hypotensive episodes requiring vasoconstrictor treatment occurred after induction of general anesthesia in patients treated on a long-term basis with an angiotensin II antagonist and receiving the drug on the morning before the operation than in those in whom angiotensin II antagonists were discontinued on the day before the surgical procedure.<sup>113</sup> Khetpal and colleagues performed a propensity-matched analysis of 12,381 noncardiac surgical cases.<sup>114</sup> Patients with long-term ACE inhibitor or angiotensin receptor blocker (ARB) and diuretic therapy showed more periods with a mean arterial blood pressure lower than 70 mm Hg, periods with a 40% decrease in SBP, periods with a 50% decrease in SBP, and vasopressor boluses than did patients receiving diuretic therapy alone. If these drugs are continued, vasopressin is the drug of choice for refractory hypotension. Investigators at the Cleveland Clinic evaluated 79,228 patients (9905 ACE inhibitor users [13%] and 66,620 [87%] non-ACE inhibitor users) who had noncardiac surgery between 2005 and 2009.<sup>115</sup> These investigators did not find any association between use of ACE inhibitors and intraoperative or postoperative upper airway complications. ACE inhibitor use was not associated with in-hospital complications or increased 30-day mortality. Investigators of the VISION trial studied the relationship between withholding ACE inhibitors/angiotensin II receptor blockers and a primary composite outcome of all-cause death, stroke, or myocardial injury after noncardiac surgery at 30 days. Withholding ACE inhibitors/angiotensin II receptor blockers before major noncardiac surgery was associated with a lower risk of death and postoperative vascular events (150/1245 [12.0%] vs. 459/3557 [12.9%]; adjusted relative risk, 0.82; 95% CI, 0.70–0.96). In an accompanying editorial, London suggested that the current study does provide strong impetus for a randomized trial but does not warrant changes in local practice until such a trial is completed.<sup>116</sup>

### ISCHEMIC HEART DISEASE

Preoperative evaluation of a patient with ischemic heart disease and a discussion of the AHA/ACC guidelines can be found in Chapters 31 and 54.<sup>117</sup> New guidelines were published in 2014 by both the AHA/ACC and the European

Society of Cardiology as well as the Canadian Cardiovascular Society in 2017.<sup>118</sup> This chapter will focus on the AHA/ACC guideline approach.<sup>119,120</sup>

### Role of Coronary Artery Bypass Graft or Percutaneous Coronary Interventions Before Noncardiac Surgical Procedures

Coronary revascularization may reduce the perioperative risk before noncardiac surgery, but the evidence suggests that it is limited to those with indications similar to the non-surgical arena. The strongest retrospective evidence comes from the Coronary Artery Surgery Study registry, which enrolled patients from 1978 to 1981. Operative mortality in patients with CABG performed before noncardiac surgery was 0.9% but was significantly higher at 2.4% in patients without previous CABG. However, a 1.4% mortality rate was associated with the CABG procedure itself.

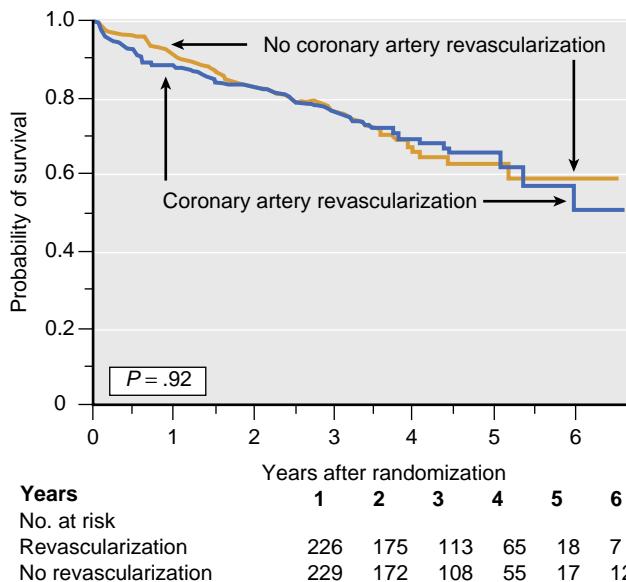
The benefit of percutaneous coronary intervention (PCI) before noncardiac surgery has also been examined in several cohort studies. Posner and colleagues used an administrative dataset of patients who underwent PCI and noncardiac surgery in Washington State.<sup>121</sup> These investigators matched patients with coronary disease who were undergoing noncardiac surgery with and without previous PCI and looked at cardiac complications. In this nonrandomized design, Posner and colleagues noted a significantly lower rate of 30-day cardiac complications in patients who underwent PCI at least 90 days before the noncardiac surgery. However, PCI within 90 days of noncardiac surgery did not improve outcome. Although the explanation for these results is unknown, they may support the notion that PCI performed “to get the patient through surgery” may not improve perioperative outcome because cardiac complications may not occur in patients with stable or asymptomatic coronary stenosis. PCI may actually destabilize coronary plaque, which becomes manifest in the days or weeks after noncardiac surgery.

Godet and associates studied a cohort of 1152 patients after abdominal aortic surgery in which 78 patients underwent PCI.<sup>122</sup> In the PCI group, the observed percentages of patients with a severe postoperative coronary event (9.0%; 95% CI, 4.4–17.4) or death (5.1% [95% CI, 2.0–12.5]) were not significantly different from the expected percentages (8.2% and 6.9%, respectively), which was confirmed by propensity analysis. PCI did not seem to significantly limit cardiac risk or death after aortic surgery.

Several randomized trials have addressed the value of testing and CABG or PCI, or both, in a subset of patients. McFalls and colleagues reported the results of a multicenter randomized trial in the VA Health System in which patients with documented CAD on coronary angiography, excluding those with left main CAD or a severely depressed ejection fraction (<20%), were randomized to CABG (59%), or percutaneous transluminal coronary angioplasty (PTCA; 41%) versus routine medical therapy.<sup>123</sup> At 2.7 years after randomization, mortality in the revascularization group was not significantly different (22%) from that in the no-revascularization group (23%; Fig. 32.4). Within 30 days after the vascular operation, postoperative MI, defined by elevated troponin levels, occurred in 12% of the revascularization group and in 14% of the no-revascularization group ( $P = .37$ ). The authors suggested that coronary revascularization is not indicated in patients with stable CAD, and

their results further support the lack of efficacy of PCI or CABG for single- or double-vessel disease before noncardiac surgery. However, in a follow-up analysis, Ward and coauthors reported improved outcome in the subset of patients who underwent CABG versus PCI.<sup>124</sup>

Poldermans and colleagues randomized 770 patients about to undergo major vascular surgery and considered to have intermediate cardiac risk, defined as the presence of 1 or 2 cardiac risk factors, to either undergo further risk stratification with stress imaging or proceed directly to surgery.<sup>125</sup> All patients received bisoprolol with a targeted heart rate of 60 to 65 beats/min initiated before and continued after the surgical procedure. The 30-day incidence of cardiac death and nonfatal MI was similar in both groups (1.8% in the no-testing group vs. 2.3% in the tested group). The conclusions of the authors were that further risk stratification in this group of patients considered to be at intermediate risk based on clinical history alone was unnecessary as long as perioperative  $\beta$ -blockers were used and that testing only delayed necessary vascular surgery. In a pilot study, Poldermans and associates tested patients with more than three risk factors; 101 (23%) showed extensive ischemia and were randomly assigned to revascularization ( $n = 49$ ) or no revascularization.<sup>126</sup> Revascularization did not improve 30-day outcome; the incidence of the composite end-point was 43% versus 33% (odds ratio [OR], 1.4; 95% CI, 0.7–2.8;  $P = .30$ ). In addition, no benefit during 1-year follow-up was observed after coronary revascularization (49% vs. 44%; OR, 1.2; 95% CI, 0.7–2.3;  $P = .48$ ). Concern was expressed by Erasmus University (Rotterdam, the Netherlands) regarding the scientific integrity of studies led by Poldermans, as detailed in Erasmus MC Follow-up Investigation Committee: *Report on the 2012 follow-up investigation of possible breaches of academic integrity, September 30, 2012* (<https://www.forbes.com/sites/larryhusten/2012/10/09/erasmus-medical-center-releases-final-report-on-cardiovascular-research-scandal/#675d592528ae>). The articles have



**Fig. 32.4** Long-term survival in patients randomized to coronary revascularization or routine care in patients with coronary artery disease on angiography and undergoing major vascular surgical procedures in the Coronary Artery Revascularization Prophylaxis trial. (From McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med*. 2004;351:2795–2804.)

not been retracted, but these data should be viewed with some skepticism. The authors of the 2014 AHA/ACCF Guidelines decided that the nonretracted decrease publications and/or other derivative studies by Poldermans that are relevant to the topic can only be cited in the text with a comment about the finding compared with the current recommendation but did not form the basis of that recommendation.

One issue in interpreting the results is that the length of time between coronary revascularization and noncardiac surgery most likely has an impact on its protective effect and potential risks. Back and coworkers studied 425 consecutive patients undergoing 481 elective major vascular operations at an academic VA Medical Center.<sup>127</sup> Coronary revascularization was classified as recent (CABG < 1 year; PTCA < 6 months) in 35 cases (7%), prior (CABG > 1 year and ≤ 5 years; PTCA > 6 months and ≤ 2 years) in 45 cases (9%), and remote (CABG ≥ 5 years; PTCA ≥ 2 years) in 48 cases (10%). Outcomes in patients with previous PTCA were similar to those after CABG ( $P = .7$ ). Significant differences in adverse cardiac events and mortality were found among patients with CABG performed within 5 years or PTCA within 2 years (6.3%, 1.3%, respectively), individuals with remote revascularization (10.4%, 6.3%), and non-revascularized patients stratified at high risk (13.3%, 3.3%) or intermediate/low risk (2.8%, 0.9%). The authors concluded that previous coronary revascularization (CABG < 5 years; PTCA < 2 years) may provide only modest protection against adverse cardiac events and mortality after major arterial reconstruction.

PCI using coronary stenting poses several special issues. Kaluza and associates reported on the outcome of 40 patients who underwent prophylactic coronary stent placement less than 6 weeks before major noncardiac surgery requiring general anesthesia.<sup>128</sup> Among these patients, 7 MIs, 11 major bleeding episodes, and 8 deaths were noted. All deaths and MIs, as well as 8 of the 11 bleeding episodes, occurred in patients subjected to surgical procedures less than 14 days after stenting. Four patients died after undergoing surgical procedures 1 day after stenting. Wilson and colleagues reported on 207 patients who underwent noncardiac surgery within 2 months of stent placement.<sup>129</sup> Eight patients died or suffered an MI, all of whom were among the 168 patients who had surgical procedures 6 weeks after stent placement. Vicenzi and coworkers studied 103 patients and reported that the risk of suffering a perioperative cardiac event was 2.11-fold greater in patients with recent stents (< 35 days before surgery) than in those who underwent PCI more than 90 days before surgical procedures.<sup>130</sup> Leibowitz and associates studied a total of 216 consecutive patients who underwent PCI within 3 months of noncardiac surgery (PTCA, 122; stent, 94).<sup>131</sup> A total of 26 patients (12%) died, 13 in the stent group (14%), and 13 in the PTCA group (11%), a nonsignificant difference. The incidence of acute MI and death within 6 months was not significantly different (7% and 14% in the stent group and 6% and 11% in the PTCA group, respectively). Significantly more events occurred in the two groups when noncardiac surgery was performed within 2 weeks of PCI. Based on the accumulating data, elective noncardiac surgery after PCI, with or without stent placement, should be delayed for 4 to 6 weeks.

Drug-eluting stents may represent an even greater problem during the perioperative period based on case reports. Nasser and coauthors described two patients with in-stent thrombosis occurring 4 and 21 months after the implantation of sirolimus-eluting stents.<sup>132</sup> Drug-eluting stents may represent an additional risk over a prolonged period (≤ 12 months), particularly if antiplatelet drugs are discontinued.<sup>133</sup> One study demonstrated that although the frequency of major noncardiac surgery in the year after drug-eluting stent placement was more than 4%, the overall risk of adverse outcomes was less than previously reported when surgical procedures were performed months after drug-eluting stent placement.<sup>134</sup> However, the risk was significantly increased in the week after major noncardiac surgery. A population-based study in Canada using administrative healthcare databases demonstrated that the earliest optimal time for elective surgery is 46 to 180 days after bare-metal stent implantation or more than 180 days after drug-eluting stent implantation.<sup>135</sup> Hawn and colleagues used a national, retrospective cohort study of 41,989 VA and non-VA operations occurring in the 24 months after coronary stent implantation between 2000 and 2010.<sup>136</sup> Among patients undergoing noncardiac surgery within 2 years of coronary stent placement, major adverse cardiac events were associated with emergency surgery and advanced cardiac disease but not stent type or timing of surgery beyond 6 months after stent implantation. The 2016 DAPT Guidelines (Fig. 32.5) suggest continuing aspirin therapy in all patients with a coronary stent and discontinuing clopidogrel for as short a time interval as possible for patients with bare-metal stents less than 30 days or drug-eluting stents less than 6 months; with DAPT it can be discontinued.<sup>136a</sup>

Based upon the non-perioperative literature, there is a suggestion that holding clopidogrel for the traditional 8 days may actually increase risk associated with a hypercoagulable rebound suggesting a shorter period of time may be optimal. A recent cohort study suggests that withdrawal of antiplatelet agents greater than 5 days is associated with increased major adverse cardiac events.<sup>136b</sup>

### Perioperative Risk Factors for Cardiac Morbidity and Mortality

A thorough history should focus on cardiovascular risk factors and symptoms or signs of unstable cardiac disease states, such as myocardial ischemia with minimal exertion, active CHF, symptomatic valvular heart disease, and significant cardiac arrhythmias. The presence of unstable angina is associated with a 28% incidence of perioperative MI.<sup>137</sup> Such patients would benefit from delaying elective surgery to address their CAD. For those patients with chronic stable angina, exercise tolerance appears to be a good method of assessing perioperative risk.

In virtually all studies, the presence of active CHF has been associated with increased perioperative cardiac morbidity.<sup>138</sup> In addition, multiple studies have demonstrated that reduced ejection fraction is associated with an increased incidence of perioperative cardiac events.<sup>139,140</sup> Flu and colleagues performed echocardiography in patients undergoing vascular surgery and found that for open surgical procedures, asymptomatic systolic left ventricular dysfunction and asymptomatic diastolic left ventricular